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Opinion

Prevention of Drug Resistant Epilepsy and Developmental Epileptic Encephalopathy: Preventative Vigabatrin Treatment in Tuberous Sclerosis Complex and the Case for Fenfluramine Treatment of Children with Newly Diagnosed Dravet Syndrome

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Abstract

Tuberous sclerosis complex (TSC) is caused by mutations of hamartin (TSC1) or tuberin (TSC2) resulting in disinhibition of the mTOR pathway of cellular proliferation and differentiation and severe neurocognitive impairment, intractable epilepsy and tumors. Epilepsy develops in ~90% folllowed by drug-resistant epilepsy (DRE). Recently, prevention of DRE and developmental encephalopathy was shown to be possible in TSC using early administration of vigabatrin. For the first time, medical treatment successfully prevented epilepsy and reduced neurocognitive and behavioural co-morbidities. The crucial difference between the preventive and standard treatment groups was the timing of treatment initiation, not the type of the intervention. This paradigm can be extended to patients with other genetic or acquired conditions, including Dravet Syndrome (DS), a severe developmental epileptic encephalopathy (DEE) with DRE and high mortality, due to a de novo mutation of the gene SCN1A which codes for the sodium channel protein *a* subunit $Na_v1.1$. Infants usually develop normally until their first seizure, commonly between 2-15 months. This is followed by DRE and developmental regression. Randomized controlled trials (RCTs) of adjunctive fenfluramine treatment in DS reduced

median convulsive seizure frequency by 55.7% over placebo at 0.7 mg/kg/day. 50% of children had 75% seizure frequency reduction, 8% had convulsive seizure freedom versus 0% with placebo, and 18% had only one convulsive seizure versus 0% with placebo. Other pivotal studies showed similar results and efficacy was sustained in for <3 years. Fenfluramine is now a first-line therapy for DS. Given the existence of a remarkably effective treatment fenfluramine for Dravet, preventive therapy presents itself as a natural extension for its application. We hypothesize that not only may seizure outcomes such as time to second seizure and evolution to DRE be positively impacted, but moreover, protective effects on mortality and cognitive outcomes may also be seen.

Keywords
Dravet syndrome; fenfluramine; tuberous sclerosis; drug refractory epilepsy; developmental epileptic encephalopathy; epilepsy prevention; genetic epilepsy; genetic testing

1. Introduction: Epilepsy Prevention and the Tuberous Sclerosis Model

Prevention of drug resistant epilepsy (DRE) and developmental encephalopathy was recently shown to be possible. Tuberous sclerosis complex (TSC), an autosomal dominant disease affecting 1 in 60,000 newborns in the United States, is caused by mutations of genes hamartin (TSC1) or tuberin (TSC2), leading to disinhibition of the mTOR pathway of cellular proliferation and differentiation and multiorgan disease [1-3]. TSC often results in early onset, drug-resistant epilepsy in >90% of patients and subsequent severe intellectual delay. Epilepsy often starts with infantile spasms (IS) for which the first-line therapy is vigabatrin, an inhibitor of GABA aminotransferase that decreases the aberrant mTOR activity in TSC [4]. In a knock-out mouse model of TSC, onset of treatment with vigabatrin before the onset of spontaneous seizures prevented seizures and mTOR pathway activation and reduced mortality.

TSC can be diagnosed prenatally with fetal ultrasound detection of cardiac rhabdomyomata. Screening TSC infants with monthly encephalograms (EEGs) showed that clinical seizures are often preceded by increased EEG excitability indicated by interictal epileptiform activity (EA), allowing identification of infants with high risk of epilepsy. A pilot open label study showed that infants treated with vigabatrin at the time of the first detection of EEG interictal epileptiform discharges, but before the onset of clinical seizures, were more likely to be seizure free at two year follow up than infants who received standard treatment of starting vigabatrin at the time of the first seizure (93% vs 35%), and had lower incidence of drug-resistant epilepsy (7% vs 42%) [5]. Fewer children on vigabatrin had developmental impairments compared to conventional vigabatrin cohort (48% vs 14% mental retardation; mean intelligence quotient [IQ] 68.7 vs 92.3). At 8-9 years follow up 50% in the preventive group never had a seizure vs. 5% in the standard treatment [6]. Median IQ was 94 in the preventive group vs. 46 in the standard treatment group.

Subsequently, the landmark European EPISTOP (NCT02098759) trial evaluated TSC infants without history of seizures [7]. TSC Infants without seizure history were followed with monthly video EEG and received vigabatrin either as conventional antiepileptic treatment started after the first electrographic or clinical seizure or preventively when interictal epileptiform EEG activity was first

detected, before seizures. They were followed until 2 years of age. Preventive treatment with vigabatrin reduced the risk of epilepsy (52% vs 84%, OR 0.21) and of drug-resistant epilepsy (DRE) (28% vs 64%, OR 0.23), and reduced risk of neurodevelopmental delay (25% vs 41%) [7]. The median time to onset of seizures was longer with preventive vigabatrin vs. conventional vigabatrin (614 vs 124 days) [7]. The long term follow up results off vigabatrin treatment in the EPISTOP study are pending.

