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Letter to the Editor

Assessment of Clinical and Functional Outcomes of SMA Under Nusinersen Using 6MWT, HFMSE, CHOP-INTEND, RULM and HINE2 can be Misleading

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Letter to the Editor

We read with interest the article by Al-Jedai *et al*. on an ambispective study of the clinical and functional outcomes of 109 patients with spinal muscular atrophy (SMA) type 1 (n=3), type 2 (n=30), and type 3 (n=76). Patients were recruited between 2017 and 2023 and treated with nusinersen. The maximum follow-up period was 60 months [1]. The median score on the extended Hammersmith Functional Motor Scale (HFMSE) was 34 at baseline and 29 after 20 months. Clinically relevant improvement (an increase in the HFMSE score of at least 2 points) was observed in only 23 patients [1]. The authors concluded that assessment using multiple motor and functional scales at baseline and during follow-up is essential to evaluate SMA progression and response to nusinersen [1].

First, the study included a retrospective component [1]. Retrospective studies have disadvantages because they rely on the analysis of medical records that were not originally intended for research purposes. The data may be incomplete, selection, classification, and recall errors can affect the results, and the reasons for treatment differences between patients and those who dropped out during the study cannot be determined, which can lead to bias [2]. Furthermore, while retrospective studies can show associations, they cannot prove causality. They do not guarantee the control of confounding variables, and it can be difficult to form representative comparison groups, which is particularly problematic for rare events [2].

Secondly, the tests used (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP-INTEND) and Hammersmith Infant Neurological Examination (HINE2) for SMA type 1, the 6-minute walk test (6MWT), HFMSE and the Revised Upper Limb Module (RULM) for SMA types 2 and 3) have several limitations. Disadvantages of the CHOP-INTEND include potential ceiling effects (the score reaches its maximum too early in highly reactive infants), the need for standardized interpretation because the results change with age (e.g., only 8 of 16 items for newborns), the problem of fatigue affecting the results, the need for careful testing conditions, and the potential confusion of maturation changes with treatment effectiveness in newborns [4]. The disadvantages of HINE include the low accuracy in coordination testing, the high resource expenditure for widespread use in clinics with high patient volume, and the limited ability to capture the entire spectrum of neurodevelopmental disorders. Disadvantages of the 6MWT include high variability due to factors such as age, sex, pain, or muscle problems; a lack of understanding of the mechanisms of action of exercise; dependence on a suitable testing environment (long corridor); and the possibility that results may depend on patient motivation [3]. Disadvantages of the HFMSE include potential ceiling and floor effects in SMA patients with very high or very low functional levels, respectively; low sensitivity for certain patient groups; reliance on trained personnel; and difficulties in determining a meaningful change score for different age groups and performance levels [5]. The RULM exhibits a potential ceiling effect (it is not sensitive enough to detect a decline in performance in stronger, ambulatory patients), performance is age-dependent, and it requires specialized, sometimes expensive, equipment. These limitations of the tests used must be considered before drawing definitive conclusions.

Third, scoliosis was the only comorbidity among the 109 included patients [1]. Since scoliosis can secondarily impair cardiac and pulmonary function by compressing the rib cage, reducing lung volume, and stressing the heart and vessels, potentially leading to reduced cardiac output, altered cardiac mechanics, and an increased risk of heart disease such as heart failure, it would be interesting to know whether the ejection fraction or fractional shortening was normal in the 27 patients with severe scoliosis.

Fourth, no additional treatment other than nusinersen was reported [1]. Since additional therapies, particularly physiotherapy,

can have a beneficial effect in SMA patients, it is important to know what type of additional treatment the included patients received.

Fifth, scoliosis was the only comorbidity among the 109 included patients [1]. Since scoliosis can secondarily impair cardiac and pulmonary function by compressing the rib cage, reducing lung volume, and stressing the heart and vessels, potentially leading to reduced cardiac output, altered cardiac mechanics, and an increased risk of cardiac problems such as heart failure, it would be interesting to know whether the ejection fraction or fractional shortening was normal in the 27 patients with severe scoliosis.

The sixth point concerns the statement that "patients with presymptomatic SMA had a significantly earlier symptom onset with a median age of 0.17 (0.08–10.42) months, followed by patients with SMA type 1," which is incomprehensible [1]. According to the results section, only one patient had presymptomatic SMA [1]. How can a median value be calculated from the data of a single patient? How can an asymptomatic patient even develop symptoms? These inconsistencies require clarification.

One limitation of the study is that the number of patients assessed based on functional outcome parameters decreased significantly with the duration of treatment. Only one patient was followed up for 60 months [1].

Overall, the assessment of clinical and functional outcomes in SMA patients receiving nusinersen therapy using the 6MWT, HFMSE, CHOP-INTEND score, RULM score, and HINE2 score can be misleading due to the inherent limitations of these scores. The use of more advanced methods to assess the effect of nusinersen does not guarantee that the overall benefit is greater than calculated in the reference study.

Declarations

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