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REVIEW

Pharmacological treatment strategies for subependymal giant cell astrocytoma (SEGA)

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ABSTRACT

Introduction: Subependymal ependymal giant cell astrocytomas (SEGAs) occur almost exclusively in the setting of tuberous sclerosis (TSC). They are low-grade gliomas which typically produce clinical symptoms through either mass effect or hydrocephalus. As do other manifestations of tuberous sclerosis, these lesions result from mutations in either the *TSC1* or the *TSC2* gene. These mutations cause hyperactivation of the mechanistic target of rapamycin (mTOR). In view of their tendency to grow slowly, clinical symptoms usually only occur when the tumors reach a considerable size. Therapy can involve surgical resection, cerebrospinal fluid diversion, or medical therapy with an mTOR inhibitor.

Areas covered: Herein, the authors discuss the diagnosis, symptoms, and practical management of SEGAs as well as providing their expert opinion.

Expert opinion: mTOR inhibitors have largely replaced surgery as the primary modality for the management of SEGAs. Surgical treatment is largely limited to tumors that present with acute hydrocephalus and increased intracranial pressure. Patients with TSC should undergo periodic screening with CT or preferably MRI scans of the brain from childhood to approximately age 25 to identify SEGAs which require treatment. In addition to avoiding potential morbidity associated with surgical resection, mTOR inhibitors have the potential to improve the clinical status of tuberous sclerosis patients generally.

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Central nervous system involvement; everolimus; mTOR inhibitor; rapamycin; sirolimus; therapy; treatment; tuberous sclerosis complex

1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal-dominant disease with a variable clinical expression, resulting from mutations in the TSC genes. The annual incidence of TSC is estimated at one in approximately 11.000 live births [1]. The protein products of the *TSC1* (hamartin) and *TSC2* (tuberin) form a dimer that serves to activate the protein Rheb (Ras homolog enhanced in the brain) [2]. mTOR exists as two distinct complexes distinguished by their cofactors. mTOR complex 1 has the cofactor Raptor (regulatory-associated protein of Tor) while mTOR complex 2 has the cofactor Rictor (rapamycin-insensitive component of Tor). mTOR complex 1 is inhibited by Rheb. Consequently, pathogenic mutations in either *TSC1* or *TSC2* lead to the inactivation of Rheb, with consequent overactivation of mTOR complex 1 [3]. Currently approved mTOR inhibitors act by causing dissociation of mTOR complex 1 from its cofactor Raptor for therefore inactivating it. These agents bind avidly to mTOR complex 1, causing their clinical effective persist days or weeks after any interruption of therapy. These agents thereby are able to restore mTOR activity to a more normal level. Patients with TSC either inherit or spontaneously develop a somatic mutation in either *TSC1* or *TSC2* early in embryonic development. Thus, every cell in apparently unaffected tissue of a patient with tuberous sclerosis carries a somatic mutation for either TSC1 or TSC2 (haploinsufficiency). Hamartomas such as subependymal ependymal giant cell astrocytomas (SEGAs) or cortical tubers occur when a second somatic mutation occurs in the unaffected allele of *TSC1* or *TSC2* [4]. This is in part responsible for the wide phenotypic variability of clinical manifestations in TSC. There is also frequent genetic mosaicism, including germline mosaicism whereby seemingly unaffected parents may have multiple children with tuberous sclerosis. mTOR plays a critical role in protein synthesis, cell growth, size, and division in all organs of the body [5]. mTOR hyperactivation produces hamartomas and malformations of various organ systems. The brain, kidney, skin, heart, and lung are the most frequently affected organ systems [6]. In the brain, these manifestations include cortical tubers, SEGAs, cortical dysplasia with neuronal hyperexcitability, therapy-resistant epilepsy, and developmental disability [7]. Interestingly, the organ manifestations of TSC present at different points within the lifespan, with brain and heart involvement being most common in infancy and early childhood while renal and pulmonary manifestations tend to occur in adolescents and adults [8]. In a prospective surveillance study, more than 95% of TSC patients with central nervous system (CNS) involvement experienced seizures [1]. CNS involvement is the most common manifestation. This may include cortical dysplasias, subependymal nodules (SEN) and SEGA, which are major diagnostic features of TSC [9] (Table 1).

