Mammalian Target of Rapamycin Inhibitors for Intractable Epilepsy and Subependymal Giant Cell Astrocytomas in Tuberous Sclerosis Complex

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Objectives To evaluate the efficacy and side effects of oral mammalian target of rapamycin (mTOR) inhibitors in children and adolescents with tuberous sclerosis complex (TSC) and intractable epilepsy or subependymal giant cell astrocytoma (SEGA).

Study design Single-center series of 13 children and adolescents with TSC who received sirolimus or everolimus (mTOR inhibitors). The anticonvulsant response was evaluated in 7 patients with TSC and refractory seizures. Six patients with SEGAs were treated with either sirolimus or everolimus for nonsurgical management. SEGA volumes were assessed longitudinally using 1.5-T magnetic resonance imaging.

Results Of the intractable seizure group (7 patients), 1 patient had >90% reduction, 4 had 50%-90% reduction, and 2 had <50% reduction. Three reported subjective improvements in learning. By 12 months of treatment, there were statistically significant reductions in the SEGA volumes in 4 patients who received mTOR inhibitors ($P < .04$). The mean SEGA volume after 6 months of treatment was 2.18 cm^3, which represents 33% reduction in the mean baseline volume of 3.26 cm^3. The mTOR inhibitors were well tolerated. Adverse effects include dyslipidaemia (3 of 13), gingivitis (1 of 13), anorexia (1 of 13), and mild gastrointestinal side effects (1 of 13).

Conclusion This case series suggests that mTOR inhibitors can improve seizures in those with TSC and refractory epilepsy. They are also an effective treatment for reducing the volume of SEGAs in patients with TSC not amenable to surgery with an acceptable side effect profile. *(J Pediatr 2014;164:1195-200)*.

The central nervous system manifestations of tuberous sclerosis complex (TSC) are most disabling and include subependymal giant cell astrocytomas (SEGAs), epilepsy, intellectual disability, and autism.[1,2] As many as 90% of patients with TSC develop epilepsy within their lifetime.[2-4] Epilepsy can be refractory to medical therapy, with relapse rates as high as 25% in those achieving remission.[1] Many children are considered for epilepsy surgery, especially if a single tuber is considered a dominant focus.[5] Preventing the development of an epileptic encephalopathy is crucial to enhance cognitive and behavioral outcomes.[4]

SEGAs are slowly growing glioneuronal tumors that can cause obstructive hydrocephalus when located near the foramen of Munro. Their prevalence can be as high as 5%-15% of all patients with TSC, with a peak incidence in the second decade of life.[6-10] SEGAs require resection, particularly if they cause obstructive hydrocephalus.[11,12] However, if not completely resected, SEGAs have a propensity to grow back.

TSC is caused by heterozygous mutations in either of the 2 tumor suppressor genes *TSC1* (hamartin) or *TSC2* (tuberin).[13] The hamartin and tuberin proteins interact, providing negative regulation of the mammalian target of rapamycin (mTOR) pathway, a complex signaling pathway that controls cell growth and size. Loss of function of this complex leads to unsuppressed mTOR pathway activation.[14] The mTOR complex regulates protein synthesis, neuronal differentiation, cell proliferation, angiogenesis, and cell survival.[15] In about 80% of cases of TSC, mutations are spontaneous, and in 20% of cases, TSC is inherited from a parent in an autosomal dominant manner. The benign hamartomas arise in tissues that have acquired a second somatic mutation in the TSC genes.

Sirolimus, also known as rapamycin, is a macrocyclic lactone-sensitive immunosuppressant that has been used in rejection prophylaxis in solid organ transplant recipients. Everolimus is a novel derivative of rapamycin that also has mTOR as its target. Sirolimus and everolimus act as signal transduction inhibitors of the mTOR complex and therefore target the specific molecular defect causing TSC. Recent trials have

AML	Angiomyolipoma
BSA	Body surface area
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
SEGA	Subependymal giant cell astrocytoma
TSC	Tuberous sclerosis complex

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shown mTOR inhibitors to be effective at reducing the size of SEGAs[16,17] and renal angiomyolipoma (AML) in TSC.[18]

We report data from a single-center series of 7 patients with TSC and refractory seizures who received sirolimus for treatment of their epilepsy and of 6 additional patients with TSC who were treated with either sirolimus or everolimus for nonsurgical management of SEGA.

Methods

This study was an open-label consecutive series of 2 groups of patients conducted through the TSC management clinic at Sydney Children's Hospital in Randwick. The first group included 7 patients with TSC with intractable daily seizures who received sirolimus. The second group included 6 patients with TSC who received sirolimus and/or everolimus for nonsurgical management of SEGA.