These findings were not confirmed in a subsequent US multi-center Phase IIb randomized, double-blind, placebo-controlled trial, PREVeNT (Preventing Epilepsy using Vigabatrin in Infants with TSC). Similar to the EPISTOP trial, TSC infants were followed with regular EEGs (q 6 weeks). Those with no history of clinical or electrographic seizures and no epileptiform activity on initial EEG were followed and randomized to receive vigabatrin or placebo when first EEG epileptiform activity appeared or EEG or clinical seizure occurred (n = 56). Subjects randomized to placebo were switched to vigabatrin if they had a clinical or EEG seizure. The primary outcome, Bayley-III cognitive composite scores at 24 months, was not statistically different between the vigabatrin and placebo-treated groups, similar to the EPISTOP study findings. Unlike in EPISTOP, however, there were no significant differences between the groups in overall epilepsy incidence at 24 months (69% vs 73%, vigabatrin vs. placebo) or in drug resistant epilepsy (48% vs. 52%), study secondary outcomes, nor in time to first seizure after randomization, or in secondary developmental outcomes. Incidence of infantile spasms was lower and time to spasms after randomization was longer in the vigabatrin group [8]. The PREVeNT results were not confirmatory of the EPISTOP results, possibly due to enrichment of the treatment group with TSC 2 (67% placebo vs 97% treatment group) and of the placebo group with TSC 1 (11% placebo vs 3% treatment group), variants of unknown significance and no mutation identified subjects (15% placebo vs 0% treatment group). This unequal loading with more significant underlying disease burden in the treatment group may have diminished apparent treatment effect.

A follow up study comparing the efficacy of preventive vigabatrin and rapamycin is underway in Poland. ViRap is an ongoing randomized, placebo-controlled, double-blind clinical trial of the efficacy and safety of rapamycin versus vigabatrin for the prevention of epilepsy and other symptoms in TSC infants (ViRap, EudraCT 2020-003231-19, contact point Katarzyna Kotulska-Jóźwiak). The goal is to enroll 60 TSC infants aged 1-4 months before onset of seizures. The primary epilepsy-related aim is to compare rates of clinical seizure development during blinded phase between the vigabatrin and rapamycin treated groups. The tumor-related primary aim is to compare the risk of new and increasing tumors between vigabatrin and rapamycin treated groups. Secondary outcome measures include severity of epilepsy, neuropsychiatric comorbidities, quality of life and change in TSC-associated tumor size. An open label phase will be available [9].

2. Future Directions

The TSC studies suggest that preventing epilepsy also reduced the risk of the child developing epileptic encephalopathy and intellectual disability. For the first time, medical treatment successfully prevented epilepsy and reduced neurocognitive and behavioural co-morbidities. The crucial difference between the preventive and standard treatment groups was the timing of treatment initiation, not the type of the intervention. This paradigm can be extended to patients

with other genetic or acquired conditions, including Dravet Syndrome (DS), with all its neurobiological, cognitive, psychological and social consequences.

3. Potential Target Condition for Prevention: Dravet Syndrome

Dravet Syndrome is a severe developmental epileptic encephalopathy (DEE) with drug-resistant epilepsy and high mortality. It affects approximately 20,000 children each in the US and in Europe [10, 11]. In >80% it is due to a de novo mutation of the gene SCN1A which codes for the sodium channel protein *α* subunit $Na_v1.1$ Infants usually develop normally until their first seizure, commonly between 2-15 months, that is often a prolonged focal or generalized convulsion in the setting of febrile illness or vaccination [12]. This is followed by further seizures of diverse semiology refractory to treatment, including bilateral tonic clonic seizures, and by developmental regression.

First-line treatments include valproate, clobazam with or without stiripentol, cannabidiol and fenfluramine [13]. Fenfluramine was approved by the FDA and EMA for treatment of seizures associated with DS in 2019 and 2020, respectively. Randomized controlled trials (RCTs) of adjunctive fenfluramine treatment in DS reduced median convulsive seizure frequency by 55.7% over placebo at 0.7 mg/kg/day. 50% of children had 75% seizure frequency reduction, 8% had convulsive seizure freedom during the 14 weeks-long treatment versus 0% with placebo, and further 18% had only one convulsive seizure vs. 0% placebo-treated patients; baseline seizure frequency was ~21 seizures/28 days [14]. Other pivotal studies showed similar results [15, 16]. Efficacy was sustained in OLE studies for up to 3 years [17, 18]. Mortality was reduced 5-fold [19]. Fenfluramine is generally well tolerated. Main side effects include decreased appetite, diarrhoea, fatigue, lethargy, somnolence, and decreased weight [14, 15]. Approximately 7% of patients treated with 0.4 mg/d fenfluramine together with stiripentol as well as other ASMs stopped treatment during a 15 weeks' long RCT [15].

