Fenfluramine significantly reduces day-to-day seizure burden by increasing number of seizure-free days and time between seizures in patients with Dravet syndrome: A time-to-event analysis.

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The number, unpredictability, and severity of seizures experienced by patients with Dravet syndrome (DS) negatively impact quality of life (QOL) for patients, caregivers, and families. Metrics are needed to assess whether patients with residual seizures have moved meaningfully toward seizure freedom after treatment with new antiseizure medications. Methods: We evaluated the time required postrandomization for each patient to experience the same number of seizures experienced during baseline (i.e., time-to-nth seizure), using a post hoc time-to-event (TTE) analysis of data from two Phase 3 placebo-controlled trials of adjunctive fenfluramine for DS (Study 1, N = 119; Study 2, N = 87). Patients aged 2-19 years were randomized to placebo or adjunctive fenfluramine (Study 1: .7 mg/kg/day or .2 mg/kg/day; Study 2: .4 mg/kg/day with stiripentol). Data were analyzed by Kaplan-Meier TTE curves and waterfall plots. Results: The proportion of patients who never reached baseline seizure frequency was greater with fenfluramine than with placebo (Study 1: fenfluramine .7 mg/kg/day, 60%; fenfluramine .2 mg/kg/day, 31%; placebo, 13%; Study 2: fenfluramine .4 mg/kg/day, 58%; placebo, 2%). Median time-to-nth seizure was longer after fenfluramine than after placebo (Study 1: fenfluramine .7 mg/kg/day, 13 weeks; .2 mg/kg/day, 10 weeks; placebo, 7 weeks; Study 2: fenfluramine .4 mg/kg/day, 13 weeks; placebo, 5 weeks; P < .001). Longest duration of convulsive seizure-free days was increased in active groups vs the placebo group (Study 1: fenfluramine .7 and .2 mg/kg/day, 25.0 and 15.0 days; placebo, 9.5 days [P = .0001; P = .0352]; Study 2: fenfluramine .4 mg/kg/day, 22.0 days; placebo, 13.0 days [P = .004]). The most common adverse events included decreased appetite, pyrexia, upper respiratory tract infection, diarrhea, and fatigue. Significance: These data demonstrate that fenfluramine can significantly reduce day-to-day seizure burden in patients with DS, providing prolonged periods of convulsive seizure-free days, which may help reduce the physical and emotional disease toll while improving health-related QOL for patients and caregivers.

Commentary

When treating a patient with an incurable developmental and epileptic encephalopathy (DEE), my immediate focus as a clinician is not seizure freedom. I use a “trees” and “forest” model to outline short term and long-term goals. I target disabling seizure type/s that might contribute to higher SUDEP risk (the tree/s). I aim to reduce the frequency and increase the time between each episode of disabling seizure/s by using an appropriate antiseizure medication (ASM). Additionally, I work with families to minimize ASM side effects and hope that this will eventually improve the quality of life (QOL) for my patient (the forest).

One way to choose a new ASM is to check the reported efficacy of said ASM in clinical trials. Positive results from FDA approved, phase 3, randomized, double blind, placebo-controlled trials (RCTs) are an indicator that said ASM has passed muster. However, the statistics used to prove ASM efficacy frequently report complex terms like median percentage reduction in monthly convulsive seizure frequency (MCSF) among others. A recent trial reporting median percentage reduction in drops of 26.5 points on ASM vs 7.6 points on placebo might not mean much for my patient who has ten generalized tonic clonic seizures per week causing drops. Each of these seizures is a potential SUDEP risk.

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The results of the pivotal trials of fenfluramine (FFA) in Dravet syndrome1,2 and the recent post-hoc analysis of the core group of patients3 not only opens new doors for the patient in my vignette above; but also highlights critical questions to be asked about RCT design.

