Everolimus for the Treatment of Subependymal Giant Cell Astrocytoma Probably Causing Seizure Aggravation in a Child with Tuberous Sclerosis Complex: A Case Report

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Abstract

We are reporting on a 13.5-year-old girl with tuberous sclerosis complex (TSC) who was treated with everolimus because of giant cell astrocytoma and bilateral angiomyolipoma. She suffered from pharmacoresistant partial epilepsy with clusters of tonic and tonic–clonic seizures. Treatment with carbamazepine and sulthiame had led to a stable situation for more than 2.5 years. The dosage of everolimus had to be increased and refractory status epilepticus followed after 12 days. In the absence of any other possible cause, we believe that the status epilepticus was provoked by everolimus. So far, only a few cases of possible seizure aggravation by everolimus have been reported. The clinical relevance of possible negative effects in epileptic patients remains unclear. Similar observations should be documented and reported.

Keywords
► tuberous sclerosis complex
► subependymal giant cell astrocytoma
► everolimus
► seizure aggravation

Introduction

Everolimus is an inhibitor of mTOR [mammalian target of rapamycin], which is responsible for the various clinical manifestations of tuberous sclerosis complex (TSC). In November 2011, it was approved in Europe for the treatment of subependymal giant cell astrocytoma (SEGA) in patients older than 3 years. Approval for treating angiomyolipoma (AML) followed in November 2012. Everolimus is a derivative of rapamycin (sirolimus) with favorable pharmacokinetic characteristics. In TSC, rapamycin leads to a significant reduction in volume of SEGA.1 The EXIST-1 study (Examining everolimus in a study of TSC) revealed a comparable efficacy of everolimus in the treatment of SEGA, which led to a reduction of volume of at least 50% in 35% of the patients.2 In addition to this intended effect on SEGA, seizure reduction was observed in a remarkable number of patients who were treated with everolimus.1,3 However, this observation was not confirmed when analyzing the EXIST-1 study population.4 Seizure aggravation was observed in 3 of 36 patients in 2 controlled clinical phase I/II trials.3,5 So far, it is not clear whether seizure aggravation may be related to everolimus therapy.

We are reporting on a 13.5-year-old girl suffering from TSC-2 manifested in brain, skin, and kidneys. We believe that in this case everolimus caused a significant increase in seizure frequency and severity leading to status epilepticus.

Case Report

Focal seizures started at the age of 9 months and TSC was diagnosed immediately after the onset of epilepsy. Subsequent antiepileptic treatment with phenobarbital (PB), valproate, ethosuximid, clobazam, oxcarbazepine, phenytoin, topiramate, clonazepam, lamotrigine, levetiracetam, lorazepam, bromide, mesuximid, zonisamide, sulthiame, and carbamazepine did
not control the seizures. Ketogenic diet led to a significant seizure reduction, but it was not tolerated.

In April 2009, the girl was treated with a combination of sulfathione (STM) and carbamazepine (CBZ) in stable doses. With this treatment, she had clusters of tonic and tonic-hypertonic seizures that lasted for 2 to 3 days, occurring every 2 weeks. Rescue medication was administered regularly and reliably stopped the clusters of seizures. Antiepileptic treatment was not varied because of a stable balance of some seizure reduction and tolerance with respect to her psychological condition. The girl was alert and able to concentrate. She was in a good mood, which was an important factor for the family’s quality of life.

Magnetic resonance imaging (MRI) detected a growth of a known AML in both the kidneys in February 2009. In September 2010, an MRI revealed multiple AML with a huge lesion in the left kidney (diameters, 4 × 4 × 4.8 cm). Therefore, a partial left-sided nephrectomy was performed in April 2011, along with the histopathology of epithelioid-cellular AML. In November 2011, an already known SEGA near the foramen Monroi was found to have grown (size, 0.9 × 0.7 × 0.6 cm on MRI). Ventricles were still small and there were no signs of disturbed circulation of cerebrospinal fluid.

Because of the combination of growing SEGA, the AML (maximum diameter 2 cm) and disabling seizures, treatment with everolimus was initiated on January 15, 2012. Dosage of CBZ (1,000 mg/d, serum level 10.8 µg/mL) and STM (150 mg/d, serum level 1.5 µg/mL) remained unchanged. Everolimus was started with a daily dose of 2.5 mg (body weight 39.6 kg, length 146 cm, body surface 1.2 m²) and was well tolerated.

