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Case Report

Use of the mTOR inhibitor everolimus in a patient with multiple manifestations of tuberous sclerosis complex including epilepsy

James W. Wheless *

Le Bonheur Children's Hospital and the University of Tennessee Health Science Center, Memphis, TN, USA

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ABSTRACT

Tuberous sclerosis complex (TSC) is a genetic disease in which overactivation of mechanistic target of rapamycin (mTOR) signaling leads to the growth of benign hamartomas in multiple organs, including the brain, and is associated with a high rate of epilepsy and neurological deficits. The mTOR inhibitor everolimus has been used in the treatment of subependymal giant cell astrocytomas and renal angiomyolipomas in patients with TSC. This article describes the case of a 13-year-old girl with TSC-associated epilepsy with refractory generalized seizures who initiated treatment with everolimus and experienced subsequent improvement in several TSC manifestations, including a reduction in seizure frequency from clusters of two or three daily to one every 2 to 4 weeks after 1.5 years of treatment.

1. Introduction

1.1. Etiology

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disease [1]. Mutation of *TSC1* and/or *TSC2* genes results in constitutive activation in mechanistic target of rapamycin (mTOR) signaling; this triggers the growth of benign hamartomas in multiple organs, including the kidneys, brain, heart, lungs, and skin [1]. Common manifestations of TSC include renal angiomyolipomas in 70% to 90% of patients; central nervous system manifestations, including cortical tubers, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs), in up to 90% of patients; and skin lesions in more than 90% of patients [1,2]. In the brain, disturbances to normal cellular development and function can lead to epilepsy and neurocognitive, behavioral, and psychiatric deficits [2,3]. Epilepsy occurs in 60% to 90% of patients with TSC and is generally evident within the first year of life [1–3].

1.2. Treatment

Optimal management of TSC-associated seizures involves antiepileptic drugs (AEDs). Vigabatrin is the recommended first-line treatment for infantile spasms, although its potential for retinal toxicity should be taken into consideration [3,4]. Adrenocorticotropic hormone can also be considered for infantile spasms if treatment with vigabatrin fails [3,4]. Depending on seizure type, conventional AEDs, such as lamotrigine, topiramate, oxcarbazepine, and levetiracetam, may be effective [5–7]. Despite this, seizures are refractory to conventional AEDs in approximately one-third of patients with TSC with epilepsy [2,8]. Epilepsy surgery may be considered in appropriate candidates if medication-resistant seizures persist and where a single or dominant seizure focus is identified [3,4]. Other treatment options include complete corpus callosotomy, vagus nerve stimulation, or dietary therapy (e.g., ketogenic diet, low glycemic index diet) [3,4]. There is a need, however, for new therapeutic options for the treatment of epilepsy in TSC that improve patient quality of life and cognitive function and provide seizure control [9]. This case study illustrates the complexities of treatment in a patient with TSC-associated epilepsy who also had SEGA, renal angiomyolipomas, and retinal astrocytomas.

2. Case report

In May 2013, a female patient was referred to the Le Bonheur Comprehensive Epilepsy Program and Tuberous Sclerosis Complex Center of Excellence at Le Bonheur Children's Hospital in Memphis, Tennessee, for diagnostic evaluation of intractable, symptomatic,

Abbreviations: AEDs, antiepileptic drugs; mTOR, mechanistic target of rapamycin; SEGA, subependymal giant cell astrocytoma; SEN, subependymal nodule; TSC, tuberous sclerosis complex.

* Corresponding author at: UTHSC — Pediatric Neurology, 51 N Dunlap Street, Suite 335, Memphis, TN 38105, USA. Tel.: +1 901 287 5207; fax: +1 901 287 5325.
E-mail address: jwheless@uthsc.edu.

