Targeted therapies in genetic epilepsies

Tuberous Sclerosis Complex

Romina Moavero

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Neurology Unit, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
Tuberous Sclerosis Complex (TSC)

- Incidence: 1 in 6000
- Autosomal dominant mode of inheritance
- Often associated with mutations in 1 of 2 genes
  - TSC1 (chromosome 9)
  - TSC2 (chromosome 16)
- Brain lesions are the major cause of mortality and morbidity in children with TSC

TSC as a multisystem disease

**Brain**
- Cortical tubers
- SENs
- SEGA
- Seizures

**Kidney**
- Angiomyolipoma
- Cysts

**Skin**
- Hypomelanotic macules
- Shagreen patches
- Ungueal fibromas

**Eye**
- Hamartoma

**Skin**
- Facial angiofibromas

**Lungs**
- LAM
- Microcystic nodular hyperplasia

**Heart**
- Cardiac rhabdomyomas

Curatolo et al., Lancet Neurol 2015
A mouse model of TSC1 reveals sex-dependent lethality from liver hemangiomas, and up-regulation of p70S6 kinase activity in Tsc1 null cells

David J. Kwiatkowski*, Hongbing Zhang, Jennifer L. Bandura, Kristina M. Heiberger, Michael Glogauer, Nisreen el-Hashemite and Hiroaki Onda

Genetics Laboratory, Hematology Division, Brigham and Women’s Hospital, Harvard Medical School, 221 Longwood Avenue, LM-302, Boston, MA 02115, USA

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**mTOR dysregulation and TSC related lesions**

- Cell growth
  - SEGAs
- Angiogenesis
  - Renal angio-myolipomas
- Glucose uptake metabolism
  - Neuronal dysfunction
- Cell orientation and migration
  - Tubers
  - WM dysplasia
  - Seizures

**Everolimus**

**mTOR Overactivity and TSC Neurologic Phenotypes**

- **mTOR activation**
  - Abnormal neuronal morphology with enlargement of somas and dendritic spines
  - Disruption of GABAergic interneuron development
  - Abnormal astrocyte glutamate uptake
  - Anomalies in number and shape of synapses
  - Impaired protein synthesis and LTP

- **Imbalance in excitation/inhibition**
  - Abnormal white matter connectivity

- **Susceptibility to epilepsy**
- **Susceptibility to autism**
- **Susceptibility to cognitive impairment**

Dysregulated mTOR Signaling in Brain

- Abnormal neuronal morphology
- Increased growth and proliferation
- Reduced autophagy and apoptosis
- Abnormal migration and orientation
- Ion channels/neurotransmitter receptors
- Synaptic plasticity

- Disruption in dendritic spines
- Dysplastic neurons
- Giant cells
- Abnormally shaped astrocytes
- Loss of 6-layered cortical structure
- Abnormal dendritic arborization
- Abnormal cortical lamination
- ↓ GABAergic inhibition
- ↑ Glutamatergic excitation

- Intellectual disability
- Autism
- Cortical tubers
- SEPs
- Epilepsy
- Cortical tubers
- SEGAs
- Epilepsy
- Cortical tubers
- White-matter abnormalities
- Epilepsy
- Neurocognitive impairment
- Cortical tubers
- Epilepsy
- Autism
- Neurocognitive impairment
- Social dysfunction

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Curatolo, Ped Neurol 2015
The identification of a specific molecular pathway underlying epilepsy in TSC paved the way for clinical trials evaluating the efficacy and safety of mTOR inhibitors in TSC-related epilepsy.

Everolimus is a selective inhibitor of the mTOR complex, initially developed as an antitumoral agent.

It can exert its antiepileptic efficacy by acting on voltage- and ligand-gated ion channel, neurotransmitter receptors, and signaling pathways, thus modulating neuronal excitability.

