Systematic review of mTOR inhibitor treatment, biomarkers and prophylaxis for tuberous sclerosis complex-associated seizures

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Introduction

- Mutations in *Tsc*1 and *Tsc*2 genes result in hyperactivation of mammalian target of rapamycin complex 1 (mTORC1) pathway, linked to epileptogenesis in tuberous sclerosis complex (TSC).
- Everolimus: mTOR inhibitor, FDA-approved for TSC-associated seizures in patients older than 2 years in 2018

Outline

1. Effectiveness of mTOR inhibitors in TSC-associated seizures [PubMed]
   - ➢ Patient stratification for treatment with mTOR inhibitors
2. Predictive, diagnostic and prognostic biomarkers of epilepsy in TSC [PubMed]
3. Seizure prophylaxis with mTOR inhibitors

Effectiveness of mTOR inhibitors in TSC-associated seizures

Everolimus:

Long-term safety: 94% of 48 TSC patients with refractory epilepsy maintained improved seizure control over 4 years; adverse effects decreased over time

White matter modification: pharmacologically modify the genetic defect of TSC (incl. normal-appearing white matter), 28 pts, 12-18 months; longer exposure & younger age (< 10) -> greater effect

Dosing and response: 5-7 ng/mL initially and 5-15 ng/mL if inadequate clinical response; more difficult for pts with higher baseline seizure frequency to respond

Patient stratification for treatment with mTOR inhibitors:

Age: more effective in <18, greatest in <6; longer exposure & early initiation -> long-term efficacy; critical time windows; more calcification in cortical tubers with age -> resistance

Baseline seizure frequency: higher baseline seizure frequency -> more difficulty becoming a responder to adjunctive **everolimus**

Calcification in cerebral parenchyma: cerebral parenchymal calcification in epileptic discharge sites -> more likely resistant to appropriate AEDs and adjunctive **rapamycin**

Refractory seizures: refractory TSC-associated epilepsy -> higher diffusivity increase, i.e., greater response to everolimus

Author Year	Medication	Condition	No. of Pts	Results
Small-scale clinical trials				
Krueger et al. 2010	Everolimus	TSC-associated SEGA	16	• Improved seizure control over 34.2 months (median) • No. of pts with no seizures reported since last visit (or more than 6 months since last seizure) increased from 38.5% at baseline to 65.2% at 24 months
Krueger et al. 2013	Everolimus	TSC-associated refractory epilepsy	20	• Well-tolerated with only mild and moderate adverse effects • Duration-dependent mechanism
Cardamone et al. 2014	Everolimus Sirolimus	TSC-associated refractory epilepsy	7	• 1, 4 and 2 patient(s) had >90%, 50%-90% and <50% reduction in seizure frequency over 18 months (median) • Patient receiving everolimus had a 25-50% seizure frequency reduction
Overwater et al. 2016	Sirolimus (adjunctive)	TSC-associated refractory epilepsy	23	• Despite seizure frequency reduction, significant benefits could not be proven • Study lacked the precision to exclude sirolimus benefits
EXIST-3 clinical trial				
French et al. 2016	Everolimus (adjunctive, low/high exposure)	TSC-associated refractory epilepsy	366	• Greater response rate, median reduction in seizure frequency and number of seizure-free days • Duration-response and dose-response • 2019 Mizuguchi et al.: Japanese study confirmed results • 2018 Curatolo et al.: patients <6 greatest benefit among paediatric population (<18)

Predictive, diagnostic & prognostic biomarkers of epilepsy in TSC

Predictive biomarkers

Electroencephalogram (EEG): epileptiform discharges in video EEG monitoring; serial routine EEGs; presence of interictal epileptiform dischargers; increased neural connectivity in TSC infants

Genetics: no mutation or mosaic mutation -> reduced risks of seizures; *Tsc*1 mutation was associated with a milder phenotype than *Tsc*2; missense mutations in the central region of *Tsc*2 (exons 23-33) -> reduced incidence of infantile spasms; increased expression of genes for cell adhesion (VCAM1, integrins and CD44) and inflammatory responses (complement factors, serpinA3, CCL2 and several cytokines); decreased expression of genes for synaptic transmission (glial glutamate transporter GLT-1 and voltage-gated channel); different gene expression in peri-tuberal cortex from control cortex

miRNAs: 4 candidate biomarker miRNAs for seizure development in TSC: miR 199a-5p, miR 21-5p, miR 29b-3q and miR 324-5p

Inflammation: increased CSF nerve growth factor; blood brain barrier dysfunction and perivascular inflammation; prenatal key inflammatory pathway activation in developing brain lesions in TSC

Other biomarkers identified by EPISTO: brain lesions in prenatal MRI; 3 SNPs were associated with epilepsy onset among 58 SNPs implicated in epilepsy GWAS: rs1046276 (T/C), rs3743123 (G/A) and rs1801133 (G/A); serum proteins showed small differences between TSC patients w/ and w/o seizures; oxidative stress

Diagnostic biomarkers

Interictal scalp fast ripples observed to occur in children with TSC-associated epilepsy exclusively, absent in controls without epilepsy

α-[^{11}C]-methyl-L-tryptophan (AMT) - only molecular probe in PET capable of localising epileptic foci in the interictal state; sensitivity ~ 70% & specificity ~ 100%

Prognostic biomarkers

Cyst-like tubers – aggressive seizures; predominance of poorly organized tubers; increased tuber count – strongly associated with infantile spasms; white matter mean diffusivity; cerebellar lesions – more severe clinical and neuroradiological phenotype

Seizure prophylaxis with mTOR inhibitors

Critical time windows for mTOR inhibition

- mTOR inhibitors to modify neural migration and synaptogenesis caused by mTOR hyperactivation
- In humans, synaptogenesis lasts until around 3.5 years old
- Dysfunction relapse after mTOR inhibitor withdrawal was shown by animal studies – seizures occurred a few weeks after stopping treatment

Clinical evidence of seizure prophylaxis in TSC

- Effectiveness of prophylaxis for epilepsy in TSC established for vigabatrin: the risk of developing clinical seizures by school age was 50% w/ vigabatrin prophylaxis (vs 96% w/o prophylaxis)
- Everolimus on seizure control in TSC patients before seizure onset was mentioned by a few anecdotal reports (Goyer et al. 2015; Chang et al. 2017; Hoshal et al. 2015)

Conclusion

- Clinical trials have proven the efficacy and safety of mTOR inhibitors, principally everolimus, for seizure control in TSC.
- Effects of everolimus were shown to be mediated by duration- and dose-dependent mechanisms and more pronounced in patients with young age, low baseline seizure frequency, low level of cerebral parenchymal calcification and refractory seizures.
- Predictive biomarkers, incl. EEGs, genetics, miRNAs and immuno-inflammation changes, could identify high-risk patients and prompt initiation of prophylaxis.
- Diagnostic and prognostic biomarkers could confirm diagnosis and monitor response to treatment and disease progression.
- Animal studies have shown that mTOR inhibitors could modify neural migration and synaptogenesis caused by mTOR hyperactivation, if given within critical time windows.
- Widespread effects of mTOR blockade are unknown and case reports of everolimus prophylaxis in TSC patients were inconclusive.
- Future clinical trials needed to study everolimus prophylaxis in young, asymptomatic patients and in combination with other AEDs.

References

Available at https://tinyurl.com/mTORinhibitor

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