ORIGINAL ARTICLE

Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis

Darcy A. Krueger, M.D., Ph.D., Marguerite M. Care, M.D., Katherine Holland, M.D., Ph.D., Karen Agricola, F.N.P., Cynthia Tudor, P.N.P., Prajakta Mangeshkar, M.S., Kimberly A. Wilson, M.S., Anna Byars, Ph.D., Tarek Sahmoud, M.D., Ph.D., and David Neal Franz, M.D.

ABSTRACT

BACKGROUND

Neurosurgical resection is the standard treatment for subependymal giant-cell astrocytomas in patients with the tuberous sclerosis complex. An alternative may be the use of everolimus, which inhibits the mammalian target of rapamycin, a protein regulated by gene products involved in the tuberous sclerosis complex.

METHODS

Patients 3 years of age or older with serial growth of subependymal giant-cell astrocytomas were eligible for this open-label study. The primary efficacy end point was the change in volume of subependymal giant-cell astrocytomas between baseline and 6 months. We gave everolimus orally, at a dose of 3.0 mg per square meter of body-surface area, to achieve a trough concentration of 5 to 15 ng per milliliter.

RESULTS

We enrolled 28 patients. Everolimus therapy was associated with a clinically meaningful reduction in volume of the primary subependymal giant-cell astrocytoma, as assessed on independent central review ($P<0.001$ for baseline vs. 6 months), with a reduction of at least 30% in 21 patients (75%) and at least 50% in 9 patients (32%). Marked reductions were seen within 3 months and were sustained. There were no new lesions, worsening hydrocephalus, evidence of increased intracranial pressure, or necessity for surgical resection or other therapy for subependymal giant-cell astrocytoma. Of the 16 patients for whom 24-hour video electroencephalography data were available, seizure frequency for the 6-month study period (vs. the previous 6-month period) decreased in 9, did not change in 6, and increased in 1 (median change, –1 seizure; $P=0.02$). The mean (±SD) score on the validated Quality-of-Life in Childhood Epilepsy questionnaire (on which scores can range from 0 to 100, with higher scores indicating a better quality of life) was improved at 3 months (63.4±12.4) and 6 months (62.1±14.2) over the baseline score (57.8±14.0). Single cases of grade 3 treatment-related sinusitis, pneumonia, viral bronchitis, tooth infection, stomatitis, and leukopenia were reported.

CONCLUSIONS

Everolimus therapy was associated with marked reduction in the volume of subependymal giant-cell astrocytomas and seizure frequency and may be a potential alternative to neurosurgical resection in some cases, though long-term studies are needed. (Funded by Novartis; ClinicalTrials.gov number, NCT00411619.)

From the Departments of Pediatrics and Neurology (D.A.K., K.H., K.A., C.T., P.M., A.B., D.N.F.) and Pediatrics and Radiology (M.M.C.), and the Translational Research Trials Office (K.A.W.), Tuberous Sclerosis Clinic, Cincinnati Children's Hospital Medical Center, Cincinnati; and Novartis Pharmaceuticals, Florham Park, NJ (T.S.). Address reprint requests to Dr. Franz at Cincinnati Children's Hospital Medical Center, MLC 2015, 3333 Burnet Ave., Cincinnati, OH 45229, or at tsclinic@cchmc.org.

N Engl J Med 2010;363:1801-11.

The tuberous sclerosis complex, an autosomal dominant disorder with a prevalence approaching 1 in 6000 live births,[1] is a potentially devastating disorder characterized by benign tumors (hamartomas) in multiple organ systems, including the brain, skin, kidney, lung, heart, and retina. Mutations in either of two tuberous sclerosis genes — *TSC1* (hamartin) or *TSC2* (tuberin) — are found in over 85% of patients with the tuberous sclerosis complex.[2] The proteins encoded by these two genes form a tumor-suppressor complex acting through the Ras homologue enriched in brain protein (RHEB) to limit activation of the mammalian target of rapamycin (mTOR) complex 1. When either *TSC1* or *TSC2* is deficient, mTOR complex 1 is constitutively upregulated, leading to abnormal cellular growth, proliferation, and protein synthesis.[3,4]

Subependymal giant-cell astrocytomas, which are slow-growing, glioneuronal tumors typically arising near the foramen of Monro,[5,6] develop in 5 to 20% of patients with the tuberous sclerosis complex.[6,7] Subependymal giant-cell astrocytomas are associated with a clinically significant risk of illness and death, including sudden death from acute hydrocephalus,[7] the risk of which is directly proportional to the volume of the subependymal giant-cell astrocytoma.[8] Subependymal giant-cell astrocytomas do not regress spontaneously, and the volume increases progressively once serial growth is shown.[8-10]

Current standard treatment is surgical resection; however, the deep location of these tumors can make resection difficult. Resection carries an important risk of perioperative and postoperative complications.[11] Incompletely resected subependymal giant-cell astrocytomas invariably recur, necessitating repeat procedures.[1] No effective alternative has been identified to date.