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Article Highlights

- SEGAs occur almost exclusively in patients with tuberous sclerosis.
- Because SEGAs typically grow slowly they are often very large at the time clinical symptoms are noted, usually due to hydrocephalus or mass effect. For this reason, periodic CT or MRI screening is recommended to identify SEGAs and document any growth.
- mTOR inhibitors have largely replaced resective surgery in the management of SEGAs in tuberous sclerosis patients.
- mTOR inhibitors commonly produce side effects that are generally mild and easily manageable.
- mTOR inhibitors can benefit multiple aspects of tuberous sclerosis in an individual patient, including reduction of hamartomas regardless of where they occur, improvement of cutaneous lesions, epileptic seizures, and developmental delays.

This box summarizes the key points contained in the article.

Table 1. Diagnostic criteria according to the 2012 International tuberous sclerosis complex consensus conference. Reproduced from [9] with permission of Elsevier.

Updated diagnostic criteria for tuberous sclerosis complex 2012
(A) Genetic diagnostic criteria
The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g. out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g. large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.
(B) Clinical diagnostic criteria
• Major features
(1) Hypomelanotic macules (≥3, at least 5-mm diameter)
(2) Angiofibromas (≥3) or fibrous cephalic plaque
(3) Ungual fibromas (≥2)
(4) Shagreen patch
(5) Multiple retinal hamartomas
(6) Cortical dysplasias*
(7) Subependymal nodules
(8) Subependymal giant cell astrocytoma
(9) Cardiac rhabdomyoma
(10) Lymphangioleiomyomatosis (LAM)†
(11) Angiomyolipomas (≥2)†
• Minor features
(1) 'Confetti' skin lesions
(2) Dental enamel pits (>3)
(3) Intraoral fibromas (≥2)
(4) Retinal achromic patch
(5) Multiple renal cysts
(6) Nonrenal hamartomas
Definite diagnosis: Two major features or one major feature with ≥2 minor features
Possible diagnosis: Either one major feature or ≥2 minor features

*Includes tubers and cerebral white matter radial migration lines.
†A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet the criteria for a definite diagnosis.

2. Subependymal giant cell astrocytoma

SEGAs are slow-growing (World Health Organization class I) glioneural tumors that can cause mass effect and obstructive hydrocephalus. They almost exclusively appear in patients with TSC and represent a major cause of morbidity and mortality [10,11]. SEGAs can occur throughout the ventricular system but they are most frequently seen in the region of the foramen of Monroe where they are particularly prone to causing cerebrospinal fluid (CSF) obstruction (Figure 1).

SEGAs have been reported infrequently in other locations, such as the pineal region, retinal, or hypothalamus [12]. When SEGAs occur in patients who do not have tuberous sclerosis are typically called subependymomas to distinguish them from those occurring in patients with tuberous sclerosis. Histologically these lesions are similar. Subependymomas may reflect genetic mosaicism for either *TSC1* or *TSC2*, whereby, instead of somatic mutations, patients have mutations limited to various tissues within the body and produced symptoms limited to the organs affected. This phenomenon is known to occur frequently with the TSC genes, as, for example, in cases of germline mosaicism or sporadic lymphangioleiomyomatosis. SEGAs can occasionally be congenital. However, they occur most commonly in patients from childhood through adolescence. It is rare for a SEGA to develop or first present with clinical symptoms after age 25 [3]. When this does occur, there has typically been a subependymal lesion identified earlier in the affected individuals' life that is later found to be progressive. SEGAs can be bilateral in as many as 40%–50% of affected individuals. This can hamper surgical resection [13]. Serial neuroimaging is recommended in TSC to identify SEGAs but also to monitor for evidence of progression. Unlike gliomas in neurofibromatosis which can exhibit spontaneous regression, once a SEGA is beginning to grow, they continue to do so although the rate at which they grow may vary widely from patient to patient. Some SEGAs appear to remain quiescent for many years, only to exhibit growth

