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Intravenous Ganaxolone in Pediatric Super-Refractory Status Epilepticus: Two Case Presentations

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Introduction

- Super-refractory status epilepticus (SRSE) is status epilepticus (SE) that continues or recurs after 24 hours or more of anesthetic therapy, including instances in which SE recurs during the reduction or withdrawal of anesthesia[1]
  - SRSE is a life-threatening neurological emergency and carries a risk for major morbidity and mortality[2,3]
- Because of the lack of high-quality comparative clinical studies of SRSE treatment strategies, therapeutic decisions mainly rely on case series or expert opinion[1,4]
  - The treatment objectives in SRSE include achieving seizure control with potential neuroprotection and avoidance of complications of anesthesia[5]
  - Ongoing or uncontrolled seizures are known to cause internalization of synaptic $GABA_A$ receptors, which may play a role in the development of pharmacoresistance.[5,6] By contrast, extrasynaptic $GABA_A$ receptors have been found to be preserved in SE[6,7] and identified as a potential site for therapeutic intervention

Ganaxolone (GNX)

- The investigational drug ganaxolone is a neuroactive steroid and a positive allosteric modulator of $GABA_A$ receptors that targets a unique binding site[8,9]
  - Ganaxolone acts on both synaptic and extrasynaptic $GABA_A$ receptors to maximize inhibitory signaling as well as maintaining activity when synaptic receptors are downregulated
  - Ganaxolone exhibited broad-spectrum antiseizure activity in preclinical models, including when benzodiazepine resistance developed[8]
- In an open-label, Phase 2 study with IV ganaxolone in refractory SE, ganaxolone had an acceptable safety profile with rapid SE cessation
- Compared to historical use of the neuroactive steroid brexanolone in patients with SRSE in the STATUS trial, the IV ganaxolone dosing regimen achieves neuroactive steroid levels 5-10 times higher[10,11]

Objectives

- To summarize single institutional experience in treating two pediatric patients with SRSE with IV ganaxolone under emergency investigational new drug (EIND) applications

Details of 2 Case Presentations

Patient #1

Clinical History

- A 17-year-old female with a remote history of sporadic seizures in early childhood was transferred to Levine Children's Hospital for inpatient rehabilitation after having recurrent refractory SE during a 7-month outside hospitalization
- Over the course of 7 months at the initial tertiary hospital, she had 6 episodes of SE and required intubation 4 times with medically induced coma for seizure suppression. She was on 5 antiseizure medications (ASMs): cannabidiol, perampanel, phenobarbital, lacosamide, and lorazepam. In addition, pyridoxine, a ketogenic diet, anakinra, and menstrual suppression were instituted when she developed seizure worsening associated with a febrile upper respiratory tract infection.
- A thorough infectious, metabolic, genetic, vascular, and autoimmune evaluation at both institutions was nondiagnostic (**Table 1**)
- While in the inpatient rehabilitation unit, the patient developed a fever of 41.7°C, and a respiratory viral panel was positive for parainfluenza. SE returned, requiring transfer to the ICU for midazolam and pentobarbital infusions.

