Possible Prevention of Tuberous Sclerosis Complex Lesions

**Abstract**

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by mammalian target of rapamycin (mTOR) activation and growth of benign tumors. Some TSC lesions, such as cardiac rhabdomyomas and cortical tubers in the brain, occur in fetuses, and some, such as renal angiomyolipomas (AMLs) and skin angiofibromas, develop over years. Recently, the mTOR inhibitor everolimus was shown to be effective in the treatment of subependymal giant cell astrocytomas (a brain tumor) and renal AMLs (kidney tumors) in TSC patients. We present monozygotic twin sisters affected with TSC. Since age 4 years, 1 of the sisters has been treated with everolimus; the other sister received no mTOR inhibitor treatment. After 24-month follow-up, everolimus treatment resulted in a significant brain tumor volume decrease in the treated twin. This child presents no facial angiofibroma, and no renal AMLs. The brain tumor in the nontreated sister is stable in size, but in the meantime, she has developed significant facial angiofibroma and renal AMLs. This observation indicates that early mTOR inhibition in TSC patients may prevent the development of TSC lesions and alter the natural history of the disease. *Pediatrics* 2013;132:e239–e242
Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the development of hamartomas in various tissues and organs: skin, brain, kidneys, heart, lungs, liver, eye, and others. Some of the TSC-related lesions, like cardiac rhabdomyomas and cortical tubers, may be detected in fetuses and newborns, whereas others, like renal angiomyolipomas (AMLs) and various skin lesions, develop over years. Cardiac rhabdomyomas and cortical tubers are seen in 80% to 90% of TSC patients. Hypomelanotic macules can be identified in newborns, and their number usually increases with age. Facial angiofibroma (AF), which has been recognized as a hallmark of TSC, usually becomes visible at preschool age. Renal AMLs are found in 16% of children aged <2 years, 42% of children between 2 and 5 years of age, and in 70% to 90% of adults with TSC. Subependymal giant cell astrocytoma (SEGA) is a rare low-grade brain tumor occurring almost exclusively in TSC patients and affecting ~15% of them. SEGAs usually develop in the first 2 decades of life, and in children and adolescents with TSC, they present the major cause of morbidity and mortality.TSC is caused by the mutation in either of 2 genes: TSC1 or TSC2, with one-third of cases being familial and two-thirds of cases resulting from sporadic mutations. The clinical picture of patients carrying TSC2 mutation is generally more severe than in TSC1 mutation cases. TSC2 disease is associated with higher incidence of epilepsy, mental retardation, subependymal nodules, kidney AMLs, and facial AF, and most symptoms develop earlier in TSC2 than in TSC1 patients. Recently, mTOR inhibitors (eg, rapamycin and everolimus) were introduced to the treatment of SEGAs associated with TSC. The EXIST-1 (Everolimus in the Treatment of SEGAs associated with Tuberous Sclerosis Complex) trial showed that everolimus reduced the size of SEGA volume in TSC patients, and based on these results, everolimus was approved by the European Medicines Agency and the US Food and Drug Administration for the treatment of TSC-associated SEGA.

Here we report the impact of 2-year everolimus treatment on TSC manifestations in a 4-year-old girl compared with the natural history of TSC in her nontreated twin sister. The study was approved by the Ethics Committee at the Children’s Memorial Health Institute, Warsaw, Poland.

CASE REPORT
Monozygotic twin girls (ZU and JU) were referred to our hospital at the age of 2 years for drug-resistant seizures. They were born to a 30-year-old healthy mother and a 31-year-old healthy father. The couple already had 1 healthy daughter, and there was no contributory family history. Both girls developed infantile spasms at age 4 months. Due to multiple cardiac tumors, multiple hypomelanotic macules, and periventricular calcifications seen on CT scans, they were diagnosed with TSC at age 4 months. On admission, the girls presented with significant psychomotor retardation and autistic features. The girls were nearly identical, and both had small forehead plaques and multiple hypomelanotic macules. The only differences were the locations of hypomelanotic macules, and hip and femoral bone malformation in 1 twin (ZU). Their weight and height were the same. In both girls, seizures were controlled with 3 antiepileptic drugs: vigabatrin, topiramate, and valproic acid. The same missense mutation in TSC2 gene (T to C at position 2129 in exon 19) was found in both sisters.

Neuroimaging studies revealed multiple cortical and subcortical tubers in both girls. They also had SEGAs located in the lateral ventricles of the brain. In 1 of the girls (ZU), serial MRI showed SEGA growth; the second twin had no previous

FIGURE 1
A, Twin sisters’ (ZU and JU) faces at age 4 years: no facial AF. B, Twin sisters faces at age 6 years, 3 months: prominent facial AF in the child who was not treated with everolimus (JU) and no AF in her sister, treated with everolimus for the previous 2 years (ZU).
MRI available to establish the growth of the tumor.