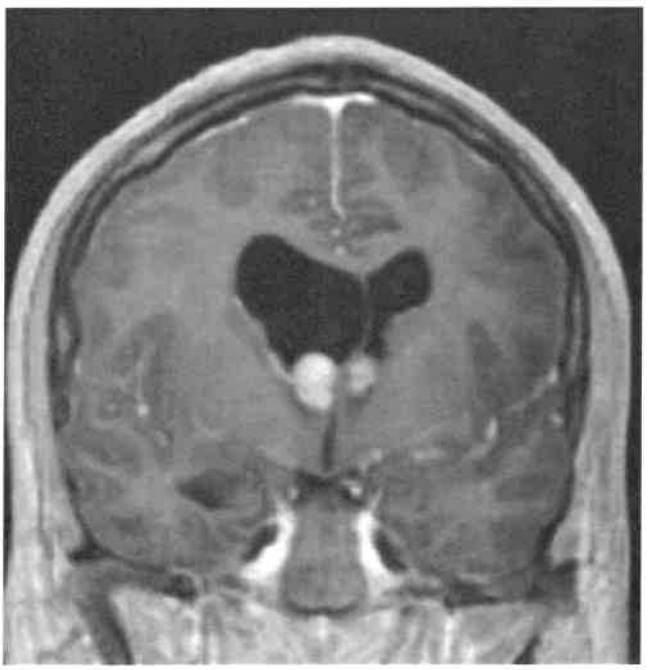

Figure 1. Bilateral subependymal giant cell astrocytoma with ventricular enlargement. Contrast-enhanced MRI.

and clinical symptoms at a later time. Retinal astrocytomas are seen in approximately 60%–70% of individuals affected with TSC. These are typically indolent lesions that change little over time. These symptoms, if any, result from disruption of the retinal fibers where they occur with resultant visual field disturbance. Histologically retinal astrocytomas are indistinguishable from SEGAs, and they may exhibit serial growth as SEGAs more commonly do. When this occurs, they may cause progressive visual impairment or intraocular hemorrhage. A Consensus Conference for TSC in 2012 defined SEGA as 'a lesion at the caudothalamic groove with either a size of more than 1 cm in any direction or a subependymal lesion at any location that has shown serial growth on consecutive imaging regardless of size. Most SEGA will show avid enhancement after contrast administration; however, a growing subependymal lesion even in the absence of enhancement should be considered a SEGA' [9,14]. SEGAs can be located unilateral or bilateral [15]. Signs and symptoms may include increase or alteration in seizure frequency, behavioral disturbances, regression or loss of cognitive skills, headache, ventriculomegaly, increased intracranial pressure, sleep disorders, eye movement abnormalities, visual impairment, papilledema, and neuroendocrine dysfunction. Of note, in a recent study, 42.5% of the patients were asymptomatic [16]. The negative influence of seizures and/or early development in tuberous sclerosis complex is appreciated [17]. Historically, a diagnosis of TSC was made when an individual presents with one of its many clinical features, oftentimes seizures [18]. Today, the implementation of standardized antenatal screening programs with fetal ultrasound, magnetic resonance imaging, genetic testing, and increased awareness of TSC has resulted in progressively earlier diagnosis [1,19]. Because of its typically slow growth, most SEGA will remain asymptomatic, until eventually symptoms are produced due to mass effect and/or obstruction of CSF pathways and resultant obstructive hydrocephalus [15]. Nevertheless, as many as 40%–50% of SEGAs are asymptomatic at the time they are identified, due to current practices of serial neuro-imaging in this population. Once identified, close neuroimaging surveillance and clinical follow-up are recommended, typically every 1–3 years in asymptomatic patients [20]. Patients with larger lesions, incipient hydrocephalus or obstruction, or atypical enhancement patterns are imaged more frequently. The specific frequency of neuroimaging in an individual patient is at the discretion of the treating physician.