Everolimus (RAD001, Novartis) inhibits mTOR complex 1, correcting the specific molecular defect causing the tuberous sclerosis complex.[12] Several case reports suggest that mTOR inhibition leads to shrinkage or stabilization of renal angiomyolipomas,[13,14] lymphangioleiomyomatosis,[13,15,16] facial angiofibromas,[17] and subependymal giant-cell astrocytoma.[18,19] In the present study, we examined the effect of everolimus on subependymal giant-cell astrocytomas and seizures in patients with the tuberous sclerosis complex.

METHODS

ROLES OF THE SPONSOR AND AUTHORS

Novartis provided the study drug and financial support for the study. The statistical analysis plan was agreed on by Cincinnati Children's Hospital Medical Center (CCHMC) and Novartis. The authors vouch for the fidelity of this report to the trial protocol and statistical plan (available with the full text of this article at NEJM.org). Novartis prepared electronic case report forms into which data were entered and which were verified by CCHMC staff. All efficacy and safety data in the database were completely verified against the source data by a contract research organization working on behalf of Novartis. CCHMC and Novartis independently analyzed the data. The principal academic investigator had access to all the data, vouches for the veracity and completeness of the data and data analyses, and made the decision to submit the manuscript for publication.

PATIENTS

Eligible patients were 3 years of age or older and had a definitive diagnosis of the tuberous sclerosis complex (according to the modified Gomez criteria[20] or a positive genetic test) and serial growth of a subependymal giant-cell astrocytoma (defined as an increase in size, as compared with baseline, on at least two successive magnetic resonance imaging [MRI] scans). Patients also had to be medically stable, without signs of cerebral herniation or critical hydrocephalus.

Written informed consent was obtained before enrollment from all adult patients; patients under 18 years of age provided oral assent if they were able, and written informed consent was obtained from a parent or guardian. The institutional review board approved the protocol, and a data and safety monitoring board reviewed the progress of the trial semiannually.

STUDY DESIGN AND END POINTS

This prospective, open-label, phase 1–2 study was designed to evaluate the safety and efficacy of everolimus in patients with subependymal giant-cell astrocytomas. The study was conducted at CCHMC. The core treatment phase lasted for 6 months, after which patients could transition into an open-ended extension of the treatment period.

Everolimus was administered orally at a starting daily dose of 3.0 mg per square meter of body-surface area and was subsequently adjusted to attain a whole-blood trough concentration of 5 to 15 ng of the drug per milliliter. Doses were withheld or were reduced by 25% in patients who had severe side effects at the current dose.

The primary efficacy end point was the change in the volume of subependymal giant-cell astrocytomas during the core 6-month treatment phase. Volumetric assessment, based on brain MRI, was performed at baseline, at 3 and 6 months, and every 6 months thereafter. Local assessments of the volumes were calculated on the basis of data obtained with the use of a Vitrea 2 workstation based on reformatted images of 1-mm-thick coronal views acquired from MRI: either postcontrast sagittal, three-dimensional, spoiled-gradient recalled acquisition in steady-state 1.5-tesla MRI (General Electric Medical Systems and Siemens Medical Systems) or three-dimensional, T_1-weighted, gradient-echo sequence 3.0-tesla MRI (Siemens). An independent central review of the volumes was also conducted.

Effects on seizures, quality of life, and neurocognition were secondary end points. Seizure frequency was reported by all patients or their caregivers at each visit. In addition, 24-hour video electroencephalography (EEG) was performed at baseline in patients reporting at least one seizure during the previous 6 months (despite the use of antiepileptic drugs); EEG was repeated at 6 months.

The Quality-of-Life in Childhood Epilepsy (QOLCE) questionnaire[21] and neuropsychological assessments were administered, in all patients who were able to be tested, at baseline. The questionnaire was repeated at 3 and 6 months; the neuropsychological testing was repeated at 6 months. The neuropsychological assessments consisted of the standard battery of tools specific for chronologic age, including the Wechsler Preschool and Primary Scale of Intelligence (third edition), Bracken Basic Concept Scale (third edition), the Beery Visual-Motor Integration Test, the Developmental Neuropsychological Assessment NEPSY-II Phonological Processing subtest, the Behavior Assessment System for Children, the Wechsler Intelligence Scale for Children (fourth edition), the grooved pegboard test, Wisconsin Card Sorting Test, the Wide Range Achievement Test (third edition), the Judgment of Line Orientation Test, and the Wechsler Adult Intelligence Scale (third edition).

Adverse events were assessed with the use of the Common Terminology Criteria for Adverse Events (version 3.0).[22] The study protocol mandated that all infections were to be considered related to treatment. The following laboratory values were measured on a routine basis: white-cell and platelet counts and concentrations of hemoglobin, alanine and aspartate aminotransferases, alkaline phosphatase, albumin, creatinine, glucose, potassium, sodium, total cholesterol, and triglycerides.