Because of low everolimus serum concentration (0.96 µg/L; reference range, 5–15 µg/L), the dose was doubled beginning on the February 8, 2012. A mild mucositis with four little blisters was accompanied by some sleep disturbance on three consecutive nights. A cluster of severe seizures that did not respond to rescue medication started on the February 21, 2012. Initial seizures in the first night were tonic-clonic and were followed by prolonged tonic seizures which increased in duration and frequency on the second night. No effects were shown with application of 10 mg clobazam by mouth or orally and two doses of 20 mg diazepam administered rectally. The patient was admitted to the hospital on the February 23, 2012. She was experiencing tonic seizures of 30 to 90 seconds duration occurring every 3 to 5 minutes without regaining consciousness in between. The electroencephalogram (EEG) showed marked slowing and repetitive ictal amplitude decrement with fast tonic seizure patterns. Intravenously administered diazepam (10 mg), clonazepam (2 mg), and levetiracetam (50 mg/kg) did not stop the status. PB was introduced with a cumulative loading dose of 600 mg intravenously, and the therapy was continued with 100 mg/day by mouth or orally (serum level 32 µg/mL). An MRI of the brain revealed no significant changes compared with the previous findings, that is, no enlarged ventricles. Lumbar puncture and routine laboratory tests were normal without any signs of inflammation. An X-ray of the chest was normal. CBZ serum level was 12.4 µg/mL and remained stable after 2 days (12.2 µg/mL). The serum level of everolimus was 1.6 µg/L on February 21, 2013.

Because of a recent report of possible seizure aggravation by everolimus we decided to stop the everolimus therapy. It was our impression that everolimus may have provoked the status epilepticus because it was a completely unexpected event. The seizure situation had been stable for more than 2.5 years and the patient never had experienced status epilepticus before. Usually, rescue medication had stopped clusters of seizures even in the context of febrile infections. The series of seizures stopped 4 days after the onset of the status and ended immediately after PB intervention. Only a few tonic seizures followed within the next 2 days, which stopped 1 day after withdrawal of everolimus. The patient was discharged after 2 days with a combination therapy of PB, CBZ, and STM. The PB medication was stopped after several months without a second episode of status epilepticus.

### Discussion

Although not proven, we felt that increasing of the everolimus dose was the only reasonable trigger for the refractory status epilepticus in this case. There was no evidence of inflammation, increased intracranial pressure, or drug interactions. Sleep deprivation caused by pain because of a mild mucositis may have played a minor role. However, this was the first status epilepticus in the patient’s entire life despite many previous febrile infections. The everolimus dose had been doubled 12 days before the onset of status epilepticus, but a total dose of 5 mg/day and a serum level of 1.6 µg/L were still comparably low. The end of the status was associated with stopping everolimus treatment, but PB may have played the major role in ending the status. However, PB was stopped after several months without a relapse of severe disabling seizures.

Krueger et al. reported data on the effects of everolimus on seizure activity in patients from a prospective open-controlled multicenter phase I/II trial. Of the 20 patients, 12 patients had their seizures reduced by more than 50%, and 4 of them became seizure free. Seizure aggravation was observed in 2 patients. In a prospective, open-label, phase 1–2 study for the treatment of SEGA, Krueger et al reported seizure aggravation documented by 24-hour video EEG in 1 of 16 patients. In both the cases, exact temporal relation of everolimus administration and seizure aggravation was not reported.

Kotulka et al. found no cases of seizure aggravation in eight children younger than 3 years who participated in the EXIST-1 study. Of these eight patients, three patients were seizure free before everolimus was started. One child suffered from daily partial seizures and became seizure free. Two children experienced a seizure reduction of at least 50%. One patient had a transient seizure reduction during the first year of treatment. Finally, seizure frequency remained unchanged in the last child. The authors found no patient who experienced seizure aggravation.

In general, provocative effects have been described for almost all conventional antiepileptic drugs. Thus, seizure aggravation by everolimus may be a rare complication. In
conclusion, the occurrence of severe status epilepticus was potentially related to the everolimus therapy in our patient. Similar observations in both clinical routine and controlled trials should be reported to estimate the general relevance of possible seizure aggravation in individual cases with TSC treated with everolimus. The European database project “TOSCA” starting in 2013 should help to answer this question.

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References