SIROLIMUS AS AN ALTERNATIVE TO SURGERY IN TSC-ASSOCIATED BILATERAL SEGA: AN AFFORDABLE OPTION IN RESOURCE-LIMITED SETTING

Patricia C. Orduña, MD, Marissa B. Lukban, MD

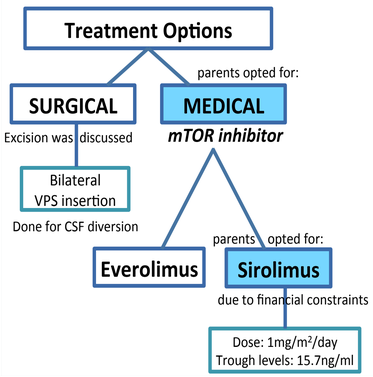
Division of Pediatric Neurology, Departments of Pediatrics and Neurosciences, University of the Philippines – Philippine General Hospital

BACKGROUND

Subependymal giant cell astrocytomas (SEGA) are the most common brain tumor in tuberous sclerosis complex (TSC) and may lead to significant neurological morbidity. Surgery is the mainstay treatment for SEGAs, but recent studies demonstrate efficacy of mTOr inhibitors in stabilizing and shrinking SEGAs. Everolimus has stronger treatment evidence but the cost limits its use among patients from resource-limited countries.

CASE REPORT

This is a **10-year-old Filipino female** with normal neurocognitive development, no history of seizures or infantile spasms who presented with a **1-year** history of **intermittent headache** associated with **projectile vomiting**. She fulfilled the clinical criteria for TSC (Figure 1, 2). Surgical resection was advised, but was lost to follow up. She came back after 2 years with blurred vision, progressing headache, vomiting and increased sleeping time. On neurologic examination, she had decreased visual acuity, bilateral lateral rectus palsy and grade 2 papilledema. Cranial CT showed **increase in size** of the SEGAs with moderate **obstructive hydrocephalus** (Figure 3). Below is the treatment algorithm that was done for our patient.



Imaging at **6 months** into therapy showed **82.5% and 64.1% reduction** on right and left respectively (Figure 3). There was no signi-ficant decrease in the renal and liver angio-myolipomas. She had no neurocognitive det-erioration, but vision was not restored.

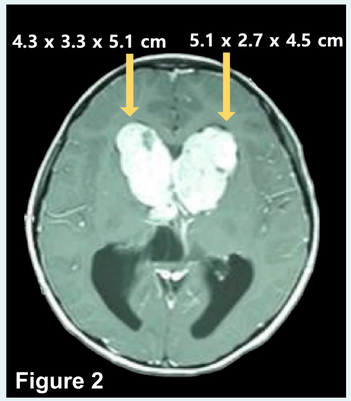


Figure 1. *Cutaneous manifestations of TSC: Multiple* ***hypomelanotic macules*** *on the trunk and extremities; multiple* ***facial angiofibromas.*** *Her father and paternal grandfather also had angiofibromas. Genotyping was not done due to financial constraints.*

Figure 2. *Contrast MRI showing* ***bilateral subependymal giant cell astrocytomas*** *and few* ***subependymal nodules.*** *Abdominal ultrasound (not seen) showed multiple* ***angiomyolipomas*** *on bilateral kidneys, liver and pancreatic head.*

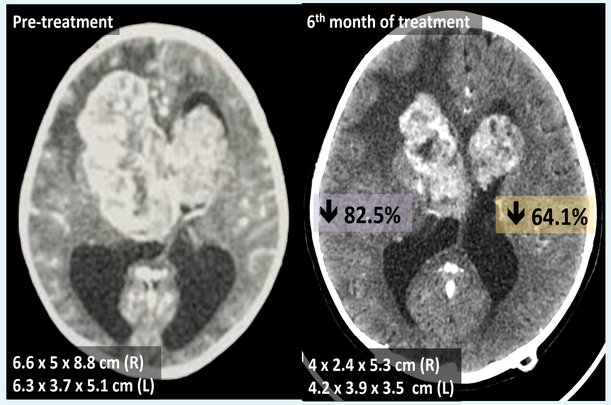


Figure 3. *Cranial CT scan prior to starting sirolimus (left) and at 6 months of treatment with sirolimus (right)*

DISCUSSION

Table 1. Comparison of Everolimus and Sirolimus in terms of efficacy and safety

EVEROLIMUS	SIROLIMUS
Pharmacologically similar[3]	
US FDA approved for ***SEGA*** treatment	**US FDA approved** for treatment of lymphangioleiomyomatosis ***(LAM)***

Evaluated through Long-term phase 2 and 3 studies[4-7]	
Prospective open-label Phase 2 study[4]	**≥30%** reduction at **6 months** in 75% of participants (P<0.001); Dose: 3mg/m²
EXIST-1 Trial: Double-blind, Phase 3 RCT [5-7]	**≥50%** reduction visible at **12 weeks** in 35% of Everolimus group (P<0.0001) Dose: 4.5mg/m²