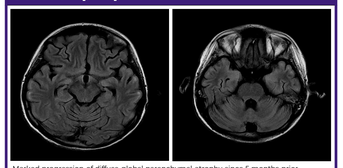
Table 1. PT#1 Diagnostic Studies

Infectious	Autoimmune/inflammatory	Metabolic
• B-cell panel: negative • HLH gene panel: negative • HIV and hepatitis: negative • COVID Ag testing ×3: negative	• CSF 4/2/20: 1 cell, 57 protein, 71 glucose • Autoimmune encephalopathy panel: negative • Pelvic US: negative for teratoma • Oligoclonal band panel: negative • NMO: negative	• Serum carbohydrate deficient transferrin: essential normal, not consistent with CDG • Serum biotinidase level, 13.8 U/L, within normal limits • Homocysteine: low 3.5 • Urine purine and pyrimidine panel: normal • Urine sulfocysteine: normal • Urine mucopolysaccharides screen: with elevated heparan sulfate, 0.33 • Serum carbohydrate deficient transferrin: not consistent with congenital disorders of glycosylation • Acylcarnitine profile: normal • Free and total L-carnitine: plasma level normal • Urine organic acids: normal • Plasma amino acids: essentially normal • CSF metabolic studies: negative
Imaging		
• Normal unenhanced and enhanced MRI of the brain (×5) • Negative MRA of the head		
Genetic		
• Epilepsy panel[a] with 5 VUS: PCDH19, POLG, DOCK7, NRXN1, PLCB1 • c.39-5T>G DOCK7 gene: ✓ father; X mother • c.2298A>G p.Met767Val NRXN1 gene: ✓ mother; X father • c.199A>C p.Ser67Arg PLCB1 gene: ✓ father; X mother • c.3131T>C p.Val1044Ala POLG gene: ✓ father; X mother • All are responsible for autosomal recessive disorders, and a second change was not found	• c.545G>C p.Gly182Ala PCDH19 gene: ✓ mother; X father • Mother asymptomatic; uncertain significance • Whole exome sequencing with mitochondrial genome (TRIO): negative	

Ag, antigen; CDG, congenital disorders of glycosylation; COVID, coronavirus disease; CSF, cerebrospinal fluid; HLH, hemophagocytic lymphohistiocytosis; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; US, ultrasound; VUS, variants of unknown significance. [a]GeneDx, Inc., Gaithersburg, MD.

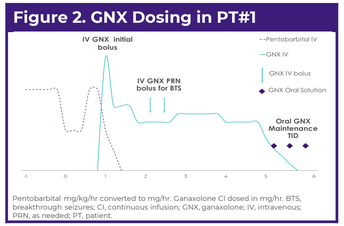
- Video-electroencephalogram (vEEG) monitoring throughout her course demonstrated multifocal seizure onset. She was seizure-free for 2 days after drips were weaned, after which seizures returned, prompting placement of a vagus nerve stimulator and a prolonged 2-week course of IV pentobarbital titrated to EEG burst suppression. Repeat magnetic resonance imaging (MRI) demonstrated progression of diffuse global parenchymal atrophy (**Figure 1**).
- After multiple failed attempts to wean pentobarbital, she was treated under the EIND approval for a trial of IV-to-enteric ganaxolone. Ganaxolone was administered using an IV bolus, followed by infusion over 4 days (with boluses as needed for breakthrough seizures) (**Figure 2**).
  - On day 1, pentobarbital was discontinued; by day 3, clinical and electrographic seizures stopped (**Figure 3A** & **B**)
  - The patient tolerated the protocol well. As pentobarbital was discontinued and ganaxolone treatment initiated, she became more alert and interactive.
  - On day 5, she was transitioned from IV to enteric ganaxolone without recurrent seizures (**Figure 3C**)

Figure 1. MRI During Prolonged Status Epilepticus in PT#1



Marked progression of diffuse global parenchymal atrophy since 5 months prior, predominantly affecting the white matter. Increasing T2 FLAIR hyperintensity in the subcortical and juxta cortical white matter. Signal abnormality is most pronounced in the U fibers of the parietal and temporal lobes.
MRI, magnetic resonance imaging; T2 FLAIR, T2-weighted fluid-attenuated inversion recovery; PT, patient.

Figure 2. GNX Dosing in PT#1



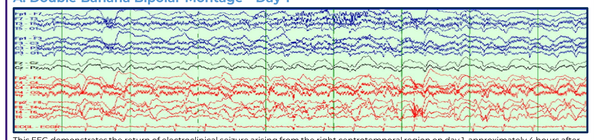
Pentobarbital mg/kg/hr converted to mg/hr. Ganaxolone CI dosed in mg/hr. BTS, breakthrough seizures; CI, continuous infusion; GNX, ganaxolone; IV, intravenous; PRN, as needed; PT, patient.

