Everolimus as adjunctive treatment in tuberous sclerosis complex-associated epilepsy in children

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ABSTRACT

INTRODUCTION: Tuberous sclerosis complex (TSC) is a rare autosomal dominant multi-organ disease. In TSC, epilepsy is frequent and often treatment refractory. Dysfunction of the tumour-suppressing hamartin/tuberin complex leads to an over-activated mammalian target of rapamycin (mTOR) signalling pathway and uncontrolled cell growth. Protocolled treatment of TSC-associated epilepsy with the mTOR inhibitor everolimus has recently been approved by The Danish Medicines Council in Denmark.

METHODS: Clinical data on the first Danish paediatric patients treated with everolimus for epilepsy and a review of the literature are presented.

RESULTS: Four patients met the inclusion criteria and had been treated for more than 12 months. Onset of epilepsy was at a median age of 1.1 years (range: 0.3-3.3 years) and current age was 3.4 years (range: 2.2-7.4 years). The previous median number of antiepileptic drugs was 5.0 (range: 2-10) and the concomitant median number of antiepileptic drugs was 2.5 (range: 1-4). Several other treatment modalities had been or were still being applied, including ketogenic diet (n = 3), vagus nerve stimulation (n = 1) and epilepsy surgery (n = 2). The number of focal seizures was in the 20-160 range per week before everolimus. All patients had a > 50% seizure reduction after 12 months of everolimus treatment. One patient became seizure free. Side effects were mild and self-limiting.

CONCLUSIONS: Early data on everolimus as an adjunctive treatment in TSC-associated epilepsy are promising with regards to both effect and tolerability.

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Tuberous sclerosis complex (TSC) is an autosomal dominant disease, which in Denmark has an estimated incidence of approximately 5-10/year and a prevalence of 200-400 cases [1, 2]. It is a multi-organ disease with highly variable comorbidity [2]. A history of seizures has been reported in up to 85% of patients. Seizure onset is often seen in the first years of life and up to two-thirds of patients are refractory to antiepileptic medication (AED). Infantile spasms or focal-onset seizures are common seizure types and epilepsy is associated with an increased risk of neuro-developmental disorders like autism spectrum disorder and intellectual disability.

Other TSC manifestations include benign tumours in organs such as the kidneys, brain, heart and skin. The most frequent tumours are renal angiomyolipomas, which are seen in approximately 70% of patients, who also often have cysts and renal functional impairment [3]. Additionally, a benign glioneuronal brain tumour, the subependymal giant astrocytoma, develops in 20% of TSC patients. These patients may have symptoms of increased intracranial pressure due to localisation at the foramen Monroi. Furthermore, in a subset of women with TSC, symptomatic lymphangioleiomyomatosis may evolve, a condition characterised by cystic destruction of the lungs with chylous pleural effusion [2]. The care and follow-up of patients with TSC is multidisciplinary and complex.

TSC is caused by mutations in either the TSC1 gene on chromosome 9 or the TSC2 gene on chromosome 16. In 10-15%, the genetic aetiology escapes detection and diagnosis is based on clinical criteria [4]. Overall, two-thirds of cases result from de novo variants. The variants cause dysfunction of the tumour-suppressing hamartin/tuberin complex that leads to an over-activated mammalian target of rapamycin (mTOR)-signalling (mechanistic target of rapamycin) pathway, resulting in proliferation, angiogenesis and uncontrolled cell growth (**Figure 1**). For many years, mTOR inhibitor treatment has been indicated for treatment of adult TSC patients with renal angiomyolipomas, lymphangioleiomyomatosis and for cerebral subependymal giant astrocytomas in both adults and children [5, 6].

Recent data suggest that treatment with the mTOR inhibitor everolimus is also effective in the treatment of focal-onset epilepsy. Therefore, protocolised treatment of TSC-associated epilepsy with everolimus was approved in 2017 by The Danish Medicines Council. A review of the literature and the progress in the treatment of our first paediatric patients is described herein.

