INTRODUCTION

Dravet syndrome (DS) is a rare, severe, and treatment-resistant epileptic encephalopathy that usually presents in the first year of life.

About 85% of patients have a mutation in SCN1A, the gene coding for the neuronal voltage-gated sodium channel alpha subunit.

Fenfluramine (FFA), which was originally marketed as an anorectic drug and used to treat adult obesity, was identified as having antiseizure activity in several case reports in the 1980s.

Based on these and other reports, FFA was allowed to be prescribed for pediatric refractory epilepsy in Belgium under a Royal Decree.

In 2012, Ceulemans and colleagues originally reported on a cohort of 12 DS patients who had been treated with add-on low-dose FFA for up to 19 years.

- 7 of 12 patients had been seizure-free for at least one year at the time of the report from this cohort (2010, mean seizure-free interval: 6 years, 7 months).
- Similar efficacy was sustained through the end of 2014 in the 10 patients who were still being treated.

Here we update the results of FFA treatment in this cohort through the end of 2015.

METHODS

- All patients from the original cohort who continued to receive low-dose FFA at the end of 2010 were included and prospectively followed through the end of 2015.
- Seizure frequency was derived from a seizure diary maintained by each patient’s caregiver.
- Adverse events (AEs) were recorded at each study visit.
- Detailed echocardiographic examinations to assess cardiac valve structure and function were conducted at least annually.
- At the most recent study visit, sleep quality and quality of life were assessed by the patients and their parents/caregivers using 11-point visual analog scales (0=very poor, 10=very good).

RESULTS

- 10 patients (5 males, 5 females) from the original cohort continued to receive FFA from 2010 until the end of 2015 (Table 1).
- The mean age at the most recent study visit was 25.1 years (range: 9.4-37.6 years).
- The mean current dose of FFA was 16 mg/day (0.26 mg/kg/day; range: 0.12-0.42 mg/kg/day).
- The mean treatment duration was 17.2 years (range: 7-28 years).

Annual seizure frequency during the 6-year follow-up is shown in Figure 1.

- 7 patients (70%) experienced prolonged periods of seizure freedom – 3 patients were seizure-free for the entire 6 years.
- 4 patients experienced seizure-free intervals of at least 2 years during the study period.
- All the most recent visit both caregivers and patients were reported to have good quality of sleep and good quality of life (Table 2).

Table 2: Quality of Sleep and Quality of Life Assessments in Patients and Their Parents

<table>
<thead>
<tr>
<th>Quality of Sleep (0-10)</th>
<th>Quality of Life (0-10)</th>
</tr>
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<tbody>
<tr>
<td>Patient</td>
<td>Parent</td>
</tr>
<tr>
<td>8.7</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Mean value at last examination

CONCLUSIONS

- Low-dose FFA continues to provide long-term, durable control of convulsive seizures while being well-tolerated in this cohort of DS patients.
- Patients/caregivers reported high degrees of sleep quality and quality of life.
- After up to 28 years of treatment, no patient has developed any clinically meaningful signs or symptoms of cardiac valvulopathy or pulmonary hypertension.
- Controlled Phase 3 trials are ongoing to confirm the significant improvement in convulsive seizures and safety observed in this cohort.

REFERENCES


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