Available treatment options for epilepsy in TSC only provide a symptomatic treatment for seizures, while mTOR inhibitors act on the pathogenesis, thus having the potential of acting as a disease-modifying systemic therapy.
Rapamycin Prevents Epilepsy in a Mouse Model of Tuberous Sclerosis Complex

Ling-Hui Zeng, MD, PhD,1,2 Lin Xu, PhD,1,2 David H. Gutmann, MD, PhD,1 and Michael Wong, MD, PhD1,2

Ann Neurol 2008;63:444–453

**EARLY TREATMENT**
- Rapamycin at P14
- Prevention of seizures and premature death

**LATE TREATMENT**
- Rapamycin at 6 weeks
- Suppression of seizures and prolonged survival

**TSC1GFAPCKO mice**
Epilepsy: preclinical data

- mTOR pathway is involved in epileptogenesis\(^1\)
- mTOR-i can prevent or treat epilepsy in animal models\(^1\)\(^-\)\(^4\)
- Antiepileptogenic potential?\(^1\)
- Preliminary data suggest continuous treatment is necessary to maintain efficacy\(^1\)\(^,\)\(^5\)
- Animal models showed mTOR-i can also benefit cognitive and behavioral manifestations associated with epilepsy\(^6\)

<table>
<thead>
<tr>
<th>Model</th>
<th>Timing</th>
<th>Neuropathological effects</th>
<th>Effects on</th>
<th>Persistent efficacy after withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cell size/number</td>
<td>Megalencephaly</td>
<td>Other</td>
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<tr>
<td>Tsc1GFAPCKO mice</td>
<td>P14 pre-epilepsy</td>
<td>Yes</td>
<td>Yes</td>
<td>Neuronal dispersion, Git1 expression</td>
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<td></td>
<td>P42 postepilepsy</td>
<td>Yes</td>
<td>Yes</td>
<td>Neuronal dispersion</td>
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<tr>
<td>Tsc2Δc mice</td>
<td>Adult mice</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Tsc1Emx-Cre CKO mice</td>
<td>P13-P40</td>
<td>Yes</td>
<td>Yes</td>
<td>Increased cortical myelination</td>
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<tr>
<td>Tsc1Nes-Cre+ mice</td>
<td>Pregnant dams</td>
<td>No</td>
<td>No</td>
<td>increase in layer IV-V cell density</td>
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<tr>
<td></td>
<td>Prenatal and postnatal</td>
<td>No</td>
<td>No</td>
<td>increased neuronal cell density in cerebral cortex</td>
</tr>
<tr>
<td>Tsc1+ and Tsc2Δc mice</td>
<td>Adult NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms of action

**Reduction of neuronal excitability**
- Prolonged opening of Ca and K channels
- Increased expression Kv1.1 in cortical and hippocampal neurons
- Reduced expression AMPA receptor – modulation of Glu neurotransmission

**Other mechanisms**
- Neuroprotection
- Modulation of synaptic plasticity
- Regulation of neuronal death
- Regulation of neurogenesis
- Long-term effects on metabolism and protein synthesis

Chronic treatment leads to changes in synaptic membrane with reduced excitability and increase of GABA mediated synaptic activity (*in vitro, cortex slices*)

Terashima et al., 1998; Raab-Graham et al., 2006; Wang et al., 2006; Ruan et al., 2008
**Epilepsy and mTOR-inh: Preliminary data**

**EXIST-1**

**Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus (n=24)</th>
<th>Placebo (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Week 24</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Frequency, median (range)</strong></td>
<td>5.85 (1.0, 42.6)</td>
<td>3.99 (0.0, 31.6)</td>
</tr>
<tr>
<td><strong>Change from baseline, median (95% CI)</strong></td>
<td>$-2.92 (-4.00, -1.00)$</td>
<td>$-4.06 (-10.89, 5.78)$</td>
</tr>
<tr>
<td><strong>P-value for treatment effect</strong></td>
<td><strong>0.2988</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **16/28 epilepsy**
  - 9/16 $\rightarrow$ sz frequency reduction
  - 6/16 no changes
  - 1/16 increase

$(p=0.02)$
Rapamycin Reduced Tuberous Sclerosis

Jennifer Muncy, BA, Ian J. Lauder, MB, ChB, MRCPCH, and John J. Aicardi, MD

In a patient with tuberous sclerosis complex (TSC), there was a decrease in the number or size of her cortical tubers. Throughout the treatment course, the patient received topiramate (6.5 mg/kg/d) and oxcarbazepine (35 mg/kg/d). Our success with rapamycin in this young girl with tuberous sclerosis complex in reducing her seizures suggests that rapamycin may be a beneficial adjunctive therapy for seizure control in tuberous sclerosis complex. Additionally,

