An Online Survey of Caregivers of Patients with KCNQ2 Developmental and Epileptic Encephalopathy (KCNQ2-DEE)

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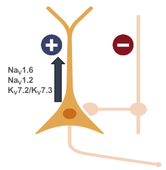
INTRODUCTION

Genetic Mutations and Related Epileptic Encephalopathies

- Caused by single gene de novo mutations in voltage gated ion channels
- Severe phenotypes characterized by frequent refractory seizures, severe developmental delays, autistic features, motor disabilities, and increased SUDEP risk
- Selective ion channel modulators may directly target disease causal gene, with potential to treat epileptogenesis and improve long term outcomes
- Mutations in KCNQ2 are amongst the most common resulting in pediatric epilepsies

Mutation	EIEE	Drug Strategy
Partial GOF $Na_V1.6$	EIEE13	Selective inhibition $Na_V1.6$
Partial GOF $Na_V1.2$	EIEE11	Selective inhibition $Na_V1.2$
Partial LOF $K_V7.2$	EIEE7	Selective opener $K_V7.2/7.3$ tetramers
Partial LOF $K_V7.3$	Unassigned	Selective opener $K_V7.2/7.3$ tetramers
Partial LOF $Na_V1.1$	EIEE6	Selective opener $Na_V1.1$



About KCNQ2-DEE

- Rare, severe neurodevelopmental disorder caused by variants in the *KCNQ2* gene causing significant loss of $K_V7.2$ mediated potassium current
- Presents during first week of life
  - Frequent, daily refractory focal tonic seizures, status epilepticus is common
  - Most often associated with severe developmental delay and motor disabilities
  - Present with language/social impairment, outbursts, repetitive and self injurious behaviors
  - Seizure activity typically decreases with age with some patients becoming seizure free or experiencing a more minor seizure burden by 3 to 5 years of age
  - No approved treatments
- Inherited autosomal dominant truncation mutations cause Self-Limiting (Benign Familial) Neonatal Seizures
- Minority of patients have $K_V7.2$ gain-of-function variants and a different phenotype

METHODS

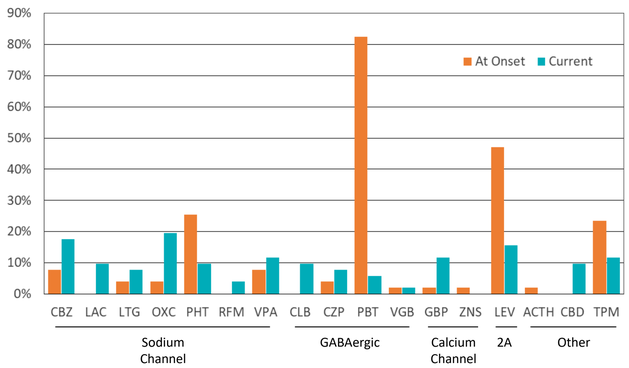
- We performed an on-line survey of caregivers to better understand the symptoms and their experiences with KCNQ2-DEE and perceived gaps in pharmacologic treatment
- The 28-question survey, was conducted by Xenon in collaboration with The KCNQ2 Cure Alliance
- Survey included items such as demographics, comorbidities, seizure onset and frequency, prior and current antiseizure medication (ASM) use, and history of ezogabine use
- Families were recruited by targeted email outreach, social media campaign and an educational webinar
- Survey responses collected over a three-week period in 2019

RESULTS

Preliminary Demographics and Seizure Burden of Survey Patients

Demographics	
Data available	68 complete survey responses received 17 exclusions from preliminary analysis as follows: • 7 from non-IRB approved jurisdictions • 6 with known gain-of-function variants • 4 with atypical phenotype
Locations (n)	USA (32); Canada (5); UK (7); Australia (7)
Patient Age, n (%)	19 (37%) younger than 4 years 32 (63%) 4 years and older
Age of seizure onset after birth (n=51)	Day 0=25%; Day 1=41%; Day 2=24%; Days 3-5=10%
Initial seizure frequency (n=51)	61% had more than 10 seizures per day 35% had between 2-10 seizures per day 2% had 1 seizure per day
Current seizure frequency (n=51)	29% had seizures over the past month 39% had seizures over the past 3 months 47% had seizures over the past 6 months (54% of these were ≥ 4 years)