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generalized seizures associated with TSC. She was 13.5 years old at the time of initial observation and had a diagnosis of TSC and refractory seizures. She was first diagnosed with TSC when a cardiac rhabdomyoma was discovered at the age of 2 months. There was no family history of TSC. Infantile spasms were diagnosed at 11–12 months of age. In the first year after her seizures were diagnosed, she was treated with clonazepam, phenobarbital, prednisone, topiramate, and divalproex sodium. Between the ages of 2 and 4 years, she was seizure-free and off all medications. However, she subsequently developed refractory seizures that did not respond adequately to treatment with AEDs (carbamazepine, phenobarbital, prednisone, clonazepam, divalproex sodium, topiramate, levetiracetam, lamotrigine, clorazepate, oxcarbazepine, vigabatrin, and rufinamide) or vagus nerve stimulation.

Her seizure pattern included clusters of two to three seizures daily, typically after waking in the morning. She had generalized tonic elevation or extension of both arms briefly for a period of seconds. Between seizures, she was usually confused, moving about, fidgeting, and not fully responsive. Developmentally, she could walk and was able to speak but had mental impairment and autism spectrum disorder. She underwent periodic nephrology monitoring with renal MRI every 6 months, cardiology evaluation with Holter every 2 years with occasional echocardiogram, and ophthalmologic monitoring. Her treatment included vagus nerve stimulation, with the first vagus nerve stimulator placement in 2006. The patient's parents believed that this helped reduce the frequency of generalized tonic seizures. At the time of our first visit, she was taking multiple AEDs, namely divalproex sodium, lamotrigine, vigabatrin, and clobazam. She also received other medications, including folate, taurine, carnitine, multivitamin, laxative, and Depo-Provera (since the start of menarche—with a slight decrease in seizure frequency and more stable emotions).

A CT scan of the brain without contrast found multiple small, calcified SENs along the lateral ventricular margins consistent with TSC. Small, partially calcified bilateral SENs in the region of the intraventricular foramina were also identified, and these were thought to be consistent with small SEGAs. There was a small focus of subcortical white matter hypodensity in the paramedian left frontal lobe near the vertex that was consistent with cortical tubers. Small, irregularly calcified lesions, which were most likely small retinal astrocytomas, were apparent along the posterior margin of both globes near the optic nerve heads. Magnetic resonance imaging of the brain and brain stem, with and without gadolinium contrast, and functional MRI (fMRI) found parenchymal stigmata of TSC with multiple cortical tubers, white matter lesions, and SENs. Magnetic resonance imaging findings were consistent with those from the CT. Multiple small SENs were apparent along the margins of both lateral ventricles, and some of them demonstrated mild enhancement and calcification reflected by susceptibility effect. Small SENs were identified in the region of the intraventricular foramina bilaterally, and there were SEGAs in the region of the left and right foramen of Monro measuring up to 14 mm and 7 mm, respectively. A subtle susceptibility effect was seen along the posterior margins of both globes corresponding to the calcified retinal lesions seen on prior CT. The orbits were otherwise unremarkable. During fMRI, positive activation of the somatosensory cortex was observed for the bilateral hands during activity, and bilateral paracentral lobule activation was observed during movement of the feet; anatomic localization of primary sensorimotor cortices was normal. In addition, positive activation was identified in the left middle temporal gyrus suggestive of left cerebral hemispheric language lateralization.

Magnetic resonance imaging of the patient's abdomen, with and without gadolinium contrast, found multiple, bilateral, cortically based angiomyolipomas. The largest lesion (3.4 cm × 3.9 cm) was within the inferior polar region of the left kidney. There were also multiple, small, bilateral renal cysts. There was no evidence of hydronephrosis or hydroureter, and the liver, gallbladder, spleen, adrenal glands, pancreas, stomach, bowel, and descending abdominal aorta all appeared normal. In addition to the imaging results, physical examination revealed a facial plaque on the right side of her face below the eye extending down to the cheek, hypopigmented macules, poliosis in the left frontal head region, prominent bilateral facial angiofibromas, and a periungual fibroma on the left hand at the fourth digit. There was no shagreen patch or dental pitting.

