Neuromuscular Physiatry Sharing Session #1

Attendees:

1. Dr. Stephanie Plamondon – Presenter and Lead
2. Dr. Colleen O'Connell
3. Dr. Ming Chang
4. Dr. Jessica Theriault
5. Dr. Xavier Rodrigue
6. Dr. Rodney Li PI
7. Dr. Alasdair Rathbone
8. Dr. Geoffrey Frost
9. Dr. Beatrice Soucy
10. Dr. Lindsay Hubenig
11. Dr. Daria Trojan

Summary of Case Study

Case presentation

- A thirty-six-year-old female with SMA type II, experiencing chronic respiratory failure, a possible asthma component, and allergies, is under the care of Dr. Plamondon. In January 2015, she initiated Bilevel Positive Airway Pressure (BiPAP) therapy, followed by daytime mouthpiece ventilation in 2016, along with the use of breath stacking and cough assist devices. She was hospitalized for pneumonia in 2016, and a mild infection managed at home in 2021. Her vital forced capacity (FVC) has been of 0.85L or 26% since 2016. She is currently followed every 6 months by a respiratory therapist.
- Treated surgically at age 15 with posterior luque rods and cerclage wires, she currently has a severe S-shaped rotary kyphoscoliosis and chest wall deformity, which after assessment by a spine orthopedics in 2014, was considered too risky to intervene surgically. The current management consists in seating and physiotherapy.
- She also presents other symptoms, such as chronic intermittent neck and right trapezius pain, oropharyngeal dysphagia, trismus, and gastroesophageal reflux disease.
- She lives with her parents in an accessible house in a rural location. She is able to self-feed, having 2 meals per day, to groom with care support, to access her computer, and to drive her power chair with joystick. She relies on assistance for donning and doffing BiPAP, breath stacking and cough assist procedures.
- Supported by the AISH, provincial program that provides financial and health-related benefits to eligible adult Albertans, she works part-time, and she manages her own medical care, medications, and finances.
- She disposes of equipment such as a power chair, a commode, home access lifts, and an adapted van.
- In 2019 she experienced a gradual onset of increased weakness, particularly in the neck and arms, with more pronounced fatigue in the right arm. Daily activities such as grooming and feeding became more difficult. Examinations and interventions, including MRI, EMG, X-rays, conservative treatment for possible right ulnar cubital tunnel syndrome, and metabolic workup, were conducted to rule out other potential causes. Her seating, occupational therapy, and physiotherapy care were optimized, and her nutrition was also addressed by suggesting she eat multiple small meals per day.
- She was prescribed oral salbutamol, followed by potassium supplementation and mestinon. In 2017, she applied unsuccessfully to the Biogen SMA 360 program and the Evrysdi program. Alberta Blue Cross denied coverage for genetic treatments. The worsening of her symptoms and the denial of access to genetic treatment programs significantly impacted her mental health.

Open question: Should this patient be eligible to genetic treatment?

Summary of Selected Article

The article selected for this sharing session is "**Long-term efficacy and safety of nusinersen in adults with 5q spinal muscular atrophy: a prospective European multinational observational study**" by Gunther et al, 2024, along with the GRACE v 5.0 checklist (a tool to assess whether a study is sufficiently rigorous to be reliable enough for use in practice).

Introduction

Following the approval of nusinersen in Europe in May 2017, Günter *et al* 2024 intended to evaluate long term (over 38 months) safety and efficacy of Nusinersen on a large cohort (389 adult patients with SMA participating in the SMArtCARE registry).

Methods

Inclusion criteria: adults who had been treated with nusinersen for a minimum of 14 months and that were genetically-confirmed, 5q-associated SMA due to homozygous deletion of exons 7, 8, or both, or to compound heterozygous SMN1 mutations.

The primary outcome measure: the change from baseline in the total Hammersmith Functional Motor Scale Expanded (HFMSE) score at 14, 26, and 38 months, considering a clinically meaningful change an increase of at least 3 points.

Secondary outcome measures: changes from baseline in the Revised Upper Limb Module (RULM) score, with a clinically meaningful change defined as an increase of at least 2 points, as well as the 6-minute walk test (6MWT), where a change of at least 30 meters was considered clinically meaningful.
For safety, adverse drug reactions and procedure-related complications were evaluated.

Results and discussion

Nusinersen therapy results in an improvement or stabilization in motor function for up to 38 months in the majority of adult SMA patients based on the HFMSE, RULM and 6MWT score, while 30% of patients experienced a decline in motor scale assessments over the same period. In particular, less severely affected patients, such as those with SMA type 3 who are ambulatory without spondylodesis, have shown sustained and clinically relevant improvement in motor function. For what concern safety, 732 adverse drug reactions or procedure-related complications were documented in 91% of participants, but no severe adverse reactions, including death, were reported.

This study provides real-world evidence of motor function during nusinersen treatment on SMA adult patients.

Group Discussion

Upon review of the article using the Grace checklist, it was noted a trend of excluding the latest timepoint data from the analysis. It was pointed out that this exclusion could introduce bias. Due to a significant number of missing values, which reached up to 69% at the 38-month timepoint, the authors used the fully conditional specification method to conduct an exploratory sensitivity analysis of the HFMSE score. Through this statistical method, the significance of the changes from baseline was lost at 26 and 38 months, although it remained at 14 months. Additionally, missing data regarding dose dropout and any significant differences compared to the mean were not analyzed by the authors.

For what concern the study design, the study does not report a comparison between treated and untreated groups, but instead focuses on changes from baseline and comparisons with historical data published between 2011 and 2022, which may be suboptimal for capturing changes. It was highlighted that the authors did not mention the reason why the observational study did not extend to untreated individuals.

Another issue is the lack of explanation regarding the eligibility criteria. In particular, the authors did not specify the criteria concerning the eligibility to receive nursinersen.

While the outcome measures of this study primarily focus on motor assessment, the respiratory function was not evaluated.

Open discussion: How SMA patients are cared for across Canada

Across Canada, SMA patients are typically cared for by both physiatrists and neurologists, with the latter primarily responsible for treatment. Physiatrists as SMA treaters depends on location/clinic. The follow-up visits are generally scheduled every 6 months or once a year. However, there are challenges associated with conducting all outcome measures in a single visit, due to the wide number of assessments and the patients' fatigue. In some cases, for instance when patients are difficult to mobilize and lack access to treatment, even simply scheduling follow-up visits is particularly challenging (especially if they are not receiving disease-modifying treatment).

According to some participants, to improve SMA care, it might be beneficial to have a discussion regarding the implementation of multidisciplinary clinics and comprehensive multidisciplinary care. Dr. O'Connell did note that there is currently a report being developed on outcome measures for SMA to help promote consistency in the data collected.