Screening neuroimaging is important because by the time a SEGA has reached sufficient size to produce clinical symptoms it is often much more difficult to resect. Patients often undergo a rapid progression once clinical symptoms were first noted and have a much-increased risk of residual permanent neurologic sequelae such as a compressive optic neuropathy, cognitive impairment, and need for long-term CSF diversion. Patients with a large or growing SEGA should undergo MRI scans and clinical follow-up more frequently [14,20]. In a recent large-scale study in patients with TSC, conducted at 170 sites across 31 countries, SEGA was reported in 30.3% (671 of 2,211 patients) [21]. There is evidence that in individuals with *TSC2* mutations SEGAs occur more frequently and are more prone to exhibit progressive growth compared to individuals with *TSC1* mutation [16,21]. Generally speaking, however, there is no specific TSC mutation that correlates with the likelihood for developing a SEGA.

2.1. Surgical treatment strategies for SEGA

Surgical resection can be necessary for patients with acute symptomatology; CSF diversion may also be necessary [20]. Historically, this was the only treatment available. Not uncommonly, individuals with TSC were judged not to be candidates for resective surgery, either due to severe intellectual disability, intractable epilepsy, autism, or other comorbidities. Morbidity and mortality of resective surgery for SEGA have decreased in the modern era but can still be substantial. SEGAs are typically resected through either a transcallosal or transcortical transventricular approach. Obtaining a gross total resection is important as any residual tumor will almost certainly grow back. Creation of an operative corridor for tumor resection such as by balloon tractotomy can be valuable in decreasing long-term morbidity and improving the odds of a gross total resection. Many patients tolerate surgical resection well; however, potential complications including shunt dependence, intraoperative hemorrhage, infections, transient, or persistent focal neurologic deficits occur. Also, there is the possibility of postoperative hydrocephalus and the requirement of a second surgery [22]. Incompletely resected SEGA tends to regrow [15]. Newer modalities such as magnetic resonance-guided laser interstitial thermal therapy (Visualase®) can be of value in select cases and offer the possibility of decreased operative morbidity and more rapid recovery [23]. Of note, the surgical experience in each treatment center should be taken into account [13].

Recent case series is challenging the view that SEGAs with symptomatic hydrocephalus must invariably be treated with surgery. A number of patients with long-standing symptoms of hydrocephalus and SEGA have responded favorably to treatment with mTOR inhibitors and in some cases have avoided surgery altogether. In other cases, initial treatment with mTOR inhibitors has allowed lesions to be reduced in size so that they may be more easily resected [24,25].

2.2. Pharmacological treatment strategies for SEGA

mTOR inhibitors are distinctive from other treatment options for TSC as they act as disease-modifying agents and address the molecular basis of the disease [26]. Understanding that the lesions of tuberous sclerosis result from hyperactivity of mTOR led to first case reports and then clinical trials in humans of the commercially available mTOR inhibitors rapamycin and everolimus in this disease. First successful treatment of a tuberous sclerosis-related hamartoma, in this case an angiomyolipoma of the kidney, was reported by Wienecke in 2006 [27]. This was followed in the same year, the report of a series of four patients with SEGA and one with a hypothalamic glioma who all exhibited a reduction in tumor volume following treatment with rapamycin [28]. This was followed by an open-label clinical trial in which 28 patients with SEGA were treated with everolimus [29]. All patients exhibited a regression in tumor volume [30]. Based on this single site trial the FDA

granted provisional approval of everolimus for the treatment of SEGA not amenable to surgical resection. The EXIST-1 (Everolimus in the Treatment of SEGAs associated with Tuberous Sclerosis Complex) was a double-blind placebo-controlled randomized trial to prospectively establish the results of the initial single-center study. Patients were randomized to receive either active treatment with everolimus or placebo. After the blinded core phase of 6 months, all patients received active treatment. Highly significant reductions in SEGA volume compared to placebo were noted [31]. Side effects of both studies consisted primarily of oral aphthous ulcers, pneumonia, and arthralgias which typically resolved with short-term interruption of therapy. Significant laboratory abnormalities included thrombocytopenia, transaminase elevation, increased serum lipids, and neutropenia. Adverse effects tended to be mild to moderate in severity. Patients were followed for a total of 2 years after study enrollment. Based on these results, everolimus was formally approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for treatment of SEGA is not amenable to surgical resection in patients with tuberous sclerosis from birthdate to age 65 [29,30]. There is also evidence that long-term everolimus therapy reduces seizure frequency in patients with TSC-associated treatment-refractory seizures [32]. In a retrospective multicenter study, everolimus treatment in TSC patients under the age of 2 years demonstrated to be safe and showed beneficial effects on SEGA size, early epilepsy, and other TSC manifestations [33]. In a study with five patients younger than 12 months everolimus for congenital SEGA was safe and effective (all patients achieved at least a 50% reduction of SEGA volume within 6 months) [34].