Subsequent evaluation took place in the epilepsy monitoring unit from May 6–10, 2013. Transcranial magnetic stimulation confirmed normal motor localization, and a dual-energy X-ray absorptiometry (DEXA) scan was normal. Neuropsychologic testing results included a Stanford–Binet Intelligence Scale composite score of 47 and a Peabody Picture Vocabulary Test composite score of 22, both of which are consistent with a developmental-level age of 3.5 years. The patient had a marked decrease in fine motor skills, more so on the left hand than the right. Interictal single photon emission CT of the brain showed multiple areas of decreased blood flow over temporal, parietal, frontal, and occipital head regions. Magnetoencephalography showed epileptiform dipoles over both frontal head regions, more on the right than on the left. Prolonged video-EEG monitoring showed interictally that her wake background EEG was normal, but that she had few normal sleep patterns. Both during waking and in sleep, generalized epileptiform discharges were observed. Three generalized tonic seizures were observed lasting 37 to 49 s in duration, which progressed to complex partial seizures with diffuse EEG onset. Genetic testing of *TSC1* and *TSC2* showed that the patient had a *TSC2* mutation. Her VEGF-D serum level was 503 pg/mL (normal is <600 pg/mL).

The patient's medications were altered as follows: divalproex sodium was discontinued because her parents were not sure it was benefitting her; the dose of lamotrigine was increased to compensate for the lack of pharmacokinetic interaction with discontinuation of divalproex sodium; and vigabatrin and clobazam were continued. The patient's vagus nerve stimulator was decreased from 3.0 to 2.5 mA, and her intermediate cycling paradigm was slightly altered. Due to the nature of her seizures, focal resection was not an option; corpus callosotomy was considered but deemed unnecessary at this time. Based on the size of the largest angiomyolipoma in the patient's left kidney and following a discussion with her family, it was decided that she would benefit from treatment with everolimus. Everolimus was initiated at 5 mg/day, and serum levels were checked 4 weeks later.

At a 1.5 year follow-up in the fall of 2014, the patient was maintained on everolimus 5 mg a day with a serum level of 6.9 ng/mL. She had had no significant side effects from everolimus and no cold sores. The large angiomyolipoma in the left kidney decreased about 65% in size, and no other new, large lesions were seen. The patient had no worsening of her brain SEGA. Her retinal hamartomas were small and unchanged in size. Her facial angiofibroma, which had been quite prominent and red, was dramatically less red and no longer bled when she scratched her face. Her other skin lesions were unchanged. Her seizures decreased from daily events to one every 2 to 4 weeks; these seizures were brief, with essentially no postictal phase, and did not interfere with her activities of daily living. Furthermore, none of the seizures now resulted in falls. The patient's parents were happy with her treatment.

3. Discussion

Following the addition of the mTOR inhibitor everolimus, this patient experienced improvements in several TSC manifestations including epilepsy. The mTOR signaling pathway has been shown to play a role in epilepsy [10–12]. Genetic mutations in *TSC1* and/or *TSC2* genes or brain injuries can result in hyperactivation of mTOR signaling in TSC, thus, stimulating neuronal hyperexcitability and promoting seizures [10,13–15]. Beneficial effects of mTOR inhibition with everolimus have been reported previously in patients with TSC and epilepsy [9,16–19]. Everolimus treatment improved seizure control in prospective phase I/II studies in patients with TSC [9] and in patients with TSC-associated SEGA [16]. In one of these studies, Krueger et al. examined 20 patients with confirmed TSC with refractory epilepsy.