Patient Disposition & Update

- One month after ganaxolone initiation, the patient was transferred to inpatient rehabilitation service; she was discharged home 1 month later
- She has been weaned off the ketogenic diet, anakinra, and felbamate with minimal breakthrough clinical seizures (only in setting of intercurrent illness or decreasing ASMs)
- More than one year later, the patient's response to ganaxolone and seizure cessation have been sustained. Patient continues to be on ganaxolone and 4 other ASMs (valproic acid, brivaracetam, lorazepam, perampanel).
- Patient still has significant morbidity, with G-tube, trach dependent, and needs assistance with all activities of daily living more than one year after the last SE episode

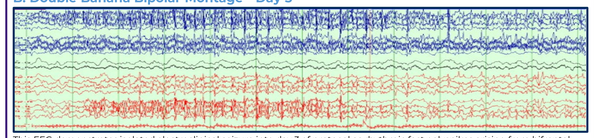
Figure 3. PT#1 vEEGs on Days (A) 1, (B) 3, and (C) 5

A. Double Banana Bipolar Montage—Day 1



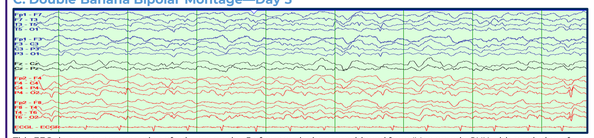
This EEG demonstrates the return of electroclinical seizure arising from the right centrotemporal region on day 1, approximately 4 hours after pentobarbital drip was discontinued and as the study drug began. Double banana bipolar montage: LFF 1 Hz, HFF 70 Hz; sensitivity, 15 μV/mm; time base, 30 mm/s. EEG, electroencephalogram; HFF, high-frequency filter; LFF, low-frequency filter.

B. Double Banana Bipolar Montage—Day 3



This EEG demonstrates isolated electroclinical seizure into day 3 of protocol as rhythmic fast polyspikes arising from bifrontal regions, which spread anteriorly over both hemispheres. Double banana bipolar montage: LFF 1 Hz, HFF 70 Hz; sensitivity, 15 μV/mm; time base, 30 mm/s. EEG, electroencephalogram; HFF, high-frequency filter; LFF, low-frequency filter.

C. Double Banana Bipolar Montage—Day 5



This EEG demonstrates cessation of seizures on day 5 of protocol when transitioned from IV to enteric GNX with resolution of seizures, improvement in interictal background, and interictal right occipital epileptiform discharges. Double banana bipolar montage: LFF 1 Hz, HFF 70 Hz; sensitivity, 15 μV/mm; time base, 30 mm/s. EEG, electroencephalogram; HFF, high-frequency filter; LFF, low-frequency filter.

Patient #2

Clinical History

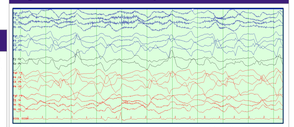
- A 7-year-old, previously healthy female presented with encephalopathy and fever and developed SRSE concordant with fever-induced refractory epilepsy syndrome (FIRES)
  - On admission, patient presented in the ED with fever, abdominal pain, and encephalopathy
  - LP: WBC 4, Protein 49
  - Patient was admitted to PICU and placed on vEEG (**Figure 4**)
  - A thorough infectious, metabolic, genetic, vascular, and autoimmune evaluation was nondiagnostic (**Table 2**)

Table 2. PT#2 Diagnostic Studies

Infectious	Autoimmune/Inflammatory
• CSF and blood cultures: negative • HSV PCR CSF: negative • CSF and serum arbovirus • CSF EBV, VZV PCR: negative • CSF RPR and VDRL (CSF) negative • Bartonella serology and PCR: Negative • Mycoplasma: Negative • COVID Ag and Ab testing negative	• CSF 12/30/20: 4 WBC, 49 protein, 71 glucose • Autoimmune encephalopathy panel: negative (serum and CSF) • Pelvic US: negative for teratoma • CSF oligoclonal band panel: negative • NMO: negative • ANA, dsDNA, ACE • Lysozyme • CSF cytokines showed no elevation and serum cytokines showed elevation of IL-6
Metabolic	**Imaging & Genetic**
• Vit B12, TSH/FT4, Folate, Copper, ceruloplasmin: normal • Acylcarnitine profile: normal • Urine organic acids: normal • Plasma amino acids: normal • Heavy metals: normal • Porphyria: negative • Very long chain fatty acids : Normal	• MRI Brain: abnormal (*) • Negative MRA/MRV of the head and neck • Epilepsy panel negative • Whole exome sequencing (TRIO): negative

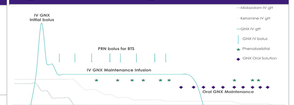
Ab, antibody; ACE, angiotensin-converting enzyme; Ag, antigen; ANA, anti-nuclear antibody; COVID, coronavirus disease; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HSV, herpes simplex virus; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; NMO, neuromyelitis optica; RPR, rapid plasma reagin; US, ultrasound; VZV, varicella zoster virus.

