Epilepsy Currents
2024, Vol. 24(2) 87-89

DOI: 10.1177/15357597231225097
journals.sagepub.com/home/epi
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Vigabatrin in Epilepsy Related to TSC: Does it PREVeNT AND OR (EPI) STOP Seizures OR… Do We Need Some More STEPS as VI RAP?

Early Treatment With Vigabatrin Does Not Decrease Focal Seizures or Improve Cognition in Tuberous Sclerosis Complex: The PREVeNT Trial

Bebin EM, Peters JM, Porter BE, McPherson TO, O'Kelley S, Sahin M, Taub KS, Rajaraman R, Randle SC, McClintock WM, Koenig MK, Frost MD, Northrup HA, Werner K, Nolan DA, Wong M, Krefting JL, Biasini F, Peri K, Cutter G, Krueger DA; PREVeNT Study Group. *Ann Neurol*. 2023. PMID: 37638552. doi:10.1002/ana.26778

Objective: This study was undertaken to test the hypothesis that early vigabatrin treatment in tuberous sclerosis complex (TSC) infants improves neurocognitive outcome at 24 months of age. Methods: A phase IIb multicenter randomized double-blind placebo-controlled trial was conducted of vigabatrin at first epileptiform electroencephalogram (EEG) versus vigabatrin at seizure onset in infants with TSC. Primary outcome was Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) cognitive assessment score at 24 months. Secondary outcomes were prevalence of drug-resistant epilepsy, additional developmental outcomes, and safety of vigabatrin. Results: Of 84 infants enrolled, 12 were screen failures, 4 went straight to open label vigabatrin, and 12 were not randomized (normal EEG throughout). Fifty-six were randomized to early vigabatrin (n = 29) or placebo (n = 27). Nineteen of 27 in the placebo arm transitioned to open label vigabatrin, with a median delay of 44 days after randomization. Bayley-III cognitive composite scores at 24 months were similar for participants randomized to vigabatrin or placebo. Additionally, no significant differences were found between groups in overall epilepsy incidence and drug-resistant epilepsy at 24 months, time to first seizure after randomization, and secondary developmental outcomes. Incidence of infantile spasms was lower and time to spasms after randomization was later in the vigabatrin group. Adverse events were similar across groups. Interpretation: Preventative treatment with vigabatrin based on EEG epileptiform activity prior to seizure onset does not improve neurocognitive outcome at 24 months in TSC children, nor does it delay onset or lower the incidence of focal seizures and drug-resistant epilepsy at 24 months. Preventative vigabatrin was associated with later time to onset and lower incidence of infantile spasms.

Commentary

In December 2017, epileptogenesis in tuberous sclerosis (TS) was the topic of discussion at the Childrens Hour at the Annual Epilepsy Society meeting. Dr Jozwiak presented the initial data of the EPISTOP trial in TS which enrolled infants less than 4 months of age between March 2014 and October 2018. Patients were divided into 2 groups—preventive treatment (PT) initiated at onset of interictal epileptiform activity (EA) on electroencephalogram (EEG) or conventional treatment (CT) upon identification of electrographic seizures (ES) or clinical seizures (CS). Each group was treated with vigabatrin (VGB) at a dose of 100 mg/kg/d. Subsequent publication indicated that compared to CT: no patients in PT developed spasms at 24 months, PT group had later onset of CS, and had significantly lower frequency of drug-resistant epilepsy (DRE).[1] *The developmental outcomes and incidence of autism at 24 months in the 2 groups were similar in EPISTOP.*

Small sample size, frequent developmental assessments during research visits, earlier institution of therapy for seizures and developmental issues; were thought to be reasons for similar developmental outcomes in the two arms. Notably, the developmental outcomes of the entire cohort were higher than that published in any other retrospective study upto that time.

This publication and several other subsequent publications were practice changing for my TS patients.[2] Most of us in the TS community were aware of a second preventive trial (PREVeNT) in the United States that had commenced 2 years after the EPISTOP trial and enrolled infants less than 6 months of age between December 2016 and March 2020 with the central hypothesis being that PT with VGB started at EA onset

would *improve* developmental outcomes at 24 months and *lower* risk of DRE. Both studies used predictive capability of EEG as a validated biomarker to determine sample sizes needed for the declared primary and secondary outcomes.[3-6]

The title of the PREVeNT paper reads: "Early Treatment With Vigabatrin Does Not Decrease Focal Seizures or Improve Cognition in Tuberous Sclerosis Complex".[7] This triggered an initial shock response of "how is that possible"- but later; triggered a deeper dive into my understanding of epileptogenesis in TS; and factors related to cognitive outcomes.

