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Original Article

Evaluation of the Efficacy of Nusinersen Treatment in Patients with Late-onset SMA Using the Hammersmith Functional Motor Scale Expanded

Geç-başlangıçlı SMA Hastalarında Nusinersen Tedavisinin Etkinliğinin Genişletilmiş Hammersmith Fonksiyonel Motor Ölçeği Kullanılarak Değerlendirilmesi

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ABSTRACT

Objective: Spinal muscular atrophy (SMA) is a hereditary disorder with progressive muscle weakness and atrophy. Nusinersen is an antisense oligonucleotide directed against SMN2 and has been shown in studies to improve the motor skills of patients. The aim of this study was to evaluate the efficacy of nusinersen treatment in patients with SMA type 2 and type 3 using the Hammersmith Functional Motor Scale Expanded (HFMSE) score.

Method: The diagnosis and differentiation of SMA type 2 and type 3 were based on clinical findings and genetic tests. The HFMSE scores of all patients were evaluated in detail before nusinersen doses.

Results: Evaluation was made of a total of 15 patients, 12 SMA type 2 and 3 SMA type 3, with a median age of 13 years. None of the patients had regression of acquired abilities after nusinersen treatment. The median HFMSE score of SMA type 2 patients before treatment was 9. After nine doses of nusinersen, the HFMSE score showed a significant increase from 9 to 30 points. Although none of the patients could walk, their motor skills improved significantly. The median HFMSE score of SMA type 3 patients before treatment was 60. After 3 doses of nusinersen treatment, HFMSE scores were found to be 63.

Conclusion: Nusinersen is an effective and safe treatment for patients with late-onset SMA. It can be suggested that different motor scales should be applied and developed for SMA type 2 (sitter) and type 3 (walker) patients due to differences in the clinical characteristics of SMA types.

Keywords: Later onset SMA, nusinersen, Hammersmith Functional Motor Scale Expanded

ÖZ

Amaç: Spinal müsküler atrofi (SMA), ilerleyici kas güçsüzlüğü ve atrofiyle giden kalıtsal bir hastalıktır. Nusinersen, SMN2'ye yönelik bir antisens oligonükleotittir ve hastaların motor becerileri düzelttiği çalışmalarla kanıtlanmıştır. Bu çalışmada SMA tip 2 ve tip 3 tanısı alan hastalarda nusinersen tedavisinin etkinliğini HMFSE skoru ile değerlendirmeyi amaçladık.

Yöntem: SMA tanısı; klinik ve genetik bulgulara göre konuldu. SMA tip 2 ve tip 3 ayrımı klinik bulguların başlangıcı ve gelişim basamaklarına göre yapıldı. Tüm hastaların nusinersen dozları öncesi ve sonrası HMFCSE skorları değerlendirildi.

Bulgular: Çalışmamıza 12 SMA tip 2 ve 3 SMA tip 3 olmak üzere toplam 15 hasta dahil edildi. Hastaların ortanca yaşları 13 yaştı. Nusinersen tedavisinden sonra hiçbir hastada kazanılmış yeteneklerde gerileme olmadı. SMA tip 2 hastalarının tedavi öncesi median HFMSE skoru 9 idi. Dokuz doz nusinersen tedavisi sonrası HFMSE skorlarını anlamlı bir şekilde 9'dan 30 puana çıkardı. Hastaların hiçbiri yürüyemese de motor becerilerinde anlamlı iyileşme görüldü. SMA tip 3 hastalarının tedavi öncesi medyan HFMSE skoru 60 oldu. Üç doz nusinersen tedavisi sonrasında HFMSE skorları 63 olarak belirlendi.

Sonuç: Nusinersen geç başlangıçlı SMA hastaları için etkili ve güvenli bir tedavi yöntemidir. SMA tiplerinin klinik özelliklerindeki farklılıklar nedeniyle SMA tip 2 (oturan) ve tip 3 (yürüyen) hastalarına farklı motor ölçeklerin uygulanması ve geliştirilmesi önerilebilir.