Effective everolimus treatment of infantile spasms in a patient with tuberous sclerosis complex

Marta Perek-Bעבוד, MD, PhD, MS, and Katarzyna Kowalczuk, MD

Effective everolimus treatment of infantile spasms in a patient with tuberous sclerosis complex. Improvement. Moreover, after 6 weeks of everolimus treatment the patient stopped to have epileptic seizures and is still seizure free. As no anticonvulsants modifications were done contemporarily, it is likely that everolimus either potentiated the antiepileptic effect of the drugs taken by the patient or exerted an antiepileptic effect per se. In the study of Zeng et al.
Preliminary clinical results of the use of mTORi in TSC related epilepsy

**mTOR dysregulation and tuberous sclerosis-related epilepsy**
Paolo Curatolo\textsuperscript{a}, Romina Moavero \textsuperscript{a,b}, Jackelien van Scheppingen\textsuperscript{c} and Eleonora Aronica\textsuperscript{c,d}

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type</th>
<th>No. of pts.</th>
<th>Age range</th>
<th>mTOR Inhibitor</th>
<th>Responders</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiegand et al. [237]</td>
<td>Prospective, single-center, open label</td>
<td>7</td>
<td>2–12 years</td>
<td>Everolimus</td>
<td>4 (57%) with 25–100% seizure (sz) reduction</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Cardamone et al. [238]</td>
<td>Prospective, single-center, open label</td>
<td>7</td>
<td>3–17 years</td>
<td>Sirolimus</td>
<td>5 (71%): 4 pts. with 50–90% reduction, 1 pt. &gt;90% reduction</td>
<td>6–36 months</td>
</tr>
<tr>
<td>Krueger et al. [236]*</td>
<td>Prospective, multicenter, open-label, phase I/II clinical trial</td>
<td>18</td>
<td>2–21.3 years</td>
<td>Everolimus</td>
<td>13 (72%) with ≥50% sz frequency reduction</td>
<td>48 months</td>
</tr>
<tr>
<td>Overwater et al. [240]</td>
<td>Randomized controlled trial</td>
<td>23</td>
<td>1.8–10.9 years</td>
<td>Sirolimus</td>
<td>75% with ≥50% sz frequency reduction</td>
<td>6 months</td>
</tr>
<tr>
<td>Samueli et al. [239]</td>
<td>Open label, single center</td>
<td>15</td>
<td>1–18 years</td>
<td>Everolimus</td>
<td>80% (12/15) of the patients were responders, 58% of them (7/12) were seizure free</td>
<td>6 months</td>
</tr>
</tbody>
</table>

70 1-21.3 80% 6-48 m
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Jacqueline A French, John A Lawson, Zuhal Yapici, Hiroko Ikeda, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J de Vries, Dennis J Dlugos, Noah Berkowitz, Maurizio Voi, Severine Peyrard, Diana Pelov, David N Franz

- Three-arm, prospective, randomised, multicentre, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of two dosing regimens of adjunctive everolimus compared with placebo

- Included TSC patients aged 2–65 years, with 16 or more seizures during the 8-week baseline phase

- At the end of the baseline phase, eligible patients entered the core phase and were randomly assigned (1:1:1) to receive:
  - Placebo
  - Everolimus titrated to a target trough concentration of 3–7 ng/mL (low-exposure everolimus)
  - Everolimus titrated to a target Cmin of 9–15 ng/mL (high-exposure everolimus)
345 patients. Core phase: 6 weeks titration+12 weeks maintenance for each patient.

*Patients enroll in the extension phase as they complete the core. Upon completion of the core phase, data will be analyzed, and if positive, the extension phase will continue until 48 weeks after last patient completes the core phase.

