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Systematic Review of The Treatment Modalities of Tuberous Sclerosis Complex (TSC) Associated Seizures

Kaylee A. Nelson[1] & Dr. Daniel Coovert[1]

Background

Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic disorder affecting 1 out of every 6,000 live births. Mutations affecting two genes, TSC1 and TSC2 have been identified as causing the disease. TSC1 and TSC2 form a complex responsible for inhibiting the mammalian target of Rapamycin enzyme (mTOR). The mTOR enzymes are part of the Phosphotidylinositol 3 kinase (PI3K) pathway, an important signaling pathway regulating protein synthesis, metabolism and cell growth. Mutations in TSC cause this genetic pathway to be constitutively active, resulting in overgrowth of cells throughout the body. TSC is associated with a significant clinical burden, resource utilization and decreased mental health well-being.1

This disease affects multiple organ systems like the heart, brain, lungs, skin and kidneys. Most notably, the growths in the brain cause seizures. People present with various degrees of severity, making it difficult to properly manage the disease. In the past, most patients with spasms or seizures have been treated with anticonvulsants. 2,3 Elucidation of the PI3K pathway and the genes responsible for TSC have permitted the development of drugs that specifically inhibit mTOR.4 Rapamycin is a macrolide antibiotic produced by a species of fungus called Streptomyces, is the first mTOR inhibitor that has been approved by the FDA for use in TSC. Rapamycin has been branded under the name Everolimus. Everolimus has been studied in more aggressive forms of TSC, but has yet to be recommended as first line treatment or as prophylaxis in patients with TSC. The mTOR inhibitors have shown to be effective in decreasing the symptoms associated with TSC.5

Better treatment options of TSC are needed. Patient groups average 22 visits to a physician, nine procedures/tests, two emergency room visits and two hospital admissions a year.1 Better control or prevention of symptoms could decrease the burden on health care that TSC inflicts. The Tuberous Sclerosis Consensus Conference sets guidelines for the proper diagnosis and management of patients with TSC. Current guidelines recommend surgical resection of acutely symptomatic Subependymal Giant Cell Astrocytomas (SEGAs) and anticonvulsants for infantile spams.6ThemTOR inhibitors have shown to be effective in decreasing the symptoms associated with TSC, however, they are indicated for severe symptoms that cannot be controlled with other treatment modalities. Through a systematic review, Everolimus will be compared with previously used treatments, such as anticonvulsants and surgical resection. The method of action of Everolimus may help to provide better efficacy in reduction of seizure frequency.

Methods

This review will report on all the studies that evaluate the treatment of TSC with one of the following treatment modalities: anticonvulsant therapy, surgical mass removal, or Everolimus therapy. Four databases will be searched: PubMed, Google Scholar, Medline and Web of Science. The Tuberous Sclerosis Alliance website was used for finding background information and ongoing research, but it is not considered a database.

[1] Indiana State University, 200 N 7th St, Terre Haute, IN 47809, USA

Studies will be included if they were written after 1990, used an experimental group of patients, and evaluated the efficacy of the above-mentioned treatment modalities. Patient's seizures must be caused by TSC and cannot have an alternative diagnosis. No case studies were included in this systematic review.

The data extracted from all relevant articles included: the treatment modality that is being evaluated (anticonvulsants, surgery or Everolimus), the number of participants, the number of patients in the control group, the number of patients in the experimental group and the efficacy of the treatment given in a percentage. The information is shown in Table 1.The term "efficacy" is further defined as any patient that demonstrated at least a 50% reduction in seizure frequency from their baseline. There are limits when using these methods to evaluate the efficacy of seizure treatment. A limitation of this review method is the lack of separation between the patients that had complete seizure control versus the patients who only had 50%. They are all considered to be categorized as successful treatment. Also, the data extraction only includes the results from the experimental group. There is no consideration of the lack of response in the control groups. Both studies with or without control groups were included in this systematic review. The strength ofeach studywas not considered. Lastly, some patients in the surgical resection category received >50% improvement in seizure control but with additional anticonvulsant therapy. They were not included in this review. The average percent of efficacy for each treatment modality was calculated and then compared to each other.

Results

From the four databases that were searched, 25 articles were included in the final systematic review. The average number of patients in the control groupswere 50.6. The patients ranged anywhere from 4 to 336. The median number of patients was 22. Quality of studies was not included in this systematic review. The were no restrictions in the number of articles that were included for each treatment modality. Every article was included for each modality that reached the inclusion criteria. At the end of the review 6 out of the 25 articles evaluated anticonvulsant therapy, 10 out of 25 for surgical resection and 9 out of 25 for Everolimus therapy. The results of the percent of efficacy are outlined in Table 2. Treatment was considered to be efficacious if seizures were reduced by >50% from their baseline.

Discussion

Through this systematic review, it was found that anticonvulsant therapy was the most efficacious at 69.3%. With an almost even distribution, it is difficult to determine whether one treatment modality is better than another without a meta-analysis. There is not enough evidence and too many limitations in this review to come to a definitive conclusion. More research is clearly needed to improve the treatment and prophylaxis of TSC.