METHODS

Treatment protocol

Patients were followed at the tertiary neuropaediatric

ORIGINAL ARTICLE

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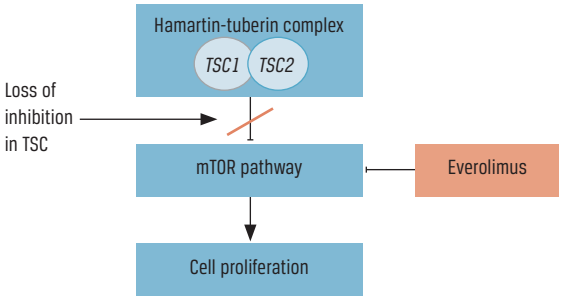
FIGURE 1 / Model of the genetic background for tuberous sclerosis complex with mode of action of everolimus marked.



mTOR = mechanistic target of rapamycin; TSC = tuberous sclerosis complex.

centre at Rigshospitalet by neuropaediatricians CHH or PB and epilepsy nurse CF. Upon approval by The Danish Medicines Council, the patients were screened to validate that they fulfilled starting criteria: a) TSC diagnosis based on clinical or genetic criteria, b) drug-resistant epilepsy based on the criteria from the International League Against Epilepsy, c) non-pharmacological treatment having been considered, including epilepsy surgery, vagus nerve stimulation or a ketogenic diet, d) weekly seizures with substantial impact, d) no contraindications to everolimus, e) expected good compliance. The stop criteria were: a) seizure reduction of less than 33% after four months of adequate serum levels of everolimus, b) seizure reduction of less than 50% after 12 months, c) intolerable adverse events. Drug-resistant epilepsy was therefore defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. The inclusion criteria for the present study were 1) age below 18 years, 2) tuberous sclerosis complex fulfilling either clinical or genetic criteria [3], 3) eligible for everolimus for epilepsy, based on Danish Medicines Council criteria.

Treatment followed recommendations by the manufacturer and experiences made by others [7].

TABLE 1 / Characteristics of the patients treated with everolimus due to refractory epilepsy.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	F	F	M	M
Age[a]	2 yrs 10 mo.s	7 yrs 5 mo.s	3 yrs 6 mo.s	2 yrs 2 mo.s
Genetic aetiology	*TSC2* variant c.5126C>T	No *TSC1/2* variant found	*TSC2* variant c.3125del	*TSC2* variant c.3611-2A>G
Ketogenic diet	Previously	Not possible	Previously	Yes, currently
Vagus nerve stimulation	No	Yes, currently	No	No
Epileptic surgery	Yes, age 10 mo.s	No	Yes, age 2 yrs 6 mo.s	No
Subependymal giant cell astrocytoma	Yes, < 10 mm	No	No	Yes, < 10 mm
Other tuberous sclerosis complex manifestations	Renal angiomyolipoma, delayed development	Renal angiomyolipoma, delayed development, ADHD	Cardiac rhabdomyoma, renal angiomyolipomas, delayed development, autism	Cardiac rhabdomyoma, renal angiomyolipomas, angiofibroma, delayed development
Antiepileptic drugs				
History	OXC, TPM, LEV, ZNS, VGB, CLB	VPA, TPM, LTG, CBZ, LEV, ZNS, VGB, SUL, CLB, RUF	LEV, CLB	Hydrocortisone, LEV, OXC
Current	VPA, RUF, CLB, cannabidiol	ETS, ESL	TPM, VGB, CBZ	VGB
Weekly seizures, n				
Prior to everolimus	140, focal impaired awareness	30, focal impaired awareness Absences: > 50 daily	20, focal impaired awareness	160, focal impaired awareness
After 4 mo.s of adequate p-everolimus level	58	30, focal impaired awareness, shorter duration Absences: 20-40 daily	0	0
After 12 mo.s of adequate p-everolimus level	66	15, focal impaired awareness Absences: 0	0 At 2 occasions febrile status epilepticus	0
Other effects	Positive psychomotor development[b]	Positive psychomotor development[b]	Positive psychomotor development[b]	Positive psychomotor development[b]
Side effects	Self-limiting mild exanthema, stomatitis and diarrhoea	Intermittent mild diarrhoea	Neutropenia during minor infections	None

ADHD = attention deficit hyperactivity disorder; CBZ = carbamazepine; CLB = clobazam; ESL = eslicarbazepine; ETS = ethosuximide; F = female; LEV = levetiracetam; LTG = lamotrigine; M = male; OXC = oxcarbazepine; RUF = rufinamide; SUL = sulthiame; TPM = topiramate; VGB = vigabatrin; VPA = valproate; ZNS = zonisamide.
a) At evaluation of medical records.
b) Not tested clinically but assessed by the parents.