Current and Prior use of Antiseizure Medications



- Mean number of ASMs used at seizure onset = 2.6
- Mean number of ASMs currently used = 1.8
- Mean number of ASMs used by patients with seizures in past month = 3.4
- 47% of patients were currently taking 2 or more ASMs

Ezogabine Use in KCNQ2-DEE (reported by 7 respondents)*

- Ezogabine treatment was initiated at 6 weeks of age in 2 patients, age 3-10 months in 3 patients and age 1-3 years in 2 patients
- Duration of ezogabine treatment was least 2 years in all 7 patients (5 treated for 2 years and 1 patient each for 3 and 5 years)
- Reasons for discontinuation of treatment were withdrawal of drug from the market in 5 patients; 1 had drug stopped by neurologist due to FDA side effect warning; 1 was still taking ezogabine at time of survey response
- No discontinuations due to adverse effects or lack of efficacy

* Patients used ezogabine and Potiga interchangeably in their responses

Caregiver Narratives: Ezogabine-specific Effects

Did you see any improvements in your child's seizures, behaviour or development while they were taking ezogabine? ALL SEVEN RESPONDENTS ANSWERED "YES"
"Cognitive improvements documented weekly by therapists who did not know the child was on Potiga and [by] parent observation."
"Started at 3 months old, achieved seizure freedom around 5 months old for approximately 6 months when infantile spasms started. With seizure freedom, my child began to respond and get stronger"
"Child was not having seizures, but starting Potiga coincided with improvements in EEG and attention/awareness."
"Seizure control and developmental gains - smiling, eating by mouth."
"We had full seizure control lasting months and only saw seizures with fevers and illness. He was showing gains of function moving his limbs more and was more aware of his surroundings."
"Alertness, better development, EEG improved."
"His seizures immediately decreased in frequency and he stopped having longer seizures about 2 months after he started Potiga. He also seemed more calm and like he felt better while on Potiga."

Caregiver Narratives: Seizure Control and Quality of Life

Which medication or combination of medications or treatments (current or previous) do you consider to be the best for your child's seizures and why?	Which medication or combination of medications or treatments (current or previous) do you consider to be the best for your child's overall quality of life and why?
"Ezogabine + Trileptol. Ezogabine may help with developmental defects."	*"Potiga and Trileptal have been the best at controlling his seizures and Potiga seem to make him feel much better so that was the best at improving his quality of life."*
"Ezogabine with onfi was the best [seizure] control we ever had."	*"We thought Potiga was the best medication for cognitive improvements. Potiga was never taken for seizure control as seizures had stopped and EEG was normal."*
"Potiga was a miracle drug in my opinion for his longer seizures which stopped about 2 months after he started Potiga. We've also noticed good improvements with Trileptal and Depakote which he is currently taking."	*"Ezogabine And onfi. While on the combo he was trying to stand on his own which was amazing!"* *"Our children tolerated Potiga well and it seemed to improve EEG and awareness/alertness."*

CONCLUSIONS

- Survey was informative regarding clinical trial design and improved knowledge of disease course and pharmacologic treatment from a caregivers' perspective
- Survey highlighted significant seizure burden at disease onset, with a significant proportion of patients continuing to experience seizures over the of age 4 years
- Caregivers reported children took ezogabine for both seizure control and other potential benefits (behavioural and developmental), and reported benefits for both
- Ezogabine was reported to be well tolerated by survey respondents
- Study limitations include retrospective reporting with possible memory bias as well as possible data overlap with published cases

Next Steps:

- Phase 3 clinical trial in KCNQ2-DEE expected to initiate by the end of 2020

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