STATISTICAL ANALYSIS

We calculated that a sample size of 28 patients would provide a statistical power of at least 90% to detect a median reduction in the volume of a subependymal giant-cell astrocytoma of at least 1 cm^3 from the baseline volume, on the basis of a one-sided Wilcoxon signed-rank test with an alpha level of 0.025. All statistical analyses were performed with the use of SAS software (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 28 patients (17 male, 11 female) were enrolled from January 2007 through December 2008. The median age was 11 years (range, 3 to 34); 22 patients were under 18 years of age (Table 1). Fifteen patients (54%) underwent genotyping; 4 had a *TSC1* mutation, 10 had a *TSC2* mutation, and 1 had no mutation identified in either gene. Thirteen patients (46%) had a secondary, smaller subependymal giant-cell astrocytoma (12 in the contralateral ventricle). Four patients (14%) had previously undergone partial resection or gamma-knife treatment of their subependymal giant-cell astrocytoma but met the enrollment criteria because the residual subependymal giant-cell astrocytoma regrew.

DURATION OF EVEROLIMUS TREATMENT

As of December 9, 2009, the median duration of treatment was 21.5 months (range, 4.7 to 34.4). One patient voluntarily discontinued treatment after 4.5 months (owing to nonadherence to the medication regimen and worsening hyperkinesis). The

Table 1. Baseline Characteristics of the 28 Patients Receiving Everolimus.*

Characteristic	Value
Age — yr	
Median	11
Range	3–34
Age group — no. (%)	
3 to <12 yr	16 (57)
≥12 to <18 yr	6 (21)
≥18 yr	6 (21)
Sex — no. (%)	
Male	17 (61)
Female	11 (39)
No. of SEGA lesions — no. (%)	
1	15 (54)
2	13 (46)
Bilateral SEGAs — no. (%)	12 (43)
Hydrocephalus — no. (%)	6 (21)
Facial angiofibroma — no. (%)	25 (89)
Previous therapy or surgery for SEGA — no. (%)	5 (18)
Surgery	4 (14)
Systemic therapy	2 (7)
No. of antiepileptic drugs in use at baseline — no. (%)	23 (82)
1	10 (36)
2	10 (36)
≥3	3 (11)

* SEGA denotes subependymal giant-cell astrocytoma.

remaining 27 patients completed the core 6-month treatment phase and then elected to continue everolimus therapy; 2 of the 27 discontinued treatment (after 17.5 and 21.5 months) because of the frequency of monitoring visits. Another patient met the prespecified criteria for treatment success (i.e., a reduction of ≥75% in the volume of the subependymal giant-cell astrocytoma) and therapy was stopped but was then restarted 4.5 months later, when regrowth of the subependymal giant-cell astrocytoma was evident.

EVEROLIMUS DOSING

The dose of everolimus was adjusted (if tolerated) to attain a whole-blood trough concentration of 5 to 15 ng per milliliter; however, the actual median concentration was 4.2 ng per milliliter (range, 2.0 to 11.0) at 3 months and 5.0 ng per milliliter (range, 1.6 to 15.3) at 6 months. Median daily doses of everolimus at 3 and 6 months were 4.7 mg per square meter (range, 0.0 to 7.8) and 5.6 mg per square meter (range, 1.5 to 10.5), respectively. The wide variation in trough concentrations associated with a specific dose was primarily attributable to the intercurrent use of potent antiepileptic drugs inducing cytochrome P-450 3A4 (CYP3A4), as well as intrapatient and interpatient variability.

EFFICACY OF EVEROLIMUS

Burden of Subependymal Giant-Cell Astrocytomas

Everolimus was associated with a clinically meaningful and statistically significant reduction in the volume of the primary subependymal giant-cell astrocytoma at 6 months (vs. baseline, $P<0.001$) (Table 2). Central review indicated that tumor volume was reduced by at least 30% during the core 6-month treatment phase, relative to baseline, in 21 patients (75%); 9 (32%) had reductions of 50% or more.

Primary-tumor shrinkage was most rapid during the initial 3 months of treatment, with evidence of a sustained response at subsequent time points during the core and extended treatment phases (Table 3). Reductions in total volume of the subependymal giant-cell astrocytomas (i.e., changes in the sum of the primary and secondary, smaller subependymal giant-cell astrocytoma) were also significant ($P<0.001$). Resolution of hydrocephalus and parenchymal dysplasia was also evident after treatment (Fig. 1).

No patient had worsening hydrocephalus or worsening symptoms attributable to increased intracranial pressure as a consequence of the reduction in volume of the subependymal giant-cell astrocytoma. Furthermore, no new lesions developed, and no patient needed to undergo surgical resection or other therapy for the tumor. One patient had initial shrinkage of the tumor (an 18% reduction in volume at 6 months relative to baseline) that was followed by progression (resulting in, at 18 months, a 16% increase relative to baseline).