FFA study 1 reported a 74.9% reduction in the mean MCSF in the group assigned to .7 mg/kg/day of FFA and a concomitant reduction from 20-7 seizures per 28 days to 4-7 seizures per 28 days.3 FFA with Stiripentol-study 2 reported a 54.0% greater reduction in mean MCSF vs placebo. The median (range) longest seizure-free interval was 22 (3.0-105.0) days with FFA and 13 (1.0-40.0) days with placebo (P = .004) in this trial.2 Both studies therefore indicated several seizure free days in the active arm compared to placebo.

If I were the PI for above RCT, it would quickly become obvious to me and the family; which patient was in the active arm in said RCT. Additionally, the risk to the fragile patient of continuing in a placebo arm for up to 20 weeks in such an RCT is huge.4 With the knowledge that patients in the placebo group are at a seven times higher risk of SUDEP,5 we must rethink end points in ASM trials.

**Time to Event (TTE): A New Way of Looking at Outcome in RCTs**

The concept of time to event (TTE) has been described before.4,6 In essence, each patient’s baseline seizure frequency is determined over a specified length of time (usually 2-6 weeks). Once a patient is randomized to a treatment arm and investigational drug is titrated to the maintenance dose, the time it takes the patient to reach this baseline (TTE) is compared between the active arm and placebo arms. TTE could also be designed as the exit point of the randomized portion of the study to allow entry into open label if available. While facilitating reduced exposure to placebo it would allow a more meaningful assessment of ASM efficacy.7

In a recent paper, Sullivan et al3 report the post hoc analysis of the above referenced pivotal FFA trials in Dravet syndrome (study 1 described effect of .7 and .2 mg/kg/day of FFA vs placebo and Study 2 described .4 mg/kg/day of FFA with Stiripentol vs placebo) using TTE analysis. TTE was defined as time required during treatment period to experience the same number of seizures as had been recorded during the 6-week baseline prior to randomization. The number of convulsive seizure free days per 28 days and longest duration of seizure free days per 28 days were also calculated.

**Convulsive Seizure Free Days Compared to Baseline**

FFA afforded 24 and 21 days free of convulsive seizures per 28 days post randomization on treatment at .7 and .2 mg/kg/day respectively (15 days with placebo). Stiripentol plus FFA at .4 mg/kg/day afforded 24 convulsive seizure free days per 28 days of treatment post randomization (20 days on placebo). On an annual basis this would amount to an additional 3-4 months of convulsive seizure free days on FFA .7 mg/kg/day and .2 mg/kg/day respectively and 2 months with Stiripentol plus FFA at .4 mg/kg/day.

**Seizure Freedom**

In study 1; Six patients (3 in each of the FFA arms) had no seizures in 14 weeks. In study 2; one patient had no seizures in 15 weeks.

**What Factors Affect Patient and Family Quality of Life (QOL)?**

In a questionnaire study of DEE patients and their caregivers; Auvin et al found that seizure free days had greater impact on QOL than seizure frequency.8 Cohen et al also sent questionnaires to patient caregivers to assess whether seizure counts as objective measures of seizure severity affected quality of life.9 These authors reported that it was not the absolute seizure frequency but the number of days per month that were minimally disrupted by seizures that positively influenced QOL.

**Should TTE Be a Primary End Point in RCTs?**

Greater thought into trial design, more studies using TTE are needed to answer this question. To understand the evolving regulatory environment and its effects on clinical trial design, the excellent review by Perucca4 is recommended. Novel trial design using TTE has been recommended by the International League Against Epilepsy (ILAE) regulatory Task Force and the ILAE Pediatric Commission in collaboration with the Pediatric Epilepsy Research Consortium.7 This trial design allows individualization of baseline, reduces exposure to placebo or ineffective treatment and allows higher trial recruitment. However, ASMs that have moderate efficacy, slower onset of action, longer titration, might not be ideal candidates for such a design. Additionally, quicker exit from the RCT while in placebo arm after TTE; complicates comparison and eventual assessment over a longer time frame of tolerability and adverse effects of the ASM.

**Conclusion**

In my “trees and forest” strategy of approaching a patient with DEE; using TTE data allows me a clearer understanding of the efficacy of an ASM to treat a disabling seizure (the trees) and might also be an important metric to correlate with the broader goal of improving QOL (the forest).
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