The study compared seizure data during the last 4 weeks of everolimus treatment (weeks 13–16) with the 4-week period before everolimus initiation (baseline, weeks 1–4) [9]. At the end of treatment, 12 patients (60%) experienced reductions in seizure frequency of 50% or more, three patients (15%) experienced reductions of 25% to 50%, and five patients (25%) had reductions of less than 25% [9]. Overall, the median seizure frequency decreased by 73% [9]. A few other small studies have found similar results. In a single-center study involving seven children and adolescents with TSC and refractory seizures treated with an mTOR inhibitor (six with sirolimus and one with everolimus), all but one of the patients experienced reductions in seizure frequency of at least 25%, with most experiencing reductions between 50% to 90% [17]. Additionally, seven patients with TSC and intractable epilepsy received everolimus in a compassionate use trial, and four of these patients had a reduction in seizure frequency ranging from 25% to 100% [18]. Cessation of seizures or a reduction in seizure frequency was also reported in a small number of pediatric patients with TSC who were treated with long-term everolimus [19]. However, more data are necessary to elucidate the potential benefits of mTOR inhibition on TSC-related seizures. A randomized, blinded, placebo controlled, phase III trial is currently in progress to evaluate the effect of everolimus on seizure activity in patients with TSC (clinicaltrials.gov identifier NCT01713946).

It should be noted that when patients receive everolimus concomitantly with AEDs, there is a need to potentially alter the dose of everolimus based on the medication they are taking. For example, a lower dose of everolimus would be started in a patient on a moderate CYP3A4 inhibitor. In patients with TSC, the recommendation is to reduce the everolimus dose by 50% [20]. In this case study, our patient was receiving lamotrigine, which does not inhibit any of the CYP isoenzymes. Rather, lamotrigine is predominantly metabolized by glucuronic acid conjugation [21]. It is also common in clinical practice for patients receiving a CYP3A4 inducer (e.g., phenytoin, phenobarbital, carbamazepine, primidone) to require a larger dose of everolimus to achieve therapeutic serum levels. So if concomitant use of strong inducers is required in patients with TSC, the dose of everolimus should be doubled [20].

Although everolimus is not currently approved for the treatment of refractory epilepsy in patients with TSC, it is approved for the treatment of TSC-associated SEGA that requires intervention but cannot be curatively resected and for the treatment of TSC-related renal angiomyolipomas that do not require immediate surgery [20]. Several clinical trials have reported the benefits of oral everolimus in reducing SEGA and renal angiomyolipoma volume and in reducing the appearance of skin lesions in patients with TSC [16,22–25]. Systemic treatment with mTOR inhibitors targets the underlying pathophysiology of TSC and has the potential for concurrent improvement of multiple lesions in a wide variety of tissues. Concurrent reduction in angiomyolipoma and SEGA volumes, seizure frequency, and skin lesions have been demonstrated previously with everolimus administration in patients with TSC [22,23,26–29].

4. Conclusion

We present the case of an adolescent girl with multiple disease manifestations of TSC and refractory epilepsy who benefitted from treatment with everolimus as demonstrated by shrinkage of renal angiomyolipoma, dramatic improvement in facial angiofibromas, and reduction in seizure frequency.