The baseline total volume of the primary and secondary (if any) subependymal giant-cell astrocytomas ranged from 0.54 to 14.2 cm^3. Before treatment with everolimus, the mean annual rate of change was +0.57 cm^3 per year; after treatment, it was −0.57 cm^3 per year. The results of preplanned evaluations according to age group and sex were consistent with those reported for the

Table 2. Response of Primary Subependymal Giant-Cell Astrocytomas (SEGAs) to Everolimus Therapy at 6 Months, among the 28 Patients, According to Type of Assessment.*

SEGA Volume	Local Investigator's Assessment		Independent Central Review	
	Baseline	6 Mo	Baseline	6 Mo
Mean — cm^3	2.25±1.66	1.24±0.90	2.45±2.81	1.30±1.48
Median — cm^3	2.00	0.96	1.74	0.93
Range — cm^3	0.35–7.10	0.19–3.40	0.49–14.23	0.31–7.98
Reduction from baseline				
Mean — cm^3	1.01±1.04		1.15±1.42	
Median (95% CI) — cm^3	0.92 (0.5–1.4)		0.80 (0.4–1.2)	
P value	<0.001		<0.001	
Percent reduction — no. (%)				
≥50	11 (39)		9 (32)	
≥30	21 (75)		21 (75)	
>0	28 (100)		28 (100)	

* Plus–minus values are means ±SD. At 6 months (i.e., the end of the core treatment phase), 1 of the 28 patients had discontinued therapy; the 6-month data for this patient were obtained from the magnetic resonance imaging performed at 3 months, according to the last-observation-carried-forward approach. CI denotes confidence interval.

overall study population. The magnitude of the reduction in tumor volume was correlated with the magnitude of the baseline values: larger subependymal giant-cell astrocytoma lesions showed the greatest percent reductions.

Exploratory post hoc analyses showed that there were concomitant reductions in ventricular volume. The mean left ventricular volume was 15.5 cm^3 at baseline and 12.3 cm^3 at 6 months, for a mean reduction of 3.2 cm^3 (range, –7.7 to 31.6). The mean right ventricular volume was 17.3 cm^3 at baseline and 14.4 cm^3 at 6 months, for a mean reduction of 3.2 cm^3 (range, –4.8 to 26.1).

Epilepsy

Everolimus therapy was associated with a clinically relevant reduction in the overall frequency of clinical and subclinical seizure (median change, –1 seizure; P=0.02). Of 16 patients for whom video EEG data were available, between baseline (the total number during the 6-month period before the study) and 6 months, 9 had a decrease in seizure frequency, 6 had no change in frequency (5 of these patients did not have an event at either time point), and 1 patient had an increase in frequency. Epileptiform activity during "stage 2" sleep also improved, although this result did not reach statistical significance.

At enrollment, 23 patients (82%) were receiving antiepileptic drug therapy, consisting of one antiepileptic drug in 10 patients (36%), two drugs in another 10 (36%), and three drugs in 3 (11%). Concentrations of antiepileptic drugs varied among patients, both before and after treatment, but this was not considered to be clinically relevant. The antiepileptic drugs that were in use in 15 patients were medications that induce CYP3A4, leading to lower everolimus trough concentrations.

QUALITY OF LIFE AND COGNITION

Overall scores on the QOLCE (which can range from 0 to 100, with higher scores indicating a better quality of life) improved over time. The mean (±SD) scores were 57.8±14 at baseline, 63.4±12.4 at 3 months, and 62.1±14.2 at 6 months. There was no evidence of differential improvement among the specific domains of the questionnaire over time.

Neuropsychological data were available for 24 patients; essentially no changes were seen in intelligence or neuropsychological measurements. The remaining 4 patients were cognitively and behaviorally impaired to an extent that standardized assessment was not possible, despite repeated attempts. Testing in many patients was hampered by substantially below-average intelligence as well as autism and other behavioral disorders.

The appearance of facial angiofibromas was believed to have improved in 13 of 15 patients at 6 months, although comparisons were made relative to the previous visit rather than the baseline visit and the evaluations were not always undertaken by the same clinician.

Table 3. Response of Primary Subependymal Giant-Cell Astrocytomas (SEGAs) to Everolimus Therapy during the 6-Month Core Treatment Phase and the Subsequent Extension Phase, among the 28 Patients, According to Type of Assessment.

SEGA Volume	Local Investigator's Assessment					
	Baseline (N=28)	3 Mo (N=26)	6 Mo (N=27)	12 Mo (N=26)	18 Mo (N=18)	24 Mo (N=8)
Mean — cm^3	2.25	1.42	1.27	1.15	1.37	1.34
Median — cm^3	2.00	1.15	1.00	1.00	1.03	0.92
Range — cm^3	0.35 to 7.10	0.18 to 4.00	0.19 to 3.40	0.25 to 3.60	0.32 to 3.90	0.53 to 4.50
Reduction from baseline						
Mean — cm^3		0.88	1.04	0.99	1.11	0.87
Median (95% CI) — cm^3		0.77	0.94	0.84	0.84	0.64
Range — cm^3		0.00 to 4.10	0.02 to 4.80	0.03 to 3.50	0.00 to 4.50	−0.18 to 2.10
Reduction — no. (%)						
≥50%		9 (35)	11 (41)	9 (35)	6 (33)	2 (25)
≥30%		16 (62)	20 (74)	21 (81)	13 (72)	6 (75)
>0%		25 (96)	27 (100)	26 (100)	17 (94)	7 (88)
No change		1 (4)	0	0	1 (6)	0
Tumor growth		0	0	0	0	1 (12)

PHARMACOKINETICS

In total, 207 samples were collected for the evaluation of trough concentrations of everolimus, including 83 that corresponded to the time of MRI. Irrespective of concurrent administration of a CYP3A4 inducer or inhibitor, there was a positive linear relationship between trough concentrations and daily dose (i.e., dose proportionality).