Everolimus starting dose in SEGA is calculated according to body surface area and a starting dose of 4.5 mg/m^2/day is recommended. A higher starting dose of 7 mg/m^2/day can be considered for patients aged 1 year to <3 years [35]. Monitoring of serum levels is a useful adjunct when using mTOR inhibitor therapy. The therapeutic range is most commonly listed as 5–15 ng/mL; however, this range is derived primarily from the drugs used as an immunosuppressant. Lower levels are often sufficient to manage tuberous sclerosis patients, on the order of 3–8 ng/mL. A recent report suggests that doses of everolimus of at least 2.5 mg/m^2/day are required to ensure a clinical response. After an initial response, lower doses may be suitable to maintain a reduction in SEGA volume [36]. Dosing recommendations for rapamycin and everolimus are complicated by the frequent occurrence of drug–drug interactions with these agents. Enzyme-inducing antiepileptic drugs and other chemicals that increase the activity of the cytochrome P450 oxidase system tend to accelerate the metabolism of everolimus or rapamycin [37]. Agents that inhibit cytochrome P450 oxidase such as macrolide antibiotics and cannabidiol can cause elevated mTOR inhibitor levels [35,38]. Everolimus and rapamycin act through the same mechanism. However, their clinical profiles differ. Interestingly, individuals may tolerate one drug better than the other and may have a greater response and/or fewer side effects with everolimus versus rapamycin or vice versa [39]. Aphthous ulcers are the most commonly encountered side effect of mTOR inhibitor therapy, affecting as many as three-fourths of patients. Patients and caregivers should be given anticipatory guidance regarding the management of aphthous ulcers. Maintenance of the best possible oral hygiene with daily or twice-daily brushing and flossing can decrease the likelihood in the severity of aphthous ulcers. There are anecdotal reports of a wide variety of treatments: for example, rinsing the mouth with warm saltwater or sucralfate solution, lysine supplementation, taking the medication in whipped cream, pudding, or other soft food. Rinsing the mouth with 8.1% dexamethasone solution has however been shown to reduce the incidence and accelerate the healing of aphthous ulcers in patients receiving mTOR inhibitors for a variety of indications, including tuberous sclerosis. Prophylactically dexamethasone mouth rinses are used once or twice daily. When aphthous ulcers occur, this is increased to 4–5 times daily while maintaining good oral hygiene [40,41].

Another clinically relevant issue is the propensity of mTOR inhibitors to raise lipid levels and mimic the physiological effects of nutrient deprivation. This can be problematic when patients are also receiving a ketogenic diet for epilepsy. Triglyceride elevations in the thousands have been seen, as well as metabolic acidosis, sometimes with associated pancreatitis. On the other hand, the addition of mTOR inhibitors to the patients on the ketogenic diet can allow for the liberalization of carbohydrate intake and still improve ketosis in patients who have difficulty achieving adequate levels of carbohydrate restriction. In effect, mTOR inhibitors with the ketogenic diet can synergistically improve seizure control and cognition to a greater extent than either intervention when undertaken separately. Conversely, mTOR inhibitors have been associated with the development of hyperglycemia and diabetes. This appears to result from both inhibition of insulin release and the development of insulin resistance [42]. Awareness of this risk is important in patient management. Modest carbohydrate restrictions, on the order of 50–80 g of carbohydrate per day, can be beneficial as our therapies for insulin resistance such as metformin. One advantage of mTOR inhibitors such as rapamycin and everolimus is that they bind rather avidly to mTOR complex 1. This means that when significant side effects, surgical procedures, or infections arise they can be safely held without immediate loss of efficacy. This is true even for TSC patients who have had a reduction in seizure frequency as a result of their mTOR inhibitor therapy. With regard to their use for the treatment of tumors like SEGAs or angiomyolipomas, discontinuation of therapy does not result in an immediate relapse. However, once therapy is stopped lesions typically begin to increase in size after a variable period of time, usually on the order of several months, they eventually reach their pretreatment volume and will continue to grow and less therapy is reintroduced. There is no evidence that lesions grow more rapidly or aggressively after mTOR inhibitors are stopped, than before treatment was initiated. It is not known if the risk of lesion regrowth eventually decreases. Therefore, mTOR inhibitor therapy must be considered a long-term treatment, unless it is being used short term to facilitate surgical resection. Fortunately, the incidence of side effects decreases with increasing duration of therapy. Most patients tolerate long-term mTOR inhibitors quite well.