EXIST-3: a Phase 3 Trial for Everolimus in TSC-Associated Epilepsy

**Seizure Count (Diaries)**

<table>
<thead>
<tr>
<th>Screening (eligibility)</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>Baseline phase (8 weeks)</td>
</tr>
<tr>
<td></td>
<td>Core phase (6 weeks titration)</td>
</tr>
<tr>
<td>V2</td>
<td>(12 weeks maintenance)</td>
</tr>
<tr>
<td>V11</td>
<td>Extension phase (48 weeks)*</td>
</tr>
</tbody>
</table>

Stable Dose of AEDs

- AEDs + everolimus 3-7 ng/ml
- AEDs + everolimus 9-15 ng/mL
- AEDs + placebo
- AEDs + everolimus 3-15 ng/mL

Randomization stratified by age subgroup:
1. 1 to <6 years
2. 6 to <12 years
3. 12 to <18 years
4. ≥18 years
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

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• Overall, 366 patients enrolled
  • EVE low exposure (n=117)
  • EVE high exposure (n=130)
  • Placebo (n=119).

• Median age 10.1 years (range 2.2–56.3) with 104 patients (28%) younger than 6 years and 67 (18%) patients aged 18 years or older
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Jacqueline A French, John A Lawson, Zuhal Yapici, Hiroko Ikeda, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J de Vries, Dennis J Dlugos, Noah Berkowitz, Maurizio Voi, Severine Peyrard, Diana Pelov, David N Franz

- 346 (95%) patients completed the core phase.
- Discontinuation in 5 (4%) patients in the placebo group, 7 (6%) in the low-exposure group, and 8 (6%) in the high-exposure everolimus. The most common reason for treatment discontinuation was adverse events in all treatment groups.
- The median seizure frequency per week at baseline was 10.5 (range 1.3–231.7) in the placebo group, 8.6 (1.4–192.9) in the low-exposure group, and 9.5 (0.3–218.4) in the high-exposure group.
Everolimus was associated with a significantly greater response rate than placebo:

- 33/117 patients in the low-exposure group (response rate 28.2%)
- 52/130 patients in the high-exposure group (response rate 40%)
- 18/119 patients in the placebo group (response rate 15.1%)
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study


• Significantly higher median seizure frequency reduction:
  • Low exposure group: **29.3%**
  • High exposure group **39.6%**
  • Placebo **14.9%**

• The odds of achieving a 50% or greater reduction in seizure frequency was 2.2-times higher for low-exposure everolimus than placebo and 3.9-times higher for high-exposure everolimus than for placebo
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Jacqueline A French, John A Lawson, Zuhal Yapici, Hiroko Ikeda, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J de Vries, Dennis J Dlugos, Noah Berkowitz, Maurizio Voi, Severine Peyrard, Diana Pelov, David N Franz

The median number of seizure-free days (per 28-day period) increased from baseline by 2 in the low-exposure group and 4 days in the high-exposure group, compared with 0.5 days in the placebo group.
Seizure reduction with everolimus treatment among multiple seizure types, and the seizure reduction findings were essentially unchanged when generalised onset seizures confirmed by EEG (reported in six patients) were included in the analysis.
## EXIST-3: safety

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=119)</th>
<th>Everolimus 3-7 ng/mL (n=117)</th>
<th>Everolimus 9-15 ng/mL (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3 or 4</td>
<td>All grades</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>92 (77%)</td>
<td>13 (11%)</td>
<td>108 (92%)</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>11 (9%)</td>
<td>0</td>
<td>64 (55%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (5%)</td>
<td>0</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>19 (16%)</td>
<td>0</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>15 (13%)</td>
<td>1 (1%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (5%)</td>
<td>0</td>
<td>23 (20%)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (3%)</td>
<td>0</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (3%)</td>
<td>0</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (9%)</td>
<td>0</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (5%)</td>
<td>0</td>
<td>3 (3%)</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>1 (1%)</td>
<td>0</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (6%)</td>
<td>0</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Acne</td>
<td>3 (3%)</td>
<td>0</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>2 (2%)</td>
<td>0</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (1%)</td>
<td>0</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Ear infection</td>
<td>1 (1%)</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (1%)</td>
<td>0</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>4 (3%)</td>
<td>0</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1 (1%)</td>
<td>0</td>
<td>6 (5%)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise specified. *Included all the related terms—mouth ulceration, aphthous ulcer, lip ulceration, tongue ulceration, mucosal inflammation, and gingival pain.
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Jacqueline A French, John A Lawson, Zuhal Yapici, Hiroko Ikeda, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J de Vries, Dennis J Dlugos, Noah Berkowitz, Maurizio Voi, Severine Peyrard, Diana Pelov, David N Franz