Dosing of the everolimus (Votubia) dispersible tablets was initiated with careful titration as doses that are effective and well-tolerable vary between patients. The starting dose was 5-9 mg/m^2, higher in younger children and if the patients were also being treated with a CYP3A4/PgP inducer. The patients were followed with general annual TSC evaluation consisting of cerebral magnetic resonance imaging (MRI), ultrasound or MRI of the kidneys, ophthalmological and cardiological examination. Prior to treatment and at regular 4-12-week intervals depending on patient tolerability, blood pressure and blood samples were analysed including a full blood count, renal and liver function, fasting glucose and lipid profile. Serum levels of everolimus were analysed after two, six and ten weeks, and when stable every three to six months. Families provided a weekly seizure diary. Adverse events were monitored closely and handled as suggested by Davies et al [7]. In general, the families were advised to seek medical advice in all cases of febrile illness or suspicion of side effects. Everolimus was paused in case of infection and dosage was reduced or stopped in case of adverse events.

Patient characteristics

Four paediatric patients at Rigshospitalet met the criteria for everolimus treatment and have been treated for more than 12 months (**Table 1**). Consent to publication from parents to all patients was obtained. Evaluation of medical records was performed in March 2019.

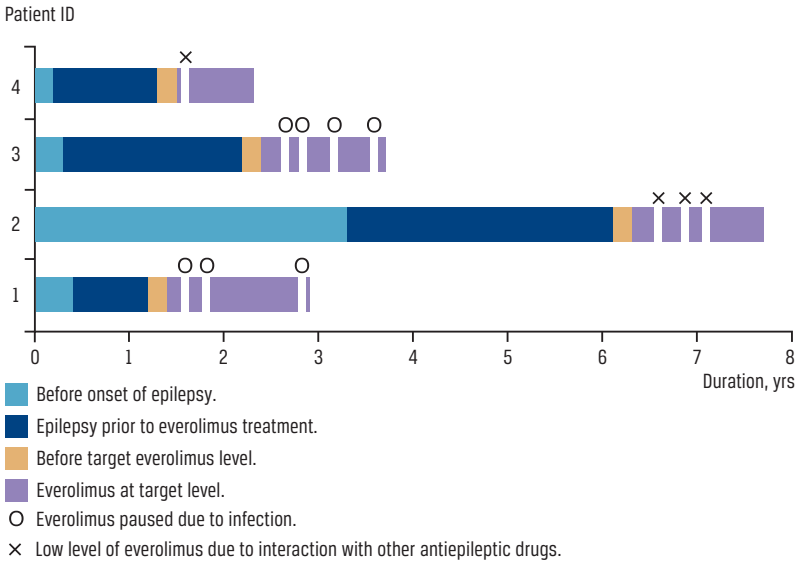
Trial registration: not relevant.

RESULTS

Epilepsy treatment prior to everolimus

The patients with treatment-resistant epilepsy and TSC who were treated with everolimus were two girls and two boys with a median age of 3.4 years (range: 2.2-7.4; Table 1) at the time of data extraction. Onset of epilepsy occurred at a median age of 1.1 years (range: 0.3-3.3 years). The patients had been treated for a period of 0.8 to 2.8 years prior to initiation of everolimus (**Figure 2**). The previous number of AEDs was 5.0 (range: 2-10) and the concomitant current number of AEDs was 2.5 (range: 1-4). One patient had been treated with hydrocortisone for infantile spasms and one patient was being treated with cannabidiol. A ketogenic diet was applied for three patients, of whom two had stopped due to insufficient response. Other concomitant or previous treatment modalities included a nervus vagus stimulator in one patient (patient two treated prior to and during the entire period with everolimus treatment) and epilepsy surgery in two patients, of whom one had a treatment response of Engel class IV (patient one had epilepsy surgery at the age of ten months and had no significant seizure reduction after surgery) and one Engel class II (patient three had epilepsy surgery at the age of two years and six months and thereafter only rarely had disabling seizures – everolimus was initiated three months before surgery).

FIGURE 2 / Timeline of the treatment of patients no. 1-4.



Other tuberous sclerosis complex manifestations

The genetic aetiology for TSC was a pathogenic variant in the TSC2 gene in 3/4 patients. In the final patient, no variant was detected by sequencing of the TSC1 gene and the TSC2 gene, but the patient met the clinical criteria for TSC [2]. In addition to treatment-resistant epilepsy, the patients had other neurological TSC manifestations of delayed development (4/4), autism (1/4) and attention deficit hyperactivity disorder (1/4). No patients had a subependymal giant cell astrocytoma. Other manifestations and symptoms included cardiac rhabdomyoma (2/2), renal angiomyolipoma (4/4), hypertension (1/4) and ungual angiofibroma (1/4).