3. Conclusion

CNS involvement is the most common manifestation of tuberous sclerosis complex. This may include cortical dysplasias, subependymal nodules (SEN), and SEGA. Serial neuroimaging is recommended in TSC to identify SEGAs but also to monitor for evidence of progression. Because of its slow growth, most SEGA will remain asymptomatic, until eventually producing symptoms because of the mass effect and/or obstruction of CSF pathways and subsequent life-threatening obstructive hydrocephalus when being symptomatic. Therefore, SEGAs represent a significant burden in patients with TSC. Surgical resection is necessary for most patients with acutely symptomatic SEGA and CSF diversion may also be necessary. mTOR inhibitors are distinctive from other treatment options for TSC as they act as disease-modifying agents and address the molecular basis of the disease. Everolimus starting dose in SEGA is calculated according to body surface area. mTOR inhibitors have positive effects on TSC patients besides reducing the size of TSC-associated tumors.

4. Expert opinion

mTOR inhibitors have largely replaced surgery as the primary modality for the management of SEGAs (Figure 5). Surgical treatment is largely limited to tumors that present with acute hydrocephalus and increased intracranial pressure. Patients with TSC should undergo periodic screening with CT or preferably MRI scans of the brain from childhood to approximately age 25 to identify SEGAs which require treatment. In addition to avoiding potential morbidity associated with surgical resection, mTOR inhibitors have the potential to improve the clinical status of tuberous sclerosis patients generally, including reduction or improvement of renal angiomyolipomas, cutaneous angiofibromas, ash leaf macules, pulmonary lymphangioleiomyomatosis, epilepsy, and cognitive impairment. When dosing rapamycin or everolimus it should be borne in mind that this is typically a disease-modifying therapy with benefits accruing primarily with long-term usage. Patients often have difficulty tolerating these agents if they are initiated at too high of a dose with consequent adverse effects such as aphthous ulcers or frequent infections. A higher incidence of side effects also leads to a more frequent interruption in therapy and hampering any potential benefit. Furthermore, many patients experience a significant reduction in their SEGA or TSC hamartomas at lower dosages, even with subtherapeutic or low therapeutic serum levels. Our strategy when using mTOR inhibitors to treat SEGA or manifestations of TSC is to start at a lower dose, at times even lower than recommended, with a view to minimizing side effects and interruptions of therapy. Not only may patients respond to a low dose, but they are also more likely to tolerate mTOR inhibitor therapy long term if they are given time to adjust to the medication. In cases of extremely large SEGAs or severe seizure therapy can always be initiated at a higher dose based on the clinician's individual judgment. Adverse events are common with mTOR inhibitor therapy, fortunately, side effects tend to be mild to moderate and decrease in severity and incidence over time. Because the effect of these agents persists for days or sometimes weeks after therapy is stopped, holding the drug can be extremely useful for acute adverse effect management. However, this has limits if the mTOR inhibitor is held frequently or for prolonged periods.

