Respiratory outcomes post Nusinersen in Spinal Muscular Atrophy Type 1

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Editorial: Respiratory outcomes post Nusinersen in Spinal Muscular Atrophy Type 1

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Time to wake up and smell the roses as the real world respiratory experiences have arrived for Spinal Muscular Atrophy type 1 (SMA1)! Nusinersen, the first drug to be approved for treatment of SMA1, has changed the natural history of the disease and has now been commercially available in many countries for up to four years(1). SMA 1, the most common cause of infant death attributed to respiratory insufficiency, results from a degeneration of alpha motor neurons in the spinal cord and brainstem resulting in progressive skeletal muscle weakness of the limbs, respiratory and bulbar muscles (2). Most patients with SMA1 will have respiratory complications in the first year of life requiring therapy to support airway clearance and ventilation (2). The pan-ethnic incidence is 1 in 11,000 births (3). Milder phenotypes occur as SMA types 2 and 3 in childhood with a much better prognosis (4) and countries may offer nusinersen for these patients also.

In this issue, Lavie and colleagues (5) offer insights into clinical *respiratory outcomes* from 3 years of prospective data collection in their cohort of 20 SMA1 patients treated before and after 2 years of nusinersen in Israel. Their work builds on the scientific evidence of efficacy of nusinersen primarily for *motor outcomes* over

the last decade. A phase 3 randomised, double-blinded, sham controlled clinical trial in patients with SMA 1 showed that those treated with nusinersen had a significant motor milestone response with a higher likelihood of event-free survival(6). This group did not show a difference in the frequency of serious respiratory adverse events between the groups, thereby leaving unanswered questions about the effect of the medication on respiratory morbidity. Over the past few years, the translatability of outcomes from randomized controlled studies to current real-world outcomes has been questioned (7-9).

A letter to the editor by LoMauro et al. involving children with SMA1 described a milder subset of children with SMA 1 [Described as type SMA 1c: onset between 3 and 6 months] treated with nusinersen who had an improvement in accessory muscle use and reduced daily hours of ventilation when compared to a natural history cohort (7). This was not reported in the more severe SMA 1a and 1b groups. Sansone et al. (8) published an observational, longitudinal cohort study looking at respiratory support requirements at baseline, 6 months and 10 months after nusinersen treatments in 118 children with SMA1. Semi-structured qualitative interviews from caregivers were collected at each interval. They showed that 77% of the cohort's respiratory requirements remained stable and more than 80% of children treated before 2 years survived in contrast to the lower survival reported in natural history studies. The limitation of this study is that they used modality and number of hours of ventilation as the surrogate for respiratory function which can be influenced significantly by respiratory care, management and patient compliance. Chen et al. (9) also published follow-up data (single-centre) in SMA 1 children treated with nusinersen in order to further understand the comprehensive real-world outcomes of this new treatment. While this study was limited by its small sample size of 9, it highlighted that children with SMA1 treated with nusinersen continued to develop considerable respiratory comorbidities. Although a large amount of data has been collected over the past 5 years, there remain gaps in the understanding of many aspects of the use of nusinersen in SMA beyond modest increases in peripheral muscle strength and in particular whether these improvements will translate into reduced respiratory morbidity and less respiratory failure with dependence upon non-invasive ventilation (NIV) (10).

The paper by Lavie et al. (5) contributes to our understanding with its focus on 'real-world' variables including starting or ongoing need for assisted ventilation, the use of mechanical insufflation-exsufflation, respiratory complications, and treatment cessation due to respiratory reasons, or death in around 15% of cases attributed to pulmonary aspiration. In essence, it is a source of modest encouragement for clinicians as the majority of children demonstrated stability of respiratory support over the first two years of treatment with nusinersen which is in itself much better than the natural history of the condition with progressive decline and death in 90% by the age of 2 years. However, there are some gaps in knowledge in this paper which will require further studies. It is unclear exactly why children started ventilation specifically, who went to tracheostomy and why others went to NIV and what their initial ventilator pressures were. Management algorithms have been available to outline this in neuromuscular diseases [11]. Further, it is unclear how many children had polysomnograms and what the results were in terms of apnoea indices, measures of hypoventilation, alterations in oxygenation and extent of transcutaneous CO_2 abnormalities, other than that they were consistent with the standards of care for the treatment of children with SMA published in 2007 [12]. Further guidelines have since emerged in the nusinersen era [13]. Certainly, the positive impact of the use of NIV on respiratory outcomes, including hospitalisations, albeit in the broader neuromuscular population, has been established [14]. As would be hoped, a reduction in admissions was seen in the present study in SMA1. Nonetheless, as all clinicians appreciate, what is prescribed and what is used for the treatment of anything in "the real world" varies widely. Think of asthma preventers or any therapies in cystic fibrosis including expensive correctors. In a prospective study on real world respiratory outcomes, the absence of information on adherence with average daily hours of support from memory cards inside the NIV devices is a short-coming of the study of Lavie et al. (5). This is something which, with serial assessment of polysomnography parameters, should be addressed in future studies in SMA1 treated patients to ascertain the true rather than potentially perceived benefit of NIV.

Lavie et al. (5) provide insight into the everyday clinical respiratory burden of patients with SMA1 treated with nusinersen while highlighting further areas of research. Specifically, they rightly suggest a beneficial

effect with the earliest initiation of nusinersen due to the possibility that nusinersen may have an effect on preserving respiratory function if started at a younger age. This mirrors data in the larger RCT where earlier treatment was associated with better motor outcomes. Logically, this could be readily achieved with emerging increase in new born screening programs including SMA genes in countries such as Australia and Belgium [15]. This would also enable quantification of the number of copies of SMN2 genes present, missing in 30% of cases in the series of Lavie et al. (5). This stratification of genotype may be more important than ever in the nusinersen era as we improve our ability to predict outcomes beyond age of presentation [Types 1a, 1b and 1c] [13]. The argument for newborn screening for SMA, with earlier diagnosis and improved outcomes for such an expensive therapy seems persuasive.

This article explores patient outcomes in a real-world setting and found that the need for assisted ventilation did not worsen as would be with the natural progression of SMA1. However, they showed no improvement either. Therefore, nusinersen is a small step forward with the promise of much more to come from gene therapy and potentially combinations of therapies. Longer term studies with international prospective data registries are warranted and should be funded by international neuromuscular societies at arm's length from pharmaceutical companies. It is as important to document respiratory outcomes rather than just predominantly modest motor outcomes not only for SMA1 but also SMA2 and SMA3, because at the end of the day in the real world, your respiratory wellbeing determines morbidity and mortality.

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