Everolimus treatment

Initiation of everolimus occurred at a median age of 2.7 years (range: 1.2-6.1 years). Prior to treatment, the patients had 20-160 weekly focal seizures with impaired awareness. One patient also had more than 50 absences daily, which some days were equivalent to absence status epilepticus. Time to reach target level of p-everolimus levels of 5-15 ng/ml was 44-72 days (median 57 days). After having reached this level, the patients had several shorter periods with levels below target due to drug interactions and/or pausing of everolimus because of neutropenia (Figure 2). None of

TABLE 2 / Literature on adjunctive everolimus for treatment-resistant focal onset epilepsy[a].

Reference	Study design	Participants	Seizure effect	AE
Wiegand et al, 2013 [8]	Compassionate use trial case series	7 patients Age 2-12 yrs Everolimus target level 5-10 ng/ml	In 4/6 patients: 25-100% reduction of seizures In 2/6 patients: 0% reduction of seizures	All had AE: increase of mild infections, triglycerides and liver tests 1 patient stopped due to flushing
Krueger et al, 2013 [9]	Prospective, open-label, multicentre, phase 1/2 trial 4 wk observation, 4 wk titration, 8 wk maintenance period	23 participants enrolled, 20 eligible Age 2-21 yrs Everolimus target level 5-15 ng/ml	12 responders, 3 partial responders Overall median seizure frequency decreased by 73%	All participants reported 2-10 AEs All mild
Krueger et al, 2016 [11]	Extension of [9] Participants with effect were followed 48 mo.s	Of the 20 eligible from [9] 18 were enrolled in the extension 14 completed Median age 8.0 yrs	13/14 reported 〉50% reduction in seizure frequency at 48 mo.s	All participants reported ≥ 1 AE 94% were graded mild or moderate
French et al, 2016 [10]	Prospective, randomised, double-blinded phase 3 study, 8 wk observation, 18 wk core phase, 48 wk extension phase, 3 arms: Placebo Low-dose everolimus: 3-7 ng/ml High-dose everolimus: 9-15 ng/ml	432 screened, 366 included 342 followed to extension phase Median age 10.1 yrs, range: 2.2-56.3 yrs	Response rate (median reduction in seizure frequency): 15.1% (14.9%) 28.2% (29.3%) 40.0% (39.6%)	Number (%) of patients with severe grade 3/4 AE: 13 (11) 21 (18) 31 (24)
Samueli et al, 2016 [19]	Open, single-centre, prospective study	18 patients Age 1-18 yrs Everolimus target level 5-10 ng/ml Observation after treatment initiation median 22 mo.s, range: 6-50 mo.s	At last observation 12/15 = 80% of the patients had reduction in seizure frequency of ≥ 50% 7/12 seizure free	Transient AEs seen in 14/15 = 93% of the patients In no case the drug had to be withdrawn
Krueger et al, 2018 [13]	Multicentre retrospective data collection to capture medical record data in infants and very young children	45 patients Everolimus in 87%, sirolimus in 24% Median age 16.1 mo.s 45% treated for refractory epilepsy	No specific data on epilepsy outcome For all indications 29/45 = 64% reported at least partial benefit	≥ 1 AE in 78% Most AEs grade 1/2 in severity, most commonly related to infections 0 life-threatening or death/disability Treatment discontinued due to an AE in 20%
Kilincaslan et al, 2017 [15]	Retrospective medical record data analysis	6 patients Median age 16.5 yrs Everolimus target level 5-15 ng/ml Follow-up 17.5 mo.s, range: 7-26 mo.s	All cases very good-moderate response for controlling epileptic seizures, 30-90% seizure reduction	The drug well tolerated with mild AE, including stomatitis Increase in levels of triglycerides, cholesterol, constipation
Franz et al, 2018 [12] al,	Post hoc analysis of EXIST-3	After completion of the core phase, patients could enter an open-label extension phase and receive everolimus for ≥ 48 wks, target exposure, 3-15 ng/ml	Response rate ≥ 50% reduction: 31% (n = 352) at wk 18 46.6% (n = 298) at 1 yr 57.7% (n = 163) at 2 yrs	Incidence of grade 3/4 AEs, any cause: 40.2% 13% discontinued because of AEs 2 deaths suspected to be treatment-related: pneumonia and septic shock

AE = adverse event.

a) Multiple adverse events have been reported in the publications listed. Only a subset is described here. Single-case reports are not included.

the patients reached a stop criterion with regard to the seizure control. Patient 1 had reduction of the number of weekly focal seizures with impaired awareness from 140 per week prior to everolimus to 58 and 66 per week after four and 12 months, respectively. Patient 2 experienced a reduction in focal seizures from 30 per week prior to everolimus to 15 per week, and the multiple absences were absent after 12 months of treatment. Patient 3 experienced 20 focal seizures per week prior to treatment and had concomitant epilepsy surgery at the time of everolimus initiation due to severe deterioration of development due to seizures. In the 12 months after everolimus initiation, the patient had none of the previous focal seizures but on two occasions the patient during fever and infection had status epilepticus. Patient 4 had 160 focal seizures per week prior to everolimus and has become seizure free at the time of data extraction – and has remained without seizures for a period of 15 months (Table 1). Adverse events were mild and self-limiting and included exanthema, stomatitis, diarrhoea and neutropenia. All families reported positive psychomotor development.