After 14 weeks of treatment, patients in the fenfluramine 0.7 mg/kg per day group had significant improvements from baseline in the BRIEF Behavioral Regulatory Index and Global Executive Composite score [14]. Post hoc analysis of a phase 3 open label extension study showed that in DS patients treated with fenfluramine profound seizure reduction was associated with improved executive functioning [20]. Currently fenfluramine treatment is indicated for DS aged 2 years and older. By that age, seizures in most DS patients have become refractory to treatment, and developmental epileptic encephalopathy has set in [21].

Fenfluramine, which is FDA-approved over the age of 2 years, is accessible via compassionate use in younger ages and appears safe and effective in this age group [22]. Fenfluramine usage below the age of 2 years in Dravet Syndrome was studied in five patients with a mean age of 14.9 months, with a mean treatment dose of 0.57 mg/kg/day and median folow-up of 13 months. Median convulsive seizure frequency decreased by 54%, 3 patients experienced ≥50% seizure frequency reduction, and one was seizure free for at least 6 months. Neuropsychological testing revealing stability or improvement in development from baseline to last follow-up [22]. No patients showed cardiac valvular hyperplasia or pulmonary artery hypertension on echocardiography and none withdrew due to adverse effects [22].

Additionally, observational data support fenfluramine's role in both the acute treatment of status epilepticus, including early infantile epileptic encephalopathy [23, 24] and super-refractory status epilepticus [25], and the prevention of recurrent status epilepticus [26]. In 78 DS patients treated in the Early Access Programme, the number of status epilepticus episodes decreased from 28% of

patients in the 6 months baseline before fenfluramine treatment to 14% during 6 month follow-up on fenfluramine treatment [27]. The treatment was well tolerated and 85% remained on fenfluramine. These data underscore the efficacy, tolerability and potential preventive role of fenfluramine in DS.

We hypothesize that early treatment of DS, after the first seizure, may similarly reduce the risk of refractory epilepsy and of cognitive slowing. Genetic testing is fast approaching standard of care for epilepsy but is not routinely performed after first seizure. However, expedited early genetic testing of children presenting with first time clonic seizure would create an opportunity for preventive treatment. If Dravet patients were diagnosed early, after the first seizure via standard multi-gene epilepsy panel, prevention with the highly effective disease specific treatments, such as fenfluramine, becomes feasible.

A proposed scheme to test this hypothesis would be to compare time to second seizure and risk of development of DRE in fenfluramine and standard of care treated Dravet patients. Secondary outcomes may include, for example, neurodevelopmental testing with the Bayley Scales of Infant Development, 3rd edition (BSID-III) [28] and quality of life measures with the Pediatric Quality of Life Inventory version 4.0 (PedsQL 4.0) [29].

Given the existence of a remarkably effective treatment for Dravet, preventive therapy presents itself as a natural extension for its application. We hypothesize that not only may seizure outcomes such as time to second seizure and evolution to DRE be positively impacted, but moreover, protective effects on mortality and cognitive outcomes may also be seen.

4. Discussion

There is some evidence to suggest that drug resistant epilepsy and developmental epileptic encephalopathy may be prevented with early institution of vigabatrin in infants with tuberous sclerosis. This represents a paradigm shift in epilepsy management from symptomatic treatment to disease modification. The natural consequence of this discovery should be the pursuit of prevention in other specific disease conditions involving DRE and DEE. Dravet syndrome, as a monogenic, refractory, severe epilepsy with ensuing cognitive decline, lends itself well to this challenge, especially as there exists a highly effective treatment, fenfluramine. In this paper, we have presented a proposed study which, if implemented and successful, would both dramatically improve the prognosis of a progressive, severe condition and spur additional efforts in the realm of preventing refractory epilepsy and cognitive decline.

Author Contributions

Dr. Amanda Pong was responsible for research, drafting and editing. Dr. Pavel Klein was responsible for concept development, research and drafting.

Competing Interests

Amanda Pong has no competing interests to report. Pavel Klein has served as a consultant, advisory board member or speaker for Abbott, Angelini, Aquestive, Arvelle Therapeutics, Aucta Pharmaceuticals, Eisai, Dr. Reddy's, Eisai, Jazz Pharmaceuticals, Neurelis, Neurona, SK Life Science, Sunovion, UCB Pharma, UNEEG, UniQure, is a member of the Medical Advisory Board of Stratus and of

the Scientific Advisory Board of OB Pharma, is the CEO of PrevEp, Inc, and has received research support from CURE/Department of Defense and from the NIH/SBIR.

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