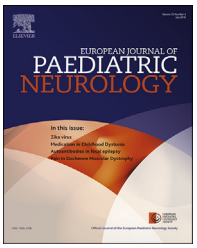
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2017) 1–4

Official Journal of the European Paediatric Neurology Society



Case study

Dramatic relapse of seizures after everolimus withdrawal

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ARTICLE INFO

Article history:
Received 22 July 2016
Received in revised form
14 February 2017
Accepted 25 July 2017

Keywords:
Everolimus
Subependymal giant cell astrocytoma
SEGA
Tuberous sclerosis complex
Epilepsy
mTOR inhibitors

ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystemic disorder caused by deregulation of the mTOR pathway, and represents one of the leading genetic causes of epilepsy.

mTOR inhibitors (Sirolimus and Everolimus) are currently approved only for the treatment of growing subependymal giant cell astrocytomas, renal angiomyolipomas and lymphangioleiomyomatosis in TSC. However, preclinical and clinical evidence supports their potential role in effectively treating TSC-associated epilepsy, but no consensus on its use in seizures has been reached yet and there are few data on epilepsy outcome after the suspension of mTOR inhibitors treatment. We report for the first time on a patient in whom discontinuation of Everolimus (prescribed for growing subependymal giant cell astrocytomas) was associated with a relapse of seizures twice, and control of seizures was regained after reintroducing the medicine. This clinical report supports the promising potential of Everolimus in treating epilepsy in TSC, and specifically underlines the non-permanent effect on seizures after withdrawal.

1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 6000 live births. It is characterized by development of benign tumors in the brain, eyes, heart, lungs, kidneys, and skin,[1] and represents one of the leading genetic causes of epilepsy. Seizures are present in about 85% of patients, and are often refractory to antiepileptic treatment.[2] TSC is caused by inactivating mutations of *TSC1* or *TSC2*, which lead to

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http://dx.doi.org/10.1016/j.ejpn.2017.07.018
1090-3798/

hyperactivation of the mammalian or mechanistic target of rapamycin complex (mTOR) pathway with consequent uncontrolled cell growth and metabolism, eventually impacting epileptogenesis as well. mTOR inhibitors (Sirolimus and Everolimus) in TSC are currently approved by the US Food and Drug Administration or the European Medicine Agency only for the treatment of growing subependymal giant cell astrocytomas (SEGAs), renal angiomyolipomas, and lymphangioleiomyomatosis. However, preclinical and clinical evidence supports the potential role of mTOR inhibitors in effectively treating TSC-associated epilepsy,[1,3–5,7] but no consensus on its use in seizures has been reached yet. We present herein a patient treated with Everolimus for SEGA, who had a dramatic relapse of seizures after suspension of the treatment.

2. Case study

We present the case of a 15-year-old girl with TSC whose diagnosis was established in childhood after seizure onset. Pregnancy and delivery were unremarkable. Psychomotor development and neurologic evaluation were normal. Neuropsychological assessment showed borderline IQ with mild attention deficit disorder.

At age 5 years she started to have focal seizures, mostly during sleep or on awakening, characterized by loss of consciousness, drooling, oro-buccal automatisms, generalized stiffening and cyanosis. EEG showed focal interictal discharges over the right fronto-temporal region.

Besides neurological involvement, the patient presented with several features of TSC enabling the diagnosis: facial angiofibromas, a fibrous cephalic plaque, a lower back Shagreen patch, ungual fibromas, millimetrical and asymptomatic renal angiomyolipomas. The diagnosis was subsequently made also in the father and in the older brother. Genetic test detected a mutation in *TSC1* (c.982C>T p.Gln328*). Seizures were promptly controlled with Vigabatrin (1000 mg/day), and she remained seizure-free for the following years.

Brain MRI evidenced multiple cortical and subcortical tubers, white matter radial migration lines, subependymal nodules and a SEGA located near the right foramen of Monro, slowly growing at the serial MRI controls.

