Clinical Outcome of Adult Spinal Muscular Atrophy Patients Treated with Nusinersen: A Case Series Review

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E-pub: 12/09/2020

ABSTRACT

Introduction: Nusinersen is an antisense oligonucleotide drug that was developed for treatment of spinal muscular atrophy (SMA). Its effectiveness for adults is limited; therefore, more clinical data are needed to guide adult SMA patients who are considering this treatment.

Methods: Through case series review, we retrospectively reviewed charts of Kaiser Permanente Southern California members who were already receiving nusinersen treatment, which has been available since August 2017. Patients were evaluated by physical therapy using the Hammersmith Functional Motor Scale (out of highest possible score of 40).

Results: We identified 4 adult patients who met our study criteria as of February 1, 2020. All patients were mobility device dependent. Patient age ranged from 23 to 56 years. A generalized linear model was used to assess trendlines for repeated measures within subjects. In this small sample, there appears to a significant increase in scores on repeated measures (p = 0.0027).

Conclusion: Based on this small study, some adult SMA patients may benefit from treatment with nusinersen.

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disease caused by homozygous deletion or mutation of the survival motor neuron 1 (SMN1) gene, which leads to progressive muscle weakness and paralysis. Its phenotype is divided into 5 subtypes: SMA0 to SMA4, with SMA 0 being the most severe form and earliest age of onset. Individuals who have SMN1 deletion or mutation have a variable number of survival motor neuron 2 (SMN2) genes, with fewer SMN2 copies correlating with the more severe SMA phenotype. It is the second most common fatal autosomal recessive disorder, behind cystic fibrosis, with incidence 1 in 10,000 live births and a prevalence of 1 per 100,000 persons.

Nusinersen (Spinraza) is a new pharmacological treatment that increases production of survival motor neuron protein by altering the splicing of SMN2 pre-mRNA as an antisense oligonucleotide. A randomized clinical trial has demonstrated clinical benefit in SMA patients who were infants and children up to age 15. Based on these data, nusinersen was approved by the Food and Drug Administration in December 2016 for SMA treatment of all subtypes. However, clinical data for nusinersen in adult SMA patients is lacking because there has been no randomized clinical trial evaluating its use in this age group. We report our experience with nusinersen for adult SMA patients in our medical center.

METHODS

Study Design and Participants

This is a small, nonfunded case series study approved by the Kaiser Permanente Southern California Institutional Review Board with informed consent waived.

All participants are members of our integrated health care system Kaiser Permanente Southern California with a diagnosis of SMA confirmed by genetic testing. We found a total of 12 patients currently on or having received nusinersen treatment, which has been available since August 2017.

Motor Function Assessment

All patients were required to have had at least 1 physical therapy evaluation using the Hammersmith Functional Motor Scale (HFMS) before the start of nusinersen treatment and were evaluated every 3 to 6 months after starting medication. The HFMS is a standardized, well-studied tool that was developed to evaluate the motor abilities of patients with SMA. It consists of 20 items, with each item scored on a scale of 0 to 2, for a total highest possible score of 40; a higher score indicates better function. Evaluation using the HFMS was done by physical therapists who had been trained to work with neuromuscular patients. We chose this scale because it is the most comparable tool to other literature and is most frequently used within the Kaiser Permanente Southern California health care system.

Drug Therapy

All patients received nusinersen medication intrathecally lumbar following the prescribing information about every 3 to 4 months as part of the current standard medical therapy. All patients also attend a multidisciplinary clinic composed of neurologists, pulmonologists, physical therapists, respiratory therapists, and social workers at least once a year at Kaiser Permanente Los Angeles Medical Center for routine follow-up.

Statistical Analysis

A generalized linear model was used to assess trendlines for repeated measures within subjects and to determine

Keywords: adult therapy, assessment, musculoskeletal, neurology, patient experience, performance, research
statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). Statisticians from Kaiser Permanente Regional Research Statistical Support provided their service for data analysis.

RESULTS

After applying the selection criteria as described above, 6 patients were identified in the study. To focus our investigation on the adult SMA population, we excluded 2 patients from the final analysis who were under the age of 18 years. Data were collected up to February 1, 2020. All patients were mobility device dependent. All identified patients had attended physical therapy sessions with HFMS evaluation and were followed until at least 18 months from the start of the therapy. The final group ranged in age from approximately 23 to 56 years at the time the data were collected (Table 1). All patients had no copies of SMN1 and at least 2 copies of SMN2. All patients were women by coincidence.