• Everolimus treatment of mixed-type seizures in patients with TSC can lead to a clinically meaningful reduction in seizure frequency with a favourable benefit–risk ratio that improves with ongoing treatment

• Everolimus, a disease-modifying drug targeting the underlying molecular pathology of tuberous sclerosis complex, represents a new treatment option for patients with treatment-resistant seizures associated with tuberous sclerosis complex
Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial

- 299 paediatric patients enrolled in the trial:
  - 104 pts < 6y
  - 195 pts 6-18 y
- In both age groups greater RR and greater median reduction in sz frequency was observed in the everolimus treatment arms than placebo
- Better response for <6y subgroup

Response rate and reduction in sz frequency at the end of the core phase. Error bars represent 95% CI

Curatolo et al, Lancet Child & Adolesc Health, 2018
Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial

<table>
<thead>
<tr>
<th>Core phase</th>
<th>Younger subgroup (n=104)</th>
<th>Older subgroup (n=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Placebo (n=34)</td>
<td>Low-exposure everolimus (n=33)</td>
<td>High-exposure everolimus (n=37)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (15%)</td>
<td>15 (45%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9 (26%)</td>
<td>15 (45%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>9 (26%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>6 (18%)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (18%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (9%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (9%)</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (6%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (9%)</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1 (3%)</td>
<td>5 (15%)</td>
</tr>
</tbody>
</table>

Data are n (%). Adverse events were reported in patients during the core (≥20% of patients in either of the everolimus treatment groups for both age groups) and extension phases (≥20% of patients in either of the age groups). Patients in the younger subgroup were younger than 6 years old, and those in the older subgroup were aged 6 years old or older, and younger than 15 years. Extension phase data are both phases combined.

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Curatolo et al, Lancet Child & Adolesc Health, 2018
# mTOR inhibitors & AEDs

<table>
<thead>
<tr>
<th>AEDs reducing Everolimus serum levels</th>
<th>AEDs whose serum levels might be increased by Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Valproate</td>
</tr>
<tr>
<td>PHT</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine/oxcarbazepine</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
</tr>
</tbody>
</table>

**Caution in patients on ketogenic diet (lipids increase)**

romina.moavero@uniroma2.it
A brief treatment with rapamycin in adult mice led to a recovery of synaptic plasticity and behavioral disturbances.

The Interaction between Early Life Epilepsy and Autistic-Like Behavioral Consequences: A Role for the Mammalian Target of Rapamycin (mTOR) Pathway

In animal model rapamycin treatment before and after seizure onset led to a reduction of increased glutamatergic transmission and of seizure susceptibility, also improving subsequent “autistic behaviors.”
A Critical Time Window May Exist in Using Targeted Therapy to Prevent Seizures in infants with TSC related epilepsy

The road toward encephalopathy: an age dependent pathway

TSC gene mutation → mTOR activation

DELETERIOUS EFFECTS ON NEUROPSYCHOLOGICAL ABILITIES

Seizure onset

Encephalopathy

Developmental delay/behavioral phenotype

Too late

Conclusion

- Treatment with adjunctive everolimus resulted in sustained reduction in seizure frequency over time regardless of mutation status and regardless number and type of prior or concomitant AEDs in patients with TSC-associated treatment-refractory seizures.

- Reduction in seizure frequency with everolimus was both time and exposure dependent.

- The recommended TDM is to target everolimus’ serum level within a range of 5-7 ng/ml but no unexpected toxicity/safety concerns was observed over longer periods of time with higher exposures (9-15 ng/mL).

- Evidence of a better response in younger patients, suggesting everolimus should be considered early during the course of epilepsy.

- Available treatment options for epilepsy in TSC only provide a symptomatic treatment for seizures, while mTOR inhibitors act on the pathogenesis, thus having the potential of acting as a disease-modifying systemic therapy.

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