This study was an open-label case series of TSC patients treated in our multidisciplinary TSC clinic with mTOR inhibitors. Approval was sought on an individual case by case basis from our Istitutional Review Board (the South Eastern Syndey Area Health Service Drug Committe) for approval for patients to be provided sirolimus by the hospital pharmacy (and everolimus by Novartis AG, Basel, Switzerland) with informed written consent obtained for off-label use of these medications from the parents of all participants. After application for individual patient use by the South Eastern Sydney Area Health Service Drug committee, the hospital pharmacy provided sirolimus. Informed written consent for the off-label use of these medications was obtained from the parents of all participants.

All children were aged 3 years or older and had a definitive diagnosis of TSC according to international criteria.[19] Entry criteria for the first group was intractable epilepsy defined as the failure of ≥3 medications to control seizures at a frequency of >1 seizure per month for ≥12 months. The second group had an SEGA >1-cm diameter in any plane with documented growth over ≥2 consecutive magnetic resonance imaging (MRI) scans. Patients with SEGA were considered for surgical resection but not eligible; the 2 reasons for ineligibility were failure of previous SEGA surgery and refusal of the family to provide consent for surgery.

Everolimus or sirolimus was administered orally daily. For patients receiving everolimus, those with a body surface area (BSA) of ≤1.2 m^2, the starting daily dosage was 2.5 mg; for BSA 1.3-2.1 m^2, the starting daily dosage was 5 mg; and for BSA ≥2.2 m^2, the starting dosage was 7.5 mg. The initial dosage for sirolimus was based on BSA at 1 mg/m^2/d. No loading dose was given. Dose adjustments were made according to trough blood levels with a target level of 5-15 ng/mL for everolimus and 4-10 ng/mL for sirolimus. If the concentrations were <5 ng/mL, the daily dosage for everolimus was increased by 2.5 mg every 2 weeks subject to tolerability and efficacy. That meant that if efficacy was established, then no dose increase was made.

All patients were assessed regularly in a multidisciplinary TSC clinic for adverse events and drug tolerability. The data were prospectively collected and summarized from the clinical record. All patients underwent routine laboratory evaluation, including full blood count, electrolytes, renal function, liver function tests, and calcium, magnesium, phosphorus, fasting glucose, cholesterol, and triglyceride levels. This was collected at baseline and monitored every 3 months.

For group 1, seizure outcome was classified as the following: (1) seizure freedom; (2) >90% seizure reduction; (3) 50%-90% seizure reduction; (4) 20%-50% seizure reduction; or (5) <25% seizure reduction. Not all families maintained a seizure chart, so seizure frequency was determined at baseline and follow-up by parental clinical interview. For group 2, the primary efficacy end point was the change in volume of the SEGA during treatment. MRI results were obtained as per usual clinical practice of regular surveillance scans, with more frequent scans ordered according to clinical need. The volumes of the SEGAs were calculated with the use of ANALYZE 10 software program (AnalyzeDirect Inc, Overland Park, Kansas) using a 1.5-T MRI device.

We used a 1-sided paired *t*-test to evaluate the mean reduction in the volume of an SEGA from baseline volume using an α level of .05. All statistical analyses were performed using Microsoft Excel software (Microsoft Corp, Redmond, Washington) (M.C.).

Results

Sirolimus was introduced in 7 patients with TSC who had refractory epilepsy. The median age was 6 years (age range 3-17). The median age of onset of epilepsy was 11 months. At baseline, 6 of the 7 were having multiple daily seizures of mixed type including generalized tonic, focal dyscognitive seizures, and/or generalized tonic-clonic seizures. One patient with fortnightly focal seizures started everolimus therapy for the treatment of increasing growth of a renal AML. Previous anticonvulsant trials varied from 4 to 8 with a median of 5 previous anticonvulsant trials. Two of the patients had undergone a trial of the ketogenic diet. All had undergone extensive presurgical epilepsy work-up but were not considered candidates for focal resection. None of the patients with refractory seizures had SEGAs.

The median duration of treatment to the most recent follow-up was 18 months (range 6-36 months). Two patients became seizure free for at least 6 months and 1 for 12 months followed by >90% reduction in seizures thereafter. Only 1 patient had no significant change in seizure frequency (**Table I**).

mTOR Inhibitors for TSC and SEGAs

A total of 6 patients (5 male and 1 female) with TSC and SEGAs were treated from 2008 through to July 2012 (**Table II**). The median age was 12 years, and the range was 4-16 years. One patient received 3 mg/d sirolimus, and the other 5 received everolimus at a median daily dosage of 5 mg (range 5-10 mg). The median duration of treatment was 20 months (range 5-48).

Figure 1 shows the SEGA volume-response curves for 6 patients treated. The baseline SEGA volume was