A response to everolimus, as assessed by means of imaging, was observed for several patients with trough concentrations below the targeted therapeutic range (at levels as low as 2 ng per milliliter). In other patients, daily everolimus doses of 10 to 15 mg per square meter were required to achieve trough concentrations of approximately 5 ng per milliliter.

ADVERSE EVENTS

All patients had at least one adverse event (Table 4). Self-limited infections, primarily upper respiratory illness, accounted for the majority, but stomatitis was also common. These events are consistent with the known safety profile of everolimus and were generally grade 1 (mild) or grade 2 (moderate) events. Events rated as severe adverse events (grade 3) were reported in 10 patients, and one grade 4 event (convulsion) occurred in a single patient.

Four patients had serious adverse events. One patient with a history of reactive airway disease was hospitalized after recurrent upper respiratory infection (grade 3 viral bronchitis) developed, with cough and sinusitis that exacerbated breathing difficulties and was associated with leukopenia. Another patient was hospitalized for grade 3 pneumonia; later in the study, this same patient also had grade 3 vomiting. Two additional patients were hospitalized for convulsions (grade 2 and grade 4).

No consistent laboratory abnormalities were noted, with the exception of increases in the concentrations of total cholesterol (163.5±33.7 mg per deciliter [4.2±0.9 mmol per liter] at baseline; 185.1±34.4 [4.8±0.9] at 6 months), low-density lipoprotein cholesterol (96.8±32.0 mg per deciliter [2.5±0.8 mmol per liter] at baseline; 109.0±34.3 [2.8±0.9] at 6 months), and triglycerides (84.3±55.9 mg per deciliter [1.0±0.6 mmol per liter] at baseline; 129.6±85.2 [1.5±1.0] at 6 months). In one patient with laboratory abnormalities, the preexisting statin regimen was adjusted; all other affected patients were counseled regarding low-fat diets or did not need intervention.

DISCUSSION

In this prospective trial of everolimus in patients with subependymal giant-cell astrocytoma, we observed a significant reduction in the volume of subependymal giant-cell astrocytomas, consistent with a correction of the constitutive activation of

Independent Central Review					
Baseline (N=28)	3 Mo (N=26)	6 Mo (N=27)	12 Mo (N=26)	18 Mo (N=18)	24 Mo (N=8)
2.45	1.47	1.33	1.26	1.45	1.05
1.74	0.84	0.93	0.84	0.90	0.57
0.49 to 14.23	0.25 to 8.32	0.31 to 7.98	0.29 to 8.18	0.33 to 5.20	0.33 to 3.66
	1.08	1.19	1.07	1.46	1.01
	0.63	0.83	0.85	0.74	0.46
	–0.12 to 5.91	0.06 to 6.25	0.02 to 6.05	–0.24 to 9.03	0.12 to 3.79
	10 (38)	9 (33)	9 (35)	8 (44)	3 (38)
	17 (65)	21 (78)	20 (77)	12 (67)	6 (75)
	25 (96)	27 (100)	26 (100)	16 (89)	8 (100)
	0	0	0	1 (6)	0
	1 (4)	0	0	1 (6)	0

mTOR complex 1 in lesions related to the tuberous sclerosis complex. Everolimus therapy also was associated with a significant reduction in seizure frequency. This reduction in seizure frequency is particularly important, since the inhibition of mTOR complex 1 is achieved through a mechanism different from that of traditional antiepileptic drugs.

Everolimus may be a promising treatment option for patients represented by our study population and may provide an alternative therapy to deep intracranial surgery and its associated morbidity and mortality. Subependymal giant-cell astrocytomas have the potential for rapid growth; asymptomatic lesions can grow large enough to obstruct the foramen of Monro in as little as 18 months.[23] Spontaneous resolution or stabilization of subependymal giant-cell astrocytomas, once serial growth is evident, has not been documented. A reduction in the volume of subependymal giant-cell astrocytomas by 30% or more is generally sufficient to alleviate or reduce the risk of hydrocephalus or parenchymal invasion. Several patients in our study had ventricular dilation that resolved. Furthermore, the prevention of further growth represents a clinical benefit for patients whose tumors had previously shown serial enlargement — as indicated by the 50% or greater reduction in volume of the subependymal giant-cell astrocytomas.

Our patients had typical features of the tuberous sclerosis complex.[20] The presence of a historical control group may have proved to be beneficial to provide further insight into the observed treatment effect but, to our knowledge, such control data are unavailable in the literature.