Anahtar kelimeler: Geç başlangıçlı SMA, nusinersen, Genişletilmiş Hammersmith Fonksiyonel Motor Skalası

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INTRODUCTION

Spinal muscular atrophy (SMA) is a hereditary disorder characterized by progressive muscle weakness and atrophy caused by the degeneration of spinal anterior horn cells and loss of alpha motor neurons[1]. The incidence of SMA ranges from 4 to 10 per 100,000 live births[2-4]. In 95% of cases, the cause is a homozygous deletion of 5q13 survival motor neuron 1 (SMN1)[5]. Differences in SMN protein activity and phenotypic expression appear to be related in part to a modifier gene called SMN2[6]. A small amount (approximately 10-15%) of mRNAs from SMN2 can produce functional, full-length SMN protein[7]. Thus, the loss of SMN1 protein is partially compensated by SMN2 protein synthesis. This is a mechanism that explains some, but not all, of the phenotypic variability in patients with SMA[8]. The classification of SMA subtypes is determined by age at onset, and the clinical severity and life expectancy[9]. The natural history and examination findings in SMA depend on phenotypic variation[10]. Genetic testing is usually adequate to confirm the diagnosis of SMA. SMN2 copy number detection is usually performed simultaneously to give prognostic indication[11]. Although the main treatment in SMA is supportive care[12] modifying therapies such as nusinersen, onasemnogene abeparvovec and risdiplam have been recently developed[13]. Nusinersen is an antisense oligonucleotide directed against SMN2[14] which alters SMN2, enables pre-RNA splicing for the inclusion of exon 7, and increases the expression of functional SMN protein[14]. Nusinersen treatment for 5q-SMAs was approved by the Food and Drug Administration in December 2016[15].

The purpose of this study was to examine the changes in the Hammersmith Expanded Functional Motor Scale (HFMSE) before and after treatment in SMA type 2 and type 3 patients treated with nusinersen.

MATERIALS and METHODS

The study included SMA type 2 and type 3 patients treated with nusinersen between 2018 and 2023. Age, gender, age at onset of clinical findings, physical examination findings and genetic test results of all the patients were analyzed. The diagnosis and differentiation of SMA type 2 and type 3 was based on age at symptom onset, maximum motor skills acquired, severity of symptoms and genetic testing. In SMA type 2, symptoms appear at 6 to 18 months of age; the patient can sit but has hypotonia, areflexia, and progressive proximal weakness affecting the extremities disproportionately[9]. SMA type 3 usually occurs after the 18th month of life. Patients can walk but may need a wheelchair as the disease progresses[9,16].

The HFMSE was administered by a physiotherapist to all patients before each dose of nusinersen treatment. The HFMSE consists of 33 items investigating the child's ability to perform various activities. Each activity (item) is scored with a 2-point scoring system; 2 points for no assistance, 1 point for assistance and 0 points for incapacity. All items are tested without spinal jackets or orthoses. The total score of all the individual items ranges from a minimum score of 0 to a maximum score of 66[17].

The nusinersen injection was administered intrathecally [5 mL (12 mg) solution] by a pediatric neurologist or interventional radiologist according to the patient's degree of scoliosis. All patients were hospitalized and monitored for at least 24 hours after the application for the observation of possible side-effects. The doses were administered as four loading doses on day 0, day 14, day 28 and day 63, followed by maintenance doses every four months[18].

Ethical approval for this study was secured from the Non-Interventional Research Ethics Committee at University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval number: 2023/09-68, dated: 20/11/2023). Because of the study's retrospective nature, obtaining parental consent was impossible.

Statistical Analysis

The data analysis was analyzed via Statistical Package for the Social Sciences software. The Shapiro-Wilk test was used to check for normal distribution of the data. For data that followed a normal distribution, mean and standard deviation were calculated, whereas median and interquartile range were determined for non-normally distributed data.

Categorical variables were analyzed with chi-square tests or Fisher's exact tests. To assess differences between groups for continuous variables, independent samples t-tests or Mann-Whitney U tests were applied. For comparisons involving more than two groups, analysis of variance or Kruskal-Wallis tests were used. Post-hoc analyses were conducted to pinpoint specific differences between groups. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

We evaluated 15 patients with a median age of 13 years. The median age at diagnosis was 12 months (minimum 9-maximum 18 months). The patients comprised 7 (46.7%) females and 8 (53.3%) males, as 12 (80%) who were followed up with a diagnosis of SMA type 2 and 3 (20%) with a diagnosis of SMA type 3. There was a history of consanguineous parents in 3 (20%) patients and one (6.7%) patient had a family history of SMA. The median SMN2 copy number was 3 copies (minimum 2-maximum 4). The median age at first nusinersen treatment was 8 years (minimum 1 months-maximum 15 years).