DISCUSSION

Since protocolled treatment with mTOR inhibitor everolimus of treatment-resistant epilepsy in patients with TSC became possible in Denmark in 2017, a total of ten patients have initiated treatment. Four of these patients have been treated more than 12 months and the results for these patients are presented here. The

patients were young and had been treated with multiple drugs and non-pharmacological approaches prior to everolimus initiation. They had many seizures weekly and all fulfilled the criterion that was a requirement from The Danish Medicines Council, i.e., that a more than 50% seizure reduction was seen after 12 months of treatment. The effect of everolimus on our patients is described. Nevertheless, it should be taken into account that the patients had other concomitant modalities, which continued, were adjusted for or initiated during the course of everolimus treatment. To which degree the treatment effect is, in fact, owed to everolimus is difficult to ascertain. Adverse events were mild and self-limiting, and families experienced a positive effect on psychomotor development.

The first papers on everolimus with a focus on epilepsy were the case series by Wiegand et al [8] and the phase 1/2 study by Krueger et al [9]. The highest degree of evidence was contributed by the EXIST-3 study, which was a randomised, double-blind phase 3 multicentre study describing adjunctive everolimus in TSC patients with refractory epilepsy. The patients received 1-3 AEDs and were randomised to low (3-7 ng/ml) or high (9-15 ng/ml) serum levels of everolimus or placebo. The median age was 10.1 years. The median seizure frequency prior to treatment was 35, 38 and 42 seizures per 28 days, respectively. There was a significant seizure reduction with median seizure reduction rates of 29.3% and 39.6% as compared to 14.9% in the placebo arm after 18 weeks of treatment [10].

A long-term effect was described by Krueger et al in the 2016 extension study of the prospective, open-label study by Krueger et al from 2013. Participants with effect in the initial study were followed for 48 months and of the 14 who were treated for the full period, 13 reported a > 50% reduction in seizure frequency [11]. Extension data from the EXIST-3 study have recently been published, describing 366 patients in the extension phase [12]. At weeks 42, 54 and 66 of treatment, the median seizure reduction was 42.2%, 41.3% and 43.5%, respectively, as compared with baseline. The safety and tolerability for patients receiving everolimus for epilepsy was similar to that for patients receiving everolimus for benign tumours. In the EXIST-3, the most frequently reported adverse events were stomatitis, diarrhoea, mouth ulceration, nasopharyngitis, upper respiratory tract infection and fever. Discontinuations due to adverse events were low in the EXIST-3 study, where adverse events causing treatment discontinuation were seen in two (2%) patients in the placebo group versus six (5%) in the low-exposure group and four (3%) in the high-exposure group. Hyperlipidaemia and neutropenia were the most frequent adverse events in blood. Standard recommendations therefore suggest that everolimus be paused during infection and do not advise concomitant treatment with a ketogenic diet. In one of our patients, neutropenia occurred frequently even during mild infections and in another patient a ketogenic diet was also used, but lipids remained at the same levels as before everolimus. The response rate with a ≥ 50% reduction after one year of treatment was 46.6% (n = 298 patients completed this length of treatment), and 57.7% (n = 163) at two years. In this very long-term follow-up, more adverse events were seen. The incidence of grade 3 and 4 adverse events was 40.2% and 13% of patients discontinued due to an adverse event. Two deaths were suspected to be treatment-related (pneumonia and septic shock).

In a recent publication, focus was on very young children who were not included in the EXIST-3 study. A total of 45 patients with a median age of 16.1 months were treated with either everolimus (87%) or sirolimus (24%). Indication for treatment was refractory epilepsy in 45%. For all indications, 29/45 (64%) reported at least partial benefit. Treatment was discontinued due to an adverse effect in 20% [13].

Other smaller series and case reports have been published reporting findings comparable to those of the larger series [14-19] (**Table 2**). With regard to quality of life, there are indications of improved quality of life with increased seizure control [20].

Early data on everolimus as an adjunctive treatment in TSC-associated epilepsy is promising with regards to both effect and tolerability. Protocolised treatment or close monitoring of efficacy and side effects is warranted.

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