Our center previously reported encouraging results with sirolimus (previously called rapamycin), another mTOR inhibitor, in a small series of four patients with subependymal giant-cell astrocytomas and one with a pilocytic astrocytoma.[18] One of these patients had regrowth of a subependymal giant-cell astrocytoma after having received sirolimus treatment that was interrupted for 4 months.[18]

We also evaluated the role of mTOR inhibition in a 2-year open-label trial of sirolimus involving 25 adult patients with angiomyolipoma associated with the tuberous sclerosis complex or sporadic lymphangiomyomatosis.[13] In the 25 patients, angiomyolipoma volume was reduced by 47%; in addition, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and residual volume were also improved, after 12 months of therapy. The design of the angiomyolipoma trial included a 12-month follow-up period in which sirolimus was discontinued.[13] A sustained reduction in angiomyolipoma volume was seen in only 5 of 18 patients (28%), with an overall mean reduction from the baseline volume of

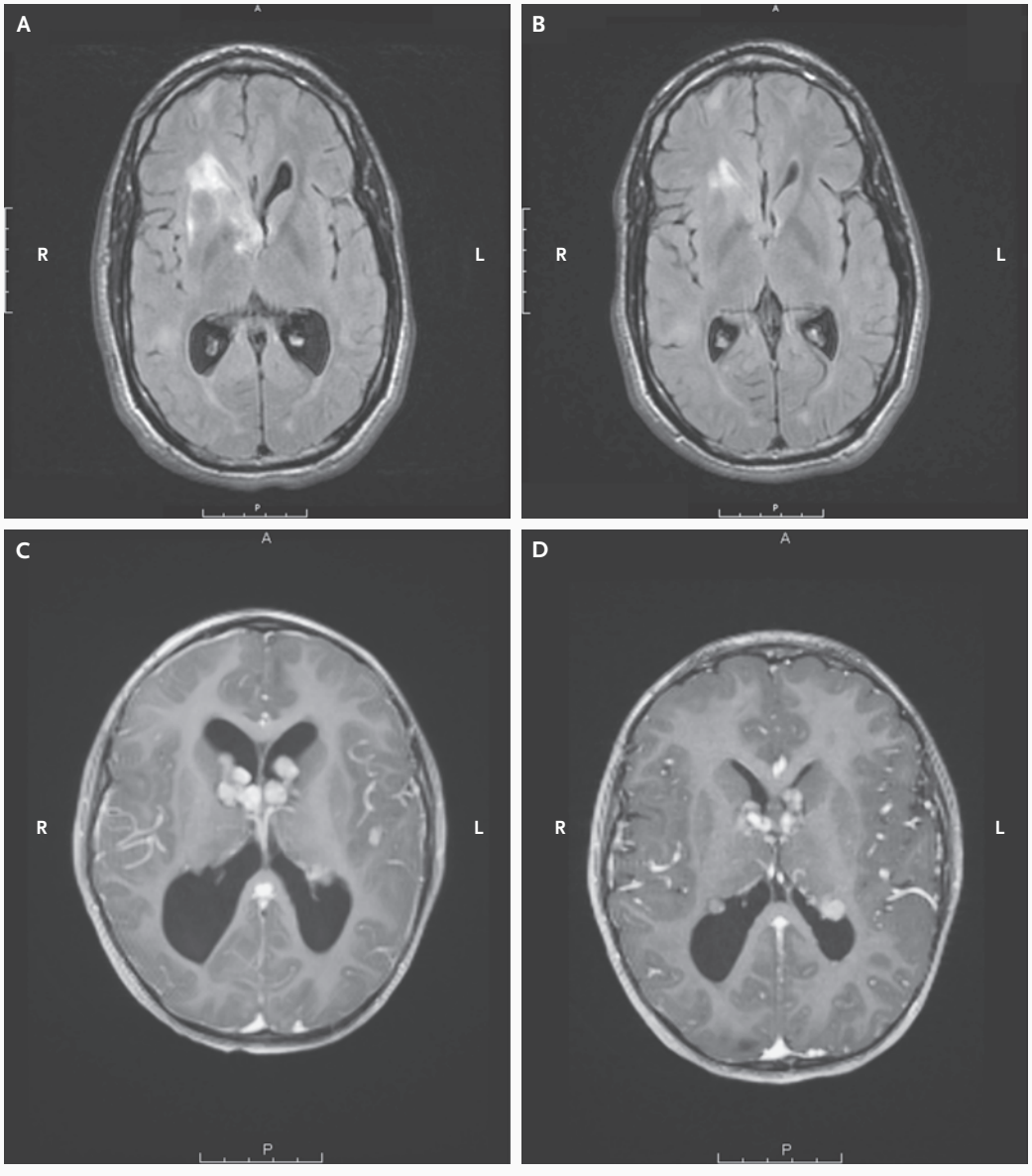

Figure 1. Effect of Everolimus on Subependymal Giant-Cell Astrocytoma (SEGA) in Two Patients.

Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) shows a SEGA with parenchymal invasion and associated white-matter dysplasia, as well as hydrocephalus (Panel A). Subtotal resection had been performed previously, and the patient was not considered to be a candidate for further surgery. After 3 months of everolimus therapy, regression of the SEGA and resolution of the abnormal white-matter signal and hydrocephalus are evident on FLAIR MRI (Panel B). Contrast-enhanced axial T_1-weighted MRI in another patient shows bilateral multinodular SEGAs with hydrocephalus (Panel C), which were judged to be nonresectable because of the bilateral and multifocal nature; after 3 months of everolimus therapy, the lesions had regressed, and the hydrocephalus had resolved (Panel D).

