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

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Table 1. Effectiveness of mTOR inhibitors in tuberous sclerosis complex-associated seizures

Author, year	Medication	Condition	Patients, n	Results
Krueger *et al*, 2010	Everolimus	TSC-associated SEGA	16	Improved seizure control over 34.2 months. Patients with no seizures since last visit increased from 38.5% to 65.2%.
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 and Sirolimus	TSC-associated refractory epilepsy	7	One, four and two patients had >90%, 50%–90% and <50% reduction in seizure frequency over 18 months (median), respectively.
Overwater *et al*, 2016	Sirolimus (adjunctive)	TSC-associated refractory epilepsy	23 (children)	Despite seizure frequency reduction, significant benefits could not be proven. Lacked precision to exclude sirolimus benefits.
French *et al*, 2016	Everolimus (adjunctive, low/high exposure)	TSC-associated refractory epilepsy	366 (aged 2–65 years old)	Greater response rate, median reduction in seizure frequency and number of seizure-free days. Duration response and dose response.

SEGA = subependymal giant-cell astrocytoma; TSC = tuberous sclerosis complex.

Introduction

Tuberous sclerosis complex (TSC) is a major genetic cause of epilepsy, characterised by benign multi-system tumours (eg brain, kidney and skin) and neurological disorders (eg epilepsy, autism and learning impairment). Mutations in *TSC1* and *TSC2* genes result in hyperactivation of mammalian target of rapamycin complex-1 (mTORC1) pathway, linked to epileptogenesis in TSC.

Materials and methods

To examine research findings on anti-epileptogenic effects of mTOR inhibitors and predictive biomarkers in TSC, PubMed searches with keywords '(((mTOR) OR (mTOR inhibitor) OR (everolimus) OR (sirolimus)) AND ((seizure) OR (epilepsy))) AND ((tuberous sclerosis) OR (TSC))' and keywords '((tuberous sclerosis) AND (epilepsy)) AND (biomarker)' were performed.

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Results and discussion

For results of effectiveness of mTOR inhibitors in tuberous sclerosis complex-associated seizures see Table 1.

Everolimus

Long-term safety: 94% of 48 TSC patients with refractory epilepsy maintained improved seizure control over 4 years; safe and tolerable. Adverse effects decreased over time.[1,2]

White matter modification: Everolimus pharmacologically modifies the genetic defect of TSC (including normal-appearing white matter) in 28 patients for 12–18 months. Longer exposure and younger age (<10 years old) are associated with greater effects.[3,4]

Dosing and response: 5–7 ng/mL initially and 5–15 ng/mL if inadequate clinical response. It is more difficult for patients with higher baseline seizure frequency to respond.[5,6]

Patient stratification for treatment with mTOR inhibitors

Age: mTOR inhibitors are more effective in those <18 years old, with greatest effects observed in those <6 years old. Longer

exposure and early initiation are associated with long-term efficacy, especially when given in critical time windows. More calcification in cortical tubers with age is associated with resistance to treatment.[7–10]

Baseline seizure frequency: Higher baseline seizure frequency is associated with more difficulty becoming a responder to adjunctive everolimus.

Calcification in cerebral parenchyma: Patients with cerebral parenchymal calcification in epileptic discharge sites are more likely to be resistant to appropriate antiepileptic drugs (AEDs) and adjunctive rapamycin.

Refractory seizures: Higher diffusivity increase is seen in refractory TSC-associated epilepsy, ie greater response to everolimus.

Predictive, diagnostic and prognostic biomarkers of epilepsy in TSC

Predictive biomarkers: Electroencephalography (EEG), genetics, miRNAs and inflammation.

Diagnostic biomarkers: Interictal scalp fast ripples (FR); alpha-[^{11}C]-methyl-L-tryptophan (AMT) as the only molecular probe in positron emission tomography capable of localising epileptic foci in the interictal state.

Prognostic biomarkers: Cyst-like tubers, predominance of poorly organised tubers, increased tuber count, white matter mean diffusivity and cerebellar lesions.

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 (including 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. Widespread effects of mTOR blockade are unknown and case reports of everolimus prophylaxis in TSC patients were inconclusive. Future clinical trials are needed to study everolimus prophylaxis in young, asymptomatic patients and in combination with other AEDs. ■

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