Mouth sores or aphthous ulcers are the most frequently encountered side effects, occurring in 70–80% of patients. Anticipatory guidance plays a large role in managing mouth sores. The patient should be advised to maintain good oral hygiene while on mTOR inhibitors. A variety of interventions can decrease the incidence of mouth sores, such as lysine supplementation, taking the medication with food, e.g. in pudding or other soft food. Dexamethasone 0.1 mg/mL oral rinse can be used daily as a prophylactic agent, and 3–4 times daily if at these ulcers occur. At these ulcers occurring in the anterior aspect of the mouth or about the lips can be managed with triamcinolone in oral paste. Other mouth rinses such as sucralfate or mixtures of equal amounts of diphenhydramine, liquid antacid, and viscous lidocaine can be useful. mTOR inhibitors can impair wound healing so we recommend them being held for 1 week prior to any elective surgery until any surgical wound is well healed. In the event of unexpected surgery, they are again held until wounds are clinically well healed. Minor procedures such as restorative dental work or suture of lacerations typically do not require interruption of therapy. Because of their immunosuppressant effects we recommend that mTOR inhibitors be held during times a significant illness such as with temperature elevations greater than 38.3 Celsius (101 Fahrenheit), clinical pneumonia, or gastroenteritis with dehydration. Nonspecific upper respiratory symptoms in the absence of significant fever do not necessarily require therapy interruption.

Although in large, symptomatic SEGA surgical resection of the tumor is the recommended treatment choice to resolve hydrocephalus, everolimus therapy has the potential as an acute treatment method with a rapid reduction in tumor size and symptomatic improvement [25]. Figures 3, 4 and 5 illustrate a dramatic case with acute symptomatic SEGA.

FDA-approval of Rapamycin in TSC for the treatment of TSC is limited for pulmonary LAM. However, in clinical practice, the mTOR inhibitors rapamycin and everolimus are used interchangeably. Interestingly, there is a reported case from the EXIST-1 study of monozygous twins showing a possible preventive role of mTOR inhibitors with significant SEGA volume decrease in the treated twin [43]. It remains to be seen if prenatally treated patients (e.g. for large obstructive cardiac rhabdomyomas) are less prone to develop SEGA and other TSC manifestations, including TSC-associated neuropsychiatric disorders.

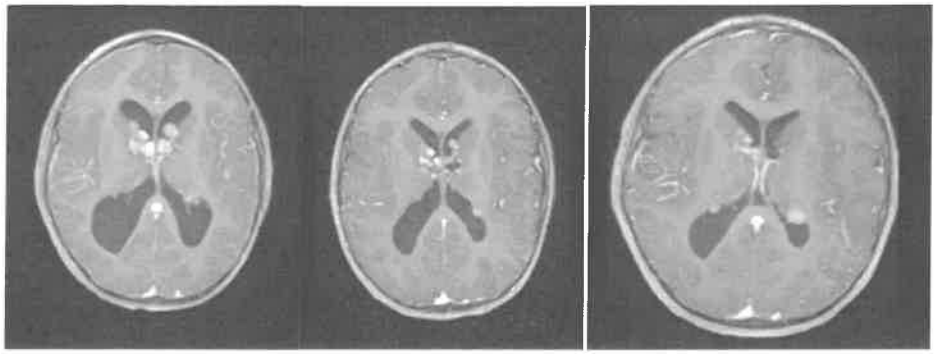

Figure 2. Asymptomatic adolescent male with bilateral SEGAs and obstructive hydrocephalus identified on screening MRI, judged to be unresectable, and response after 3 months and 24 months of everolimus therapy. Contrast-enhanced MRI. Gross total resection of bilateral giant cell astrocytomas is typically difficult and more prone to complications. Patient continues on everolimus with a total treatment duration of more than 10 years.