14%. The improvements in FEV_1, FVC, and residual lung volume also subsided after discontinuation of therapy.

Such observations suggest that mTOR inhibition may need to be continuous for the benefit to persist. In the present study, all patients completing the core 6-month treatment phase elected to continue everolimus. The optimal duration of

Table 4. Adverse Events in the 28 Patients.

Event*	Adverse Event		Adverse Drug Reaction	
	Any	Grade 3 or 4	Any	Grade 3†
	number (percent)			
Any	28 (100)	11 (39)	28 (100)	5 (18)
Stomatitis	22 (79)	1 (4)	22 (79)	1 (4)
Upper respiratory tract infection	22 (79)	0	22 (79)	0
Sinusitis	11 (39)	1 (4)	11 (39)	1 (4)
Otitis media	10 (36)	0	10 (36)	0
Pyrexia	10 (36)	0	8 (29)	0
Convulsion	7 (25)	3 (11)	0	0
Acneiform dermatitis	7 (25)	0	7 (25)	0
Diarrhea	7 (25)	0	6 (21)	0
Vomiting	6 (21)	1 (4)	2 (7)	0
Cellulitis	6 (21)	0	6 (21)	0
Body tinea	5 (18)	0	4 (14)	0
Cough	5 (18)	0	3 (11)	0
Headache	5 (18)	0	1 (4)	0
Rash	5 (18)	0	1 (4)	0
Personality change	5 (18)	0	0	0
Dizziness	4 (14)	1 (4)	0	0
Gastroenteritis	4 (14)	0	4 (14)	0
Otitis externa	4 (14)	0	4 (14)	0
Skin infection	4 (14)	0	3 (11)	0
Allergic rhinitis	4 (14)	0	0	0
Contact dermatitis	4 (14)	0	0	0
Acne	3 (11)	0	3 (11)	0
Gastric infection	3 (11)	0	3 (11)	0
Dry skin	3 (11)	0	1 (4)	0
Constipation	3 (11)	0	0	0
Skin disorder	3 (11)	0	0	0
Laboratory abnormalities reported as adverse events				
Decreased white-cell count	3 (11)	1 (4)	3 (11)	1 (4)
Hypertriglyceridemia	3 (11)	0	3 (11)	0

* Each adverse event is listed as the preferred term of the *Medical Dictionary for Regulatory Activities* (MedDRA).
† No grade 4 adverse drug reactions were reported. Grade 3 adverse drug reactions not listed here include single cases of pneumonia, viral bronchitis, and tooth infection.

treatment for subependymal giant-cell astrocytomas or angiomyolipomas in patients with the tuberous sclerosis complex is unknown. In the present study, an apparent benefit was evident at relatively low trough concentrations of everolimus.

Everolimus has been evaluated for a variety of clinical indications.[24-26] We did not observe additional safety risks in our patients, with the tuberous sclerosis complex, as compared with the general population of patients who have received this agent. Longer-term follow-up of these patients is important, as is long-term surveillance in ongoing phase 3 studies.

One of us previously reported a reduced seizure

frequency with sirolimus in 15 patients with tuberous sclerosis complex with intractable epilepsy.[27] These patients had multiple partial seizures daily, were 3 to 26 years of age (mean, 13), and had had no benefit from a minimum total of nine antiepileptic drugs administered previously. Fourteen patients had a history of infantile spasms, 9 had undergone vagus-nerve stimulation, and 4 had undergone vagus-nerve stimulation and resective epilepsy surgery. Three patients (20%) had a reduction in seizure frequency of more than 90% (on the basis of diary data), 8 patients (53%) had a reduction of more than 50%, and 4 (27%) showed no response. In 8 patients (53%), the reduction was persistent during a mean follow-up period of 18 months (range, 3 to 44). A further case report has also been published.[28]

Multiple potential mechanisms exist whereby inhibition of mTOR complex 1 may ameliorate epilepsy and cognitive function. The mTOR complex 1 regulates protein synthesis and microanatomical changes that underlie synaptic, long-term potentiation and depression.[29,30] Everolimus, by means of mTOR regulation, may therefore play a more general role in epilepsy, not just the tuberous sclerosis complex.[31,32]

In summary, in our study of patients with subependymal giant-cell astrocytoma associated with the tuberous sclerosis complex, 75% of patients had a reduction by 30% or more in the volume of the primary subependymal giant-cell astrocytoma at 6 months. Medical treatment with everolimus may be a potential alternative to neurosurgical resection in some circumstances, though long-term studies will be needed to confirm this possibility.

Supported by Novartis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the patients and their families for their participation in this study, and Mrs. Melody Gulleman (CCHMC) and Peter Berry, Nigel Yateman, and Betty Molloy (Novartis) for their assistance in the preparation of the manuscript.