At age 40 months, after informed consent from the parents, twin ZU was included in EXIST-1 trial. Her sister did not take part in the study because she had no demonstrated serial lesion growth, which was required for trial entry. For the first 8 months, ZU has been receiving placebo, and then at age 49 months, after the study had been unblinded, she was offered everolimus, which she continues on now at 27 months of therapy. At age 49 months, neither twin presented with facial AFs (Fig 1A), kidney ultrasound did not reveal AML, and the volume of SEGAs was similar in both sisters. They were both seizure free on 3 antiepileptic drugs.

By protocol, everolimus was administered orally once daily. The starting dose of the medication was 4.5 mg/m² and was subsequently adjusted to attain blood everolimus concentration of 5 to 15 ng/mL. The dose was also modified when treatment-related toxic effects occurred. Our patient experienced grade 3 stomatitis and decreased plasma fibrinogen, so the dose was reduced to 3.38 mg/m² daily. We have also observed mild hyperlipidemia, which did not require intervention. After dose reduction, the patient tolerated everolimus well.

Both sisters underwent comprehensive follow-up examinations at age 6 years, 3 months. Brain MRI revealed >50% reduction in SEGAs volume in the treated child and stable SEGAs volume in her nontreated sister. Kidney ultrasound remained normal in the treated child, whereas, in her nontreated twin, it revealed multiple AMLs ranging up to 7 mm in the right kidney and 6 mm in the left kidney as well as small cortical cysts (Fig 2). Skin examination revealed prominent facial AF only in the nontreated child (Fig 1B). Both girls received the same 3 antiepileptic drugs and were seizure-free throughout follow-up.

Comparing the serial weight and growth measurements in both children, no impact of everolimus treatment on growth rate was evident. The girls were growing and gaining weight at the same rate observed before everolimus introduction.

**DISCUSSION**

We report 2 twin sisters with identical TSC2 mutation in whom the initial development of TSC lesions was concordant and then significantly changed by everolimus treatment in 1 twin. The nontreated child developed multiple renal AMLs, kidney cortical cysts, and prominent facial AFs, whereas these lesions did not occur in her treated sister. There are few reports on TSC natural history in twins. Most of these reports show the variability in cognitive and behavioral symptoms of the disease, indicating the important role of epilepsy in the development of mental retardation in TSC patients. Hamartomas affecting organ systems, including renal AML and facial AF, however, were shown to appear at a similar age. Most TSC-associated hamartomas develop consistently with the so-called 2-hit model, in which lesion formation depends on the combined effects of germline and somatic mutations in TSC1 or TSC2 genes. Variable expressivity of disease symptoms and signs may be attributed to the chance second hits but are unlikely to the degree observed in our patients. It should also be kept in mind, that by age 6 years, the vast majority of patients with TSC2

![Figure 2](image_url)

**FIGURE 2** Renal ultrasound performed at age 6 years, 3 months. A, In the treated twin (ZU), ultrasound is normal. B, In the nontreated sister (JU), multiple AMLs as well as cortical cysts are visible.
mutations usually present with facial AF and renal AML.\textsuperscript{2,3}

We believe that the differences between the 2 sisters reported here can be ascribed for the most part to mTOR inhibition in 1 twin. The efficacy of mTOR inhibitors in children with TSC-associated SEG\textsubscript{A} is well documented, but its impact on the natural history of the disease has never been shown in humans.

Given that many TSC signs and symptoms result from organ and tissue malformations caused by the mTOR overactivity during early life, the possible use of an mTOR inhibitor for the prevention of TSC-associated lesions seems reasonable. However, to date there are only limited data from animal models supporting this approach. Early treatment with rapamycin prevented the development of epilepsy and underlying brain abnormalities associated with epileptogenesis as well as premature death in mouse models of TSC.\textsuperscript{10,11}

Despite these promising findings that support a preventative approach, it is important to note that the rapamycin-treated mutants developed enlarged brains with more brain cells, displaying marked running and developmental delay.\textsuperscript{10,12}

In our patient, everolimus treatment was well tolerated overall. The only treatment-related toxicity was grade 3 stomatitis and, possibly, decrease in plasma fibrinogen, which normalized after dose reduction. The possible impact of mTOR inhibitors on the physical development of young children poses a major concern, however. Growth inhibition has been reported in kidney-transplanted pediatric patients receiving sirolimus.\textsuperscript{13} In our case, the rate of height and weight gain was not changed by treatment. However, the long-term effect of everolimus on physical development of TSC patients is not known. Reported side effects of everolimus include stomatitis and mouth ulcerations, infections (primarily nasopharyngitis and upper respiratory tract infections), secondary amenorrhea, and laboratory abnormalities, including increased level of cholesterol and decreased white blood cells count.\textsuperscript{14}

Long-term therapy with everolimus with median treatment duration of nearly 3 years has not indicated any additional safety concerns.\textsuperscript{5,14} However, the longer follow-up reports are not available, and the data on the safety of everolimus treatment in children are limited.

Our patient derived a clinical benefit beyond reduction of SEG\textsubscript{A} tumor volume; renal AMLs and facial AFs appear to have been prevented from developing or at least delayed. Taken together, our case indicates that early mTOR inhibition in TSC patients may serve as a preventative measure and alter the natural history of the disease.

REFERENCES

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