Tachycardia with respiratory distress was observed in 1 patient (diagnosed as SMA type 2) 3 days after nusinersen administration. Respiratory tract infections and cardiac causes were investigated. Pulmonary embolism was found on thoracic tomography of the patient whose respiratory distress could not be explained by other causes. Possible causes of pulmonary embolism were analyzed. No cause was found in the etiology. No side effects were observed in any other patient.

The median pretreatment HFMSE score was 60 for SMA type 3 patients and 9 for SMA type 2 patients. During the first dose, the median age was 7 years in SMA type 2 patients and 10 years in SMA type 3 patients. The median values of the HFMSE scores of SMA type 2 and type 3 before and after nusinersen treatment are summarized in Figure 1.

The median HFMSE score of SMA type 2 patients before treatment was 9. HFMSE score increased significantly after the first 4 loading doses (p=0.001). After nine doses of nusinersen, the HFMSE score showed a significant increase from 9 to 30 points. Although none of the patients could walk, their motor skills improved significantly. The median HFMSE score of SMA type 3 patients before treatment was 60. After 3 doses of nusinersen treatment, HFMSE scores were found to be 63. When the items in the HFMSE were examined in detail, it was observed that none of the patients diagnosed with SMA type 2 showed improvement in any of the movements such as standing without support, stepping, jumping forward, climbing stairs with or without handrail, and descending stairs without handrail. It was observed that all the patients diagnosed with SMA type 3 were able to perform all of these items before treatment.

Improvements in the motor skills after nusinersen are summarized in detail in Table 1.

After the nusinersen treatment, the SMA type 2 patients with an increase of ≥10 points in the HFMSE score were compared with patients with an increase of <10 points. No significant relationship was found between SMN2 copy number, age at first treatment, and HFMSE score before first treatment (Spearman's correlation 0.290, -0.315, -0.292 respectively, p>0.05).

There was no statistically significant relationship between the age at the time of initiation of the first treatment dose and the increase in the HFMSE score (p=0.243).

DISCUSSION

Although the main treatment in SMA is supportive care, recently developed disease-modifying therapies such as the promising nusinersen are now available for patients with SMA. Nusinersen is an antisense oligonucleotide directed against SMN2[19,20]. Nusinersen is one of the few treatment options that has been clinically proven effective and approved for use, and significant benefits of treatment have been shown in later onset SMA[21].

SMA type 2 patients can sit but cannot walk independently. SMA type 3 patients on the HFMSE score reach the ability to walk independently, but over time they lose motor function and many become wheelchair-dependent[1,22]. In the current study, none of the patients lost their acquired abilities after nusinersen treatment and this was similar to the findings in literature[23].

Of the items on the HFMSE, the most frequently acquired in patients with SMA type 2 were hip flexion in supine, two hands to head in sitting, rolls supine to

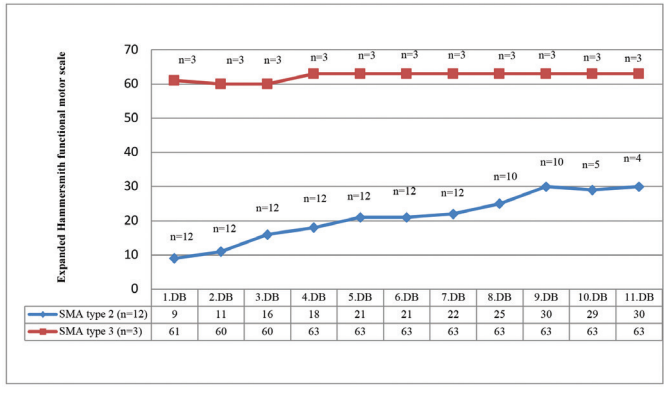

Figure 1. Hammersmith Functional Motor Scale Expanded scores before administration of each nusinersen dose (median value)

DB: Dose before, SMA: Spinal muscular atrophy

prone over, rolls prone to supine over, prop on extended arms, and long sitting, respectively.

It was observed that no patient with SMA type 2 gained ambulation ability and no improvement was found in stepping, standing unsupported, jumping forward, or ascending or descending stairs (with or without support). As far as we can see, there are no studies in the literature that have thoroughly examined the HFMSE score. However, in the study by Audic et al.[24] it was reported that none of the children could walk despite real improvements in motor function in patients with SMA type 2 who received nusinersen treatment, similar to the findings of the our study.