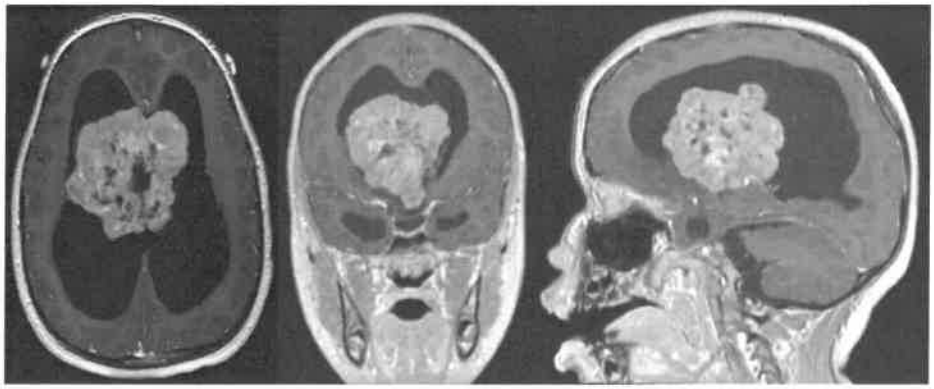

Figure 3. A large acute symptomatic SEGA at presentation in a 7-year-old. Contrast-enhanced MRI.

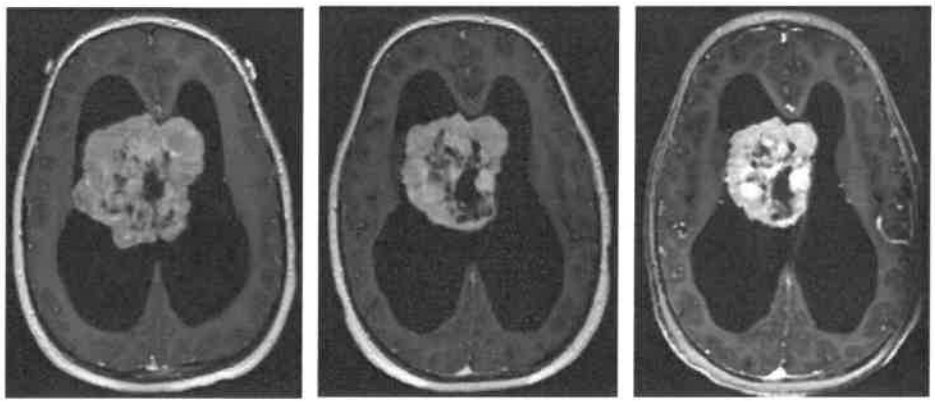

Figure 4. Same patient as Figure 2. Everolimus was administrated initially at 8 mg/m^2/day, higher than the recommended dose, to reach a therapeutic level more quickly. Significant decrease in tumor size after treatment on day 2 (left), day 12 (middle - 32% reduction of tumor size) and day 20 (right - 63% reduction of tumor size).

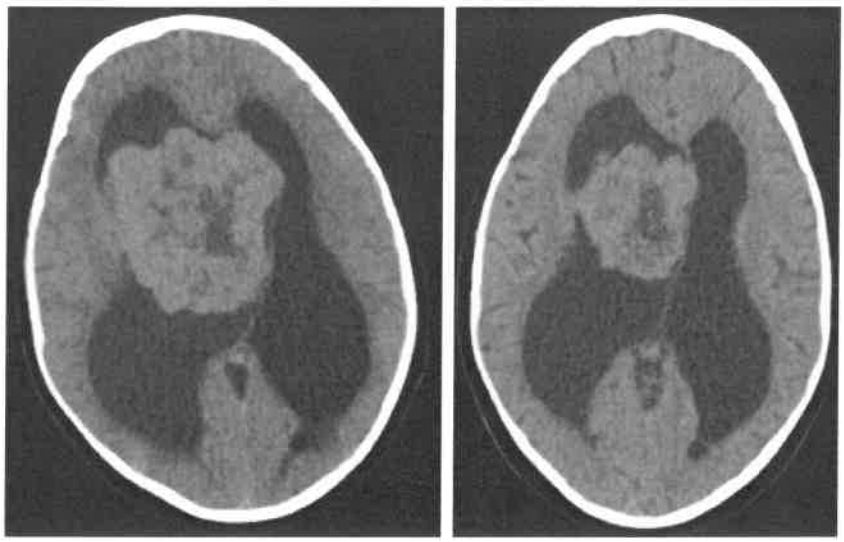

Figure 5. Patients' tumor at baseline on left and post 20 days of everolimus on right. (67% reduction of tumor size). Non-contrast CT.

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