The limitations of this review include the fact that it did not evaluate the strength of each individual study. An ideal systematic review would assess the use of control groups, significant p-values and number of patients being evaluated. There was a study researching the efficacy of anticonvulsants versus hydrocortisone in the treatment of infantile spasms that yielded a 100% efficacy in this systematic review.7The p-value in this study was found to be significant and it met all of the inclusion criteria. The extreme positive efficacy of this study may have skewed the results in favor of anticonvulsant therapy.

TSC is a difficult disease to treat properly. Patients present with several symptoms and varying degrees of severity. SEGAs are significantly burdensome for patients who suffer from this genetic disorder. They can cause TSC associated seizures and infantile spasms. The enzyme responsible for this overgrowth of specific organs in the body has been identified as mTOR. A novel drug, mTOR inhibitors (Everolimus), has been proven to decrease the size of growths and improve seizures. Everolimus has just become FDA approved for treating acutely presenting SEGAs in the last 5 years. However, infantile spasms are still being treated with anticonvulsants as first line. Many patients have drug-resistant epilepsy and eventually resort to Everolimus as the last option. The goal of this systematic review was to explore the efficacy of Everolimus and how it compared to previously used therapies, like surgical excision of SEGAs or anticonvulsants for infantile spasms. The comparison revealed a slight increased efficacy for anticonvulsant therapy. More clinical trials and research is currently being conducted about Everolimus. Elucidation about its safety and overall efficacy in treating TSC associated seizures will hopefully lead to the more widespread use of this drug from more practitioners.

Table 1.Systematic review of 25 research articles evaluating the efficacy of anticonvulsant therapy, surgical resection or Everolimusin the treatment of TSC related seizures.

Name of Paper	Author	Year	Everolimus	Anticonvulsants	Surgery	# of participants	CG	EG	Results
Everolimus for Tuberous Sclerosis Complex (TSC)	FDA	2010	x			28	0	28	32%
Everolimus for Tuberous Sclerosis Complex (TSC)	FDA	2010	x			117	78	39	34%
Everolimus treatment of refractory epilepsy in tuberous sclerosis complex	Krueger	2013	x			23	3	20	85%
Early control of seizures improves long-term outcome in children with tuberous sclerosis complex	Bombardieri	2010		x		10	0	10	50%
Surgical treatment of epilepsy in tuberous sclerosis: strategies and results in 18 patients.	Guerreiro	1998			x	18	0	18	44%
Epilepsy surgery outcome in children with tuberous sclerosis complex evaluated with alpha-[11C]methyl-L-tryptophan positron emission tom	Kagawa	2005			x	17	0	17	71%
Surgical treatment for epilepsy in cerebral tuberous sclerosis.	Bebin	1993			x	9	0	9	44%
On the surgical treatment of refractory epilepsy in tuberous sclerosis complex.	Baumgartner	1997			x	4	0	4	75%
Surgical treatment for epilepsy in 17 children with tuberous sclerosis-related West syndrome	Liu	2012			x	17	0	17	47%
Epilepsy in children with tuberous sclerosis complex: Chance of remission and response to antiepileptic drugs.	Overwater	2015		x		71	0	71	38%
Levetiracetam as adjunctive antiepileptic therapy for patients with tuberous sclerosis complex: a retrospective open-label trial	Collins	2006		x		20	0	20	40%
Randomized Trial Comparing Vigabatrin and Hydrocortisone in Infantile Spasms Due to Tuberous Sclerosis	Chiron	1997		x		22	11	11	100%
Vigabatrin in the Treatment of Infantile Spasms in Tuberous Sclerosis: Literature Review	Hancock	2014		x		77	0	77	95%
Efficacy and safety of Everolimus in children with TSC - associated epilepsy - Pilot data from an open single-center prospective study	Samueli	2016	x			15	0	15	58%
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study	French	2016	x			336	119	236	70%
Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous	Jozwiak	2011		x		45	31	14	93%
Mammalian target of rapamycin inhibitors for intractable epilepsy and subependymal giant cell astrocytomas in tuberous sclerosis	Cardamone	2014	x			7	0	7	56%
Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis	Krueger	2010	x			28	0	28	75%
Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma	Krueger	2013	x			28	0	28	65%
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.	Franz	2013	x			117	78	39	35%
Surgical resection of subependymal giant cell astrocytomas (SEGAs) and changes in SEGA-related conditions: a US national claims	Sun	2012			x	47		47	25%
Surgical management and seizure outcome in patients with tuberous sclerosis.	Avellino	1997			x	11	0	11	55%
Epilepsy surgery in tuberous sclerosis: a systematic review	Jansen	2007			x	177	0	101	57%
Epilepsy surgery outcome in children with focal epilepsy due to tuberous sclerosis complex.	Karenfort	2002			x	8	0	8	88%
Epilepsy surgery in children with tuberous sclerosis complex: presurgical evaluation and outcome	Koh	2000			x	13	0	13	77%

Table 2. Average efficacy of treatment modalities of TSC associated seizures after reviewing 25 articles.

Treatment Modality	Articles Included	Average Efficacy
Anticonvulsants	6/25	69.3%
Surgery	10/25	58.3%
Everolimus	9/25	56.7%

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