At age 12, after informed consent and ethics committee approval, the patient was offered Everolimus treatment of 10 mg/day, first enrolled in the EFFECTS study than as compassionate use at the end of the study. After 6 months of treatment the diameter of the tumor on brain MRI had decreased from 18 mm × 15 mm × 10 mm to 12 mm × 13 mm × 8 mm (corresponding to 30% volume reduction, Fig. 1). The patient continued to be seizure free, with no changes in antiepileptic treatment. No severe adverse events were noted, except for mild stomatitis and hypercholesterolemia after 3 months of treatment, which resolved with hypolipidic diet. Tumor size was stable on serial MRIs. Everolimus was withdrawn 27 months after introducing it. The patient started to present seizures with the same semiology 30 days later (loss of consciousness, drooling, oral-automatism and enuresis), and the MRI performed 4 month later showed an increased volume of the SEGA (19 mm × 17 mm × 14 mm). Treatment with Everolimus was restarted as compassionate use at the same dose (10 mg/day), and seizures were controlled at the first administration of Everolimus with no changes in AEDs.

One year after Everolimus reintroduction, the patient was admitted for a severe gastroenteritis associated with increase of liver enzymes (AST 107 UI/L, ALT 103 UI/L, GGT 136 UI/L, and ALP 266 UI/L), so therapy with the mTOR inhibitor was temporarily withdrawn for 10 days. The first day after suspension and during the following days, the patient experienced seizure relapse. Everolimus was restarted after 10 days at the resolution of gastroenteritis, but even increasing the antiepileptic therapy (Vigabatrin 2000 mg/day), seizures persist, although at a lower frequency. Brain MRI performed at 1 and 4 months after reintroducing Everolimus showed a stable decrease in volume of the SEGA (14 mm × 12 mm × 9 mm).

3. Discussion

The mTOR signaling pathway is intricately involved in multiple cellular functions including protein synthesis, cell growth and proliferation, and synaptic plasticity, which may influence neuronal excitability and precipitate epileptogenesis.[1] Everolimus is an mTOR inhibitor approved for treatment of TSC-associated SEGAs that cannot be surgically resected, and was used in our patient with such indication.

Although not approved for epilepsy, mTOR inhibitors have shown promising results as potential anti-seizure agents in animal models, including reducing seizures and improving learning and autistic behavior. Moreover, a number of reports and clinical trials have demonstrated significant reduction in seizure frequency in patients with TSC who were treated with mTOR inhibitors.[1]

In an open-label, single-center case series of seven patients with TSC and drug resistant epilepsy treated with Sirolimus, seizure freedom was obtained in two patients for at least 6 months and in one patient for 12 months, followed by >90% reduction in seizures thereafter.[6]

In a phase I/II trial of Everolimus for drug resistant, partial-onset seizures in TSC, 17 out of 20 patients experienced a clinically meaningful and statistically significant reduction in seizure frequency after 12 weeks of treatment, with an overall median decrease in frequency of 73% ($P < 0.001$) and a median 70% decrease in cumulative seizure duration ($P = 0.020$).[4] Four out of 20 patients were seizure-free after treatment for 12 weeks, mostly at the end of the maintenance phase.

Recently, data have been published on the final 5-year extension of a prospective open-label study of patients with TSC and evidence of serial growing SEGA treated with Everolimus. The proportion of patients experiencing seizures on a daily basis decreased from 26.9% (7 of 26) at baseline to 11.1% (2 of 18) at month 60. The proportion of patients who were seizure free steadily improved over the first 18 months of treatment, and was maintained over time thereafter.[3]

In addition, there are a few other single reports of seizure-free patients after treatment with Everolimus at variable times, ranging 6 weeks–9 months.[1,3]

More recently, the results of a multicenter phase 3, randomized, double-blind, placebo-controlled study on

Please cite this article in press as: Mingarelli A, et al., Dramatic relapse of seizures after everolimus withdrawal, European Journal of Paediatric Neurology (2017), http://dx.doi.org/10.1016/j.ejpn.2017.07.018