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Conflict of interest

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References

[1] Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008;372(9639):657–68.
[2] Krueger DA. Management of CNS-related disease manifestations in patients with tuberous sclerosis complex. Curr Treat Options Neurol 2013;15:618–33.
[3] Wang S, Fallah A. Optimal management of seizures associated with tuberous sclerosis complex: current and emerging options. Neuropsychiatr Dis Treat 2014;10:2021–30.
[4] Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013;49:255–65.
[5] Franz DN, Tudor C, Leonard J, Egelhoff JC, Byars A, Valerius K, et al. Lamotrigine therapy of epilepsy in tuberous sclerosis. Epilepsia 2001;42:935–40.
[6] Franz DN, Tudor C, Leonard J. Topiramate as therapy for tuberous sclerosis. Epilepsia 2000;41:87.
[7] Huerter V, Thiele EA. The role of levetiracetam in pediatric epilepsy. Epilepsia 2003;44(suppl 9):134.
[8] Thiele EA. Managing epilepsy in tuberous sclerosis complex. J Child Neurol 2004;19:680–6.
[9] Krueger DA, Wilfong AA, Holland-Bouley K, Anderson AE, Agricola K, Tudor C, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. Ann Neurol 2013;74:679–87.
[10] Meng XF, Yu JT, Song JH, Chi S, Tan L. Role of the mTOR signaling pathway in epilepsy. J Neurol Sci 2013;332:4–15.
[11] Russo E, Citraro R, Constanti A, De SG. The mTOR signaling pathway in the brain: focus on epilepsy and epileptogenesis. Mol Neurobiol 2012;46:662–81.
[12] Wong M. A critical review of mTOR inhibitors and epilepsy: from basic science to clinical trials. Expert Rev Neurother 2013;13:657–69.
[13] Osaki Y, Morita Y, Kuwahara T, Miyano I, Doi Y. Prevalence of Parkinson's disease and atypical parkinsonian syndromes in a rural Japanese district. Acta Neurol Scand 2011;124:182–7.
[14] Meikle L, Pollizzi K, Egnor A, Kramvis I, Lane H, Sahin M, et al. Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: effects on mTORC1 and Akt signaling lead to improved survival and function. J Neurosci 2008;28:5422–32.
[15] Zeng LH, Xu L, Gutmann DH, Wong M. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. Ann Neurol 2008;63:444–53.
[16] Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med 2010;363:1801–11.
[17] Cardamone M, Flanagan D, Mowat D, Kennedy SE, Chopra M, Lawson JA. Mammalian target of rapamycin inhibitors for intractable epilepsy and subependymal giant cell astrocytomas in tuberous sclerosis complex. J Pediatr 2014;164:1195–200.
[18] Wiegand G, May TW, Ostertag P, Boor R, Stephani U, Franz DN. Everolimus in tuberous sclerosis patients with intractable epilepsy: a treatment option? Eur J Paediatr Neurol 2013;17:631–8.
[19] Kotulska K, Chmielewski D, Borkowska J, Jurkiewicz E, Kuczynski D, Kmiec T, et al. Long-term effect of everolimus on epilepsy and growth in children under 3 years of age treated for subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Eur J Paediatr Neurol 2013;17:479–85.
[20] Novartis Pharmaceuticals Corporation. Afinitor (everolimus tablets for oral administration). Afinitor Disperz (everolimus tablets for oral suspension) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2014.
[21] Bullman J, Nicholls A, Van LK, Fleck R, Vuong A, Miller J, et al. Effects of lamotrigine and phenytoin on the pharmacokinetics of atorvastatin in healthy volunteers. Epilepsia 2011;52:1351–8.
[22] Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2013;381:125–32.
[23] Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381:817–24.
[24] Krueger DA, Care MM, Agricola K, Tudor C, Mays M, Franz DN. Everolimus long-term safety and efficacy in subependymal giant-cell astrocytoma. Neurology 2013;80 574–80.
[25] Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study. Lancet Oncol 2014;15:1513–20.
[26] Kotulska K, Borkowska J, Jozwiak S. Possible prevention of tuberous sclerosis complex lesions. Pediatrics 2013;132:e239–42.

[27] Tiberio D, Franz DN, Phillips JR. Regression of a cardiac rhabdomyoma in a patient receiving everolimus. Pediatrics 2011;127:e1335–7.
[28] Aguilera D, Flamini R, Mazewski C, Schniederjan M, Hayes L, Boydston W, et al. Response of subependymal giant cell astrocytoma with spinal cord metastasis to everolimus. J Pediatr Hematol Oncol 2013;36:e448–51.
[29] Cappellano AM, Senerchia AA, Adolfo F, Paiva PM, Pinho R, Covic A, et al. Successful everolimus therapy for SEGA in pediatric patients with tuberous sclerosis complex. Childs Nerv Syst 2013;29:2301–5.