Figure 4. PT#2 EEG Upon Admission



This EEG demonstrates diffuse background slowing with epileptiform discharges in the biposterior head regions. Double banana bipolar montage: LFF 1 Hz, HFF 70 Hz; sensitivity, 15 μV/mm; time base, 30 mm/s. EEG, electroencephalogram; HFF, high-frequency filter; LFF, low-frequency filter; PT, patient.

Figure 5. GNX Dosing in PT#2

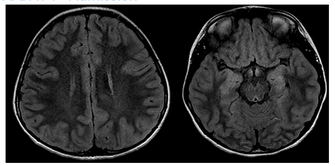


Midazolam mg/kg/hr converted to mg/hr. Ketamine IV dosed in mg/kg/hr. Ganaxolone IV dosed in mg/hr. BTS, breakthrough seizures; CI, continuous infusion; GNX, ganaxolone; IV, intravenous; PRN, as needed.

- SE persisted despite multiple ASMs (levetiracetam, valproic acid, perampanel, lacosamide, zonisamide), acetazolamide, ketogenic diet, IV anesthetics midazolam and pentobarbital, and subsequent ketamine infusions
- Immunomodulatory therapies with IV methylprednisolone and IVIG were initiated concomitantly
- After multiple ASMs, failed attempts to wean pentobarbital, and ketamine and midazolam infusions, she was treated under the EIND approval for a trial of IV-to-enteric ganaxolone
- Ganaxolone was administered on hospital day 17 using an IV bolus, followed by infusion over 6 days (with boluses as needed for breakthrough seizures (**Figure 6**)
  - Midazolam was discontinued on day 2 of GNX IV protocol; ketamine was discontinued by day 8 with the assistance of phenobarbital loads and maintenance
  - Anakinra was initiated on day 2 of GNX IV protocol (hospital day 19)
- By 4 weeks after admission, patient was more responsive; at 6 weeks, she was transferred from ICU to the floor alert and was responsive with some vocalizations
- Upon admission, MRI demonstrated FLAIR changes in bilateral temporal lobes concerning for prior seizures (**Figure 6A**). Subsequent neuroimaging during the acute hospital stay demonstrated evolving changes due to ongoing seizure activity (**Figure 6B** & **C**).
- Her acute hospital course was further complicated by bruxism, movement disorder, vagus nerve stimulator infection, neuropathic pain, and sporadic breakthrough clinical seizures

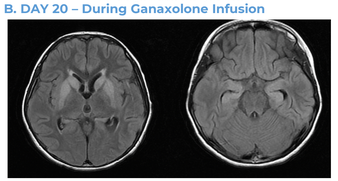
Figure 6A, B, C. PT#2 MRIs

A. DAY 1 – Admission



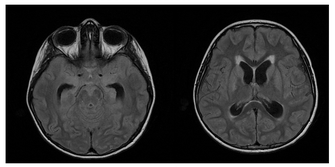
Flair changes in bilateral temporal lobes

B. DAY 20 – During Ganaxolone Infusion



Continued flair changes/hyperintensities of gray matter- temporal lobe and basal ganglia

C. 5.5 Weeks Post Admission



Atrophy

Patient Disposition and Update

- At discharge, patient remained on numerous ASMs, including levetiracetam, lacosamide, perampanel, phenobarbital, lorazepam, ganaxolone, anakinra, and tetrabenazine
- By 6 months from discharge, she was weaned off perampanel, anakinra, and tetrabenazine. She continues on levetiracetam, lacosamide, phenobarbital, lorazepam, and ganaxolone in addition to iron and pregabalin and attends school with modifications.

Conclusions

- Ganaxolone was effective in terminating SRSE in two pediatric patients, permitting IV anesthetics to be weaned. Seizure control was maintained after transitioning to adjunctive oral ganaxolone
- Further investigation of ganaxolone as a treatment for SRSE is warranted

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Atrium Health Levine Children's

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