REFERENCES

1. Krueger DA, Franz DN. Current management of tuberous sclerosis complex. Paediatr Drugs 2008;10:299-313.
2. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355:1345-56.
3. Huang J, Manning BD. The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. Biochem J 2008; 412:179-90.
4. Chan JA, Zhang H, Roberts PS, et al. Pathogenesis of tuberous sclerosis subependymal giant cell astrocytomas: biallelic inactivation of TSC1 or TSC2 leads to mTOR activation. J Neuropathol Exp Neurol 2004;63:1236-42.
5. Baskin HJ Jr. The pathogenesis and imaging of the tuberous sclerosis complex. Pediatr Radiol 2008;38:936-52.
6. Goh S, Butler W, Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology 2004;63:1457-61.
7. Adriaensen MEAPM, Schaefer-Prokop CM, Stijnen T, et al. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature. Eur J Neurol 2009;16:691-6.
8. de Ribaupierre S, Dorfmüller G, Bulteau C, et al. Subependymal giant-cell astrocytomas in pediatric tuberous sclerosis disease: when should we operate? Neurosurgery 2007;60:83-9.
9. O'Callaghan FJ, Martyn CN, Renowden S, Noakes M, Presdee D, Osborne JP. Subependymal nodules, giant cell astrocytomas and the tuberous sclerosis complex: a population-based study. Arch Dis Child 2008;93:751-4.
10. Franz DN, de Vries PJ, Crino PB. Giant cell astrocytomas in tuberous sclerosis complex. Arch Dis Child 2009;94:75-6.
11. Levine NB, Collins J, Franz DN, Crone KR. Gradual formation of an operative corridor by balloon dilation for resection of subependymal giant cell astrocytomas in children with tuberous sclerosis: specialized minimal access technique of balloon dilation. Minim Invasive Neurosurg 2006;49:317-20.
12. Easton JB, Houghton PJ. mTOR and cancer therapy. Oncogene 2006;25:6436-46.
13. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipomata in tuberous sclerosis or lymphangioleiomyomatosis. N Engl J Med 2008;358:140-51.
14. Wienecke R, Fackler I, Linsenmaier U, Mayer K, Licht T, Kretzler M. Antitumoral activity of rapamycin in renal angiomyolipoma associated with tuberous sclerosis complex. Am J Kidney Dis 2006;48(3):e27-e29.
15. Morton JM, McLean C, Booth SS, Snell GI, Whitford HM. Regression of pulmonary lymphangioleiomyomatosis (PLAM)-associated retroperitoneal angiomyolipoma post-lung transplantation with rapamycin treatment. J Heart Lung Transplant 2008; 27:462-5.
16. Taillé C, Debray MP, Crestani B. Sirolimus treatment for pulmonary lymphangioleiomyomatosis. Ann Intern Med 2007; 146:687-8.
17. Hofbauer GF, Marcollo-Pini A, Corsenca A, et al. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. Br J Dermatol 2008;159:473-5.
18. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol 2006;59:490-8.
19. Koenig MK, Butler IJ, Northrup H. Regression of subependymal giant cell astrocytoma with rapamycin in tuberous sclerosis complex. J Child Neurol 2008;23: 1238-9.
20. Roach ES, Gomez MR, Northrup H. Tuberous Sclerosis Consensus Conference: revised clinical diagnostic criteria. J Child Neurol 1998;13:624-8.
21. Sabaz M, Lawson JA, Cairns DR, et al. Validation of the quality of life in childhood epilepsy questionnaire in American epilepsy patients. Epilepsy Behav 2003;4: 680-91.
22. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, version 3.0. (http://ctep.cancer.gov.)
23. Clarke MJ, Foy AB, Wetjen N, Raffel C. Imaging characteristics and growth of subependymal giant cell astrocytomas. Neurosurg Focus 2006;20(1):E5.
24. Bruyn GA, Tate G, Caeiro F, et al. Everolimus in patients with rheumatoid arthritis receiving concomitant methotrexate: a 3-month, double-blind, randomised, placebo-controlled, parallel-group, proof-

of-concept study. Ann Rheum Dis 2008; 67:1090-5.
25. Figlin RA, Brown E, Armstrong AJ, et al. NCCN Task Force Report: mTOR inhibition in solid tumors. J Natl Compr Canc Netw 2008;6:Suppl 5:S1-S20.
26. Sánchez-Fructuoso AI. Everolimus: an update on the mechanism of action, pharmacokinetics and recent clinical trials. Expert Opin Drug Metab Toxicol 2008;4:807-19.
27. Franz DN. Rapamycin therapy of neurologic disease in tuberous sclerosis complex. Presented at the National Institute of Neurological Disorders and Stroke Curing Epilepsy 2007 Conference, Bethesda, MD, March 29–30, 2007.
28. Muncy J, Butler IJ, Koenig MK. Rapamycin reduces seizure frequency in tuberous sclerosis complex. J Child Neurol 2009;24:477.
29. Jaworski J, Sheng M. The growing role of mTOR in neuronal development and plasticity. Mol Neurobiol 2006;34:205-19.
30. Lenz G, Avruch J. Glutamatergic regulation of the p70S6 kinase in primary mouse neurons. J Biol Chem 2005;280: 38121-4.
31. Franz DN. mTOR in tuberous sclerosis and other neurological disorders. Epilepsia 2007;48:1630-1.
32. Hoeffer CA, Klann E. mTOR signaling: at the crossroads of plasticity, memory and disease. Trends Neurosci 2010;33:67-75.