In this study, no significant association was found between early age at treatment initiation and increased HFMSE score, although the motor benefit is associated with early treatment as reported in other studies in the literature[25]. This was attributed to the limited number of patients involved.

Table 1. Hammersmith Functional Motor Scale Expanded items with improvement after nusinersen treatment

Item	SMA type 2 (n=12)	SMA type 3 (n=3)
1: Plinth/Chair sitting	3 (25%)	-
2: Long sitting	6 (50%)	-
3: One hand to head in sitting	5 (42%)	-
4: Two hands to head in sitting	7 (58%)	-
5: Supine to side lying	5 (42%)	-
6: Rolls prone to supine over R	5 (42%)	-
7: Rolls prone to supine over L	6 (50%)	-
8: Rolls supine to prone over R	7 (58%)	-
9: Rolls supine to prone over L	6 (50%)	-
10: Sitting to lying	7 (58%)	-
11: Props on forearms	5 (42%)	-
12: Lifts head from prone	6 (50%)	-
13: Prop on extended arms	7 (58%)	-
14: Lying to sitting	3 (25%)	1 (33%)
15: Four-point kneeling	1 (8%)	
16: Crawling	2 (16%)	
17: Lifts head from supine	3 (25%)	
18: Supported standing	2 (16%)	
19: Stand unsupported	-	
20: Stepping	-	
21: Right hip flexion in supine	9 (75%)	
22: Left hip flexion in supine	8 (83%)	
23: High kneeling to right half kneel	4 (42%)	
24: High kneeling to left half kneel	3 (25%)	
25: High kneeling to standing, leading with left leg (through right half kneel)	2 (16%)	2 (66%)
26: High kneeling to standing, leading with right leg (through left half kneel)	2 (16%)	2 (66%)
27: Standing to sitting on the floor	2 (16%)	1 (33%)
28: Squat	1 (8%)	3 (100%)
29: Jumps 12 inches forward	-	1 (33%)
30: Ascends 4 stairs with railing	-	
31: Descends 4 stairs with railing	-	
32: Ascends 4 stairs without arm support	-	
33: Descends 4 stairs without arm support	-	

In a study by Pane et al.[26], it was observed that the increase in HFMSE score in patients diagnosed with SMA type 2 became evident after the 12th month, whereas in the current study, significant improvements were observed following first 4 loading doses, in contrast to findings in literature. In SMA type 3, an increase similar to that reported in literature was observed after the 3rd dose[26].

The variability in the severity of clinical manifestations of SMA patients is partly explained by the inverse correlation with SMN2 copy number[27,28]. Nusinersen, an antisense oligonucleotide, alters SMN2 pre-RNA splicing, thereby increasing exon 7 inclusion and increasing expression of functional SMN protein[29]. The impact of SMN2 copy number on response to treatment in symptomatic patients is still unclear[30].

No significant relationship was determined between SMN2 copy number and the efficacy of nusinersen treatment in the current study, consistent with the findings of Corrati et al.[31].

Nusinersen treatment has been proven to be a safe treatment in previous studies. In the current study, with the exception of one case of pulmonary embolism of undetermined etiology, no complications were observed in the follow-up of the patients, similar to the literature[21,25].

CONCLUSION

In conclusion, nusinersen treatment is an effective and safe treatment for patients with later onset SMA. Considering the differences in the clinical characteristics of SMA types (movements that cannot be performed by patients who cannot walk or those that are expected to be performed naturally because they can walk), there can be considered to be a need for different motor scales to be developed and applied to SMA type 2 (sitter) and type 3 (walker) patients.

Ethics

Ethics Committee Approval: This study was secured from the Non-Interventional Research Ethics Committee at İzmir Tepecik Education and Research Hospital (approval number: 2023/09-68, dated: 20/11/2023).

Informed Consent: Because of the study's retrospective nature, obtaining parental consent was impossible.

Author Contributions

Concept: Y.G., P.G., N.O.D., Design: Y.G., P.G., F.B., N.O.D., Data Collection and Processing: Y.G., A.Ö.Y., B.T., Analysis and Interpretation: Y.G., Literature Search: Y.G., F.B., Writing: Y.G.

Conflict of Interest: The authors have no conflict of interest to declare.

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