What Do Results of EPISTOP and PREVeNT Mean for the Practitioner?

1: EPISTOP tested the principle of prevention versus convention—that of proactive versus reactive therapy: In the randomized portion of EPISTOP, infants were *randomly assigned to get PT versus CT* based on EEG results which were unknown to the treating physicians or families. In the open label arm, physicians and families *chose* to enter either preventive or CT. Everyone knew that they were being treated with VGB.

EPISTOP take home message*: Proactive and presymptomatic treatment with VGB is better than reactive/CT in infants with TS. It is important to identify patients with TS as early as possible after birth to educate families about various seizure types, obtain frequent surveillance EEGs, identify seizures, identify, and treat developmental delays earlier*.

2: The PREVeNT trial tested the effect of the agent used proactively (VGB) in a double-blind randomized fashion. Primary outcome was development at 24 months: All patients were randomized to either VGB or placebo at onset of EA. Patients were switched to open label VGB at onset of ES or CS. Many patients in the placebo arm developed ES/CS. The median time to switch to open label VGB in the placebo arm was 44 days after randomization. The proportions of patients in the 2 groups with focal seizures, DRE, or developmental delay were no different at 24 months. Patients treated for interictal EA in the VGB arm had a statistically significant reduction in the incidence and time to onset of infantile spasms. Delayed treatment of spasms (upon clinical presentation) in the placebo arm did not change eventual developmental outcome. This study also reexamined the positive predictive value (0.731) and negative predictive value (0.733) of interictal EA on surveillance EEGs.

PREVeNT take home message*: A delay in treatment of EA (upto 44 days, ie, time from EA to seizures in placebo arm) might not affect ultimate development. Vigabatrin remains drug of choice for treating spasms. There remain a minority of patients who have repeated EA on sequential EEGs but do not develop seizures by 24 months of age*.

The fact that VGB may not be an effective treatment of focal seizures is not new as previously noted in the international TuberOus Sclerosis registry to increase disease Awareness (TOSCA) with data on $>$ 2000 patients.[8]

3: There are factors outside of EA on EEG that may determine eventual seizure and developmental outcomes: Earlier age at seizure onset, combination of focal seizures and epileptic spasms, earlier onset of interictal abnormalities, type of interictal abnormalities (focal/multifocal), genotype (TSC2 variant), lesion burden of tubers, and tuber/brain volume ratio on brain MRI include just some of the factors associated with ultimate seizure and developmental outcomes.[9] Additionally, as seen after the EPISTOP study, we expect several follow-up papers from the PREVeNT cohort that correlate seizure and developmental outcomes after not only 36 months follow-up but also further study the effect of genetic variation, EEG findings, and MRI data on outcomes.

4: Continued efforts at disease prevention and modification in TSC are necessary: STEPS and ViRAP: Further preventive/disease modifying studies that target mechanistic pathways in tuberous sclerosis complex (TSC) are underway (Home | ClinicalTrials.gov accessed December 6, 2023).

The TSC-STEPS: (Sirolimus TSC Epilepsy Prevention Study—NCT05104983) is a phase II study of sirolimus versus placebo with primary outcomes of safety and time to seizure onset—with expected completion in 2026. Another study: ViRAP (Efficacy and Safety of Rapamycin Versus Vigabatrin in the Prevention of Tuberous Sclerosis Complex Symptoms in Infants—NCT 04987463) is a phase II/III study comparing sirolimus versus VGB with the primary outcome of CS occurrence and volume of TSC associated tumors at 730 days with expected completion in March 2026.

Conclusion and Future Direction

1. The PREVeNT paper is another wake-up call that our work is not done. Identifying TSC infants prenatally or as soon as possible after birth to start EEG surveillance and presymptomatic treatment is the new norm.
2. There is good evidence from the above 2 trials as well as data from >9000 exposed patients that VGB is safe.[10]
3. This trial reminds us that the predictive value of the EEG is not absolute.
4. Starting VGB early—though safe and recommended may neither be enough nor the end game.
5. Many of us are familiar and like the Lamberink[11] nomogram (http://epilepsypredictiontools.info) to determine risks of seizure relapse after medication wean- where a quick summation of major risk factors allows personalization of risk data**.** *The next challenge is to Lamberink TSC and implement personalized preventive strategies in TSC treatment.*

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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