Evaluated through case reports and series in pediatric patients[8-12]		
Franz et al. (2006)[10]	Initial: 2-3mg/tab titrated to 5-7mg/tab	**52-62%** reduction at 3-5 mos
Lam et al. (2010)[8]	Loading of 15mg/day, maintained 5-9mg/day	**50-60%** decrease
Cardamone et al. (2013)[11]	3mg/day	**65%** reduction
Weidman et al. (2014)[9]	4 mg/m2/day	**53-66%** reduction at 3-6 mos
Birca et al. (2010)[12] Bilateral SEGA	Loading of 2 mg, maintained at 1mg/ day	**82.6%** (L), **46.7%** (R) reduction at 3 months

SAFETY: Both well tolerated, with few, self-limited adverse effects reported; **Common SE:** Stomatitis, mouth ulceration, acneiform rash, arthralgias, diarrhea; ***Rare SE:*** Thrombocytopenia, convulsions, hypercholesterolemia, lipoproteinemia

Immunosuppressive effects and **growth retardation** (seen in post-kidney transplant pediatric patients taking sirolimus)[8,9]

Surgery is the standard treatment for TSC-associated SEGAs.[1] Our patient was **not a good candidate for surgery**, thus medical treatment using an **mTOR inhibitor was offered**. Table 1 shows the **comparison of sirolimus and everolimus**. We opted to **start our patient at the lowest effective dose of Sirolimus dose** (1mg/m²/day) and titrate up as necessary to maintain trough levels of 10-15ng/ml. Trough levels were achieved and did not warrant titration. Sirolimus was **well tolerated by our patient**, with **minimal elevations on cholesterol and triglyceride levels** managed with simvastatin. Tumor **re-growth was evident** among patients who discontinued the medication,[8,9,10] suggesting the need for a **life-long treatment course**.

Table 2 compares the cost of everolimus and sirolimus over 1- and 6-month treatment period for our patient. **Sirolimus is significantly more affordable**, with **98% decrease in cost from the everolimus innovator brand, being beneficial** in tumor reduction and in reducing their family's financial burden.

Table 2. Comparison of Treatment Cost for Everolimus and Sirolimus

mTOR inhibitor	Dose[13] (patient's BSA = 0.93)	Cost per tab (in PhP)	Number of tabs/day	Cost per day (in PhP)	Cost per 1 month treatment (in PhP)	Cost per 6 months treatment (in PhP)
Everolimus (A)	2.5mg/tab	27,000 per 2.5mg tab	1	27,000	810,000.00	4,860,000.00
Everolimus (B)	(0.5 to 1.2mg/m²)	205.75 per 0.50mg tab	5	1028.75	30,862.50	185,175.00
Sirolimus	1mg/m²	377.50 /1mg tab	1	**377.50**	**11,325.00**	**67,950.00**

CONCLUSION

This case reinforces previous observations that mTOR inhibitors can serve as **an alternative to surgery. Sirolimus** and **Everolimus** are ***comparable*** in efficacy and safety. **Sirolimus** is significantly ***more affordable*** than Everolimus – implications in recommending its **use in resource-limited settings.** Prospective studies and clinical trials are needed to further establish its efficacy, safety and cost-effectiveness in our setting.

REFERENCES

(1) Northrup H, Krueger DA. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatric Neurology.* 2013; 49: 243-254. (2) Roth J, Roach ES, Bartels U, Jozwiak S, et al. Subependymal giant cell astrocytoma: Diagnosis, screening, and treatment. Recommendations from the International Tuberous Sclerosis Complex Consensus Conference 2012. *Pediatric Neurology.* 2013; 49: 439-444. (3) MacKeigan JP, Krueger DA. Differentiating the mTOR inhibitors everolimus and sirolimus in the treatment of tuberous sclerosis complex. *Neuro-Oncology.* 2015; 17(12):1550-59. (4) Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *New England Journal of Medicine.* 2010; 363(19): 1801–1811. (5) Franz DN, Belousova E, Sparagana S, 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. *The Lancet.* 2013; 381(9861): 125–132. (6) Franz DN, Belousova E, Sparagana S, 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 *The Lancet Oncology.* 2014; 15(13): 1513–1520. (7) Franz DN, Belousova E, Sparagana S, Bebin EM, Frost MD, Kuperman R, et al. Long-term use of everolimus in patients with tuberous sclerosis complex: final results from the EXIST-1 study. *Plos One.* 2016; 11:e0158476. (8) Lam C, Bouffet E, Tabori U, Mabbott D, Taylor M, Bartels U. Rapamycin (sirolimus) in tuberous sclerosis associated pediatric central nervous system tumors. *Pediatr Blood Cancer.* 2010; 54: 476–479. (9) Weidman DR, Pole JD, Bouffet E, Taylor MD, Bartels U. Dose-level response rates of mTOR inhibition in tuberous sclerosis complex related subependymal giant cell astrocytoma. *Pediatric Blood & Cancer.* 2015; 62(10): 1754–1760. (10) Franz DN, Leonard J, Tudor C, Chuck G, Care M, Sethuraman G, Dinopoulos A, Thomas G, Crone KR. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol 2006;59: 490–498. (11) 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: 1195–1200. (12) Birca A, Mercier C, Major P. Rapamycin as an alternative to surgical treatment of subependymal giant cell astrocytomas in a patient with tuberous sclerosis complex. *Journal of Neurosurgery: Pediatrics.* 2010; 6(4): 381–384. (13) Campen CJ, Porter BE. Subependymal giant cell astrocytoma (SEGA) treatment update. *Curr Treat Options Neurol.* 2011; 13(4): 380–385.