In this small sample there appears to be a significant increase in scores on repeated measures (p = 0.0027) (Figure 1). One patient had a 10-point increase after 22 months of treatment. However, the eldest patient had at most a 1-point improvement (Table 1). This patient had a low baseline motor function (HFMS 6/40).

During multidisciplinary clinical follow-up, 1 patient reported a 1-time headache from the intrathecal medication administration. No other patients described significant side effects. Further chart review on routine blood work drawn at each nusinersen dosing did not reveal clinically significant thrombocytopenia, coagulation abnormalities, or renal toxicities.

DISCUSSION

Our study is consistent with recent observational studies reporting that nusinersen is well tolerated in adults.6-8 In general, adult patients seem to have shown improvement in motor function as measured by HFMS after starting the

<table>
<thead>
<tr>
<th>Age as of February 2020</th>
<th>Sex</th>
<th>SMN number of copies</th>
<th>Score at day 1a</th>
<th>Score at 6 mo</th>
<th>Score at 14 mo</th>
<th>Score at 18 mo</th>
<th>Score at 22 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>Female</td>
<td>SMN 1: 0; SMN2: 3</td>
<td>6/40</td>
<td>5/40</td>
<td>7/40</td>
<td>7/40</td>
<td>7/40</td>
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<tr>
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<td>14/40</td>
<td>16/40</td>
<td>20/40</td>
<td>23/40</td>
<td>24/40</td>
</tr>
<tr>
<td>33</td>
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<td>26/40</td>
<td>28/40</td>
<td>33/40</td>
<td>33/40</td>
<td>34/40</td>
</tr>
<tr>
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<td>39/40</td>
<td>39/40</td>
<td>40/40</td>
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<tr>
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</tr>
<tr>
<td>9b</td>
<td>Male</td>
<td>SMN 1: 0; SMN 2: 2</td>
<td>0/40</td>
<td>NA</td>
<td>0/40</td>
<td>NA</td>
<td>0/40</td>
</tr>
</tbody>
</table>

a Day 1 refers to last evaluation prior to the first round of drug therapy.
b Patients excluded from final analysis because they are under the age of 18 but included in the table for discussion purposes.

NA = not available; SMN = survival motor neuron.
treatment. However, the adult patient in our cohort who had a low baseline motor function did not have significant benefit from the treatment. This is consistent with a previous observational study of adult SMA patients receiving nusinersen in Germany, in which a positive correlation between lower severity of disease and improvement of motor function was noted. Age did not seem to matter because our youngest patient, who was under the age of 18, also had low baseline motor function and did not benefit from the treatment.

One of the explanations is that restoration of functional SMN protein patients may not be beneficial at end-stage SMA disease. Although functional SMN plays important role in neurite outgrowth and neuromuscular maturation during neuronal differentiation and development, it may not have a restorative effect on motor neuron once a significant degenerative threshold is reached. Therefore, at advanced stage, further treatment with nusinersen may not yield significant benefit.

There are several limitations in this study. First, because this study is a case series, there were no control subjects, and therefore the results may be prone to bias. Second, because this study uses HFMS as a clinical measure, which is a motor assessment, clinical benefits in nonmotor domains are not captured. Third, our sample size is small, and the final group consisted of all female subjects; therefore, generalizability to larger population is limited.

Our study suggests that treatment with nusinersen in adult SMA patients can achieve clinically meaningful motor improvement. We recommend more studies to explore the hypothesis on whether patients who have low baseline motor function would benefit from this treatment.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgments
We thank our neuromuscular clinic coordinator Susan George-Ryderberg, BSN, RN, MA, for helping us identify suitable candidates for study and for managing their cases. We also thank our biostatistician Ngoc Ho, PhD, for assistance with data analysis, describing the statistical method, and creating the figure. Our neuromuscular clinic coordinator Susan George-Ryderberg, BSN, RN, MA, assisted with identifying suitable candidates for study and for managing their cases. Our biostatistician Ngoc Ho, PhD, assisted with data analysis, describing the statistical method, and creating the figure.

Authors’ Contributions
Keng Lam, MD, and Abel Wu, MD, designed the study, assisted with data collection, and wrote and edited the manuscript. Keng Lam, MD, prepared and submitted the final version of the manuscript. Abel Wu, MD, supervised the project.

How to Cite this Article

References

Funding Statement
None.