

Case Report

Sirolimus in Infants with Multiple Cardiac Rhabdomyomas Associated with Tuberous Sclerosis Complex

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Keywords

mTOR inhibitors · Sirolimus · Tuberous sclerosis complex · Cardiac rhabdomyomas · Subependymal giant cell astrocytomas

Abstract

Introduction: Cardiac rhabdomyomas represent a frequent manifestation of tuberous sclerosis. Tumor growth, mainly prenatally, can result in intrauterine fetal or neonatal deaths in almost 10% of patients. **Case Report:** We treated 3 consecutive infants aged less than 12 months with sirolimus, an oral mTOR inhibitor. All patients achieved significant reductions in cardiac rhabdomyomas. A complete response was documented in 2 patients, while a partial response with tumor debulking greater than 50% was seen in the other one. The median time to best cardiac response was 1.9 months in all patients, and 3.3 months in those with complete response. The side effects profile was acceptable. **Conclusion:** Sirolimus may have a significant role in promoting natural regression of cardiac rhabdomyomas. Prospective clinical trials are needed.

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Introduction

Tuberous sclerosis complex (TSC) is a rare autosomal dominant syndrome, with variable penetration, characterized by the presence of benign, noninvasive, tumor-like lesions (hamartomas) in the brain, heart, skin, kidney, lung, and liver [1].

Around 60% of children with TSC have been reported to have cardiac rhabdomyomas (CRs) [2]. It is known that CRs may regress spontaneously, although the regression mechanism is not yet well understood. Partial regression of the CRs has been reported in 50% of cases and complete resolution in 18% [3]. CRs have the potential for severe cardiac complications, usually observed in fetal life or the early neonatal period. Complications can be due to obstruction of the intracavitary space and/or valvar orifices, involvement of the conduction system, with first through third atrioventricular block, or generating the substrate for atrial or ventricular tachycardia. These complications can cause low cardiac output, congestive heart failure, and even sudden death. The mortality rate of cardiac complications is 9.5% [4].

The central nervous system manifestations of TSC include subependymal giant cell astrocytomas (SEGAs), epilepsy, intellectual disability, and autism [5]. In some cases, SEGAs require resection, particularly if they cause obstructive hydrocephalus [6]. However, if not completely resected, SEGAs have a propensity to grow back.

Recently, oral mammalian target of rapamycin (mTOR) inhibitors demonstrated an activity in patients with TSC, in terms of reduction of SEGAs volume and improved control of seizures in patients with intractable epilepsy [7–10]. Currently, there are no clinical studies in infants (0–36 months), and in particular in those aged less than 12 months. Moreover, some case reports suggest a hypothetical activity in CRs [11–14]. The aim of our study was to evaluate the safety and the activity of daily sirolimus treatment on CRs and SEGAs in a series of infants aged less than 12 months with TSC.

Case Presentation

This is an open-label consecutive case series of patients conducted through our academic medical center (Meyer Children's Hospital). Participants included infants, aged 0–12 months, with diagnosis of TSC according to international criteria [15]. Patients with TSC should have diagnosis of multiple SEGAs and multiple CRs to evaluate the activity of sirolimus on these tumors. Diagnosis of these findings should be made, respectively, by a Gd-enhanced magnetic resonance (MR) scan and by transthoracic echocardiogram. In order to be included in the analysis, patients should have completed at least 6 months of therapy.

Sirolimus, available as oral suspension, was administered with a weight-adapted initial dose derived from the conventional dose of 1 mg/m² once a day (using equivalence: 1 m² = 30 kg). The serum level of the drug was monitored every 4 weeks (accepted therapeutic range: 4–10 ng/L). Patients with a serum level outside the range were subjected to dose adjustment. For each patient, the treatment was approved by the local ethics committee. Informed consent was obtained from the parents or legal guardians in all cases.

Toxicity evaluation was performed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Response of SEGAs to therapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

As to CRs, we considered the best cardiac response (BCR) to therapy, which is the best response obtained in the various echo assessments on target lesions. Patients were classified into 4 different types of response (on the basis of comparison between the sum of the largest diameters of target lesions): (1) stable disease; (2) partial response, with tumor shrinkage less than 50% of the baseline; (3) partial response with tumor shrinkage more than 50% of the baseline; and (4) complete regression. Furthermore, the median time to BCR was evaluated.

The study group consisted of 3 male consecutive infants (aged 0–12 months), admitted to our hospital from September 2014 to March 2015. The mean age at the beginning of treatment was 7 months (range 1–11 months). TSC2 mutations were detected in 2 patients. Genetic assessment was not available in the other patient. [Table 1](#) summarizes the clinical features of the TSC for each patient.

All patients received prenatal ultrasound diagnosis of CRs. In 1 patient, CRs were associated with cardiac complications such as paroxysmal supraventricular tachycardia that required β -blocker prophylaxis.

All patients had a diagnosis of SEGAs by an MR scan before the first month of life. Refractory focal epilepsy was present in 2 cases. In 1 case infantile spasms were also present. Epilepsy was treated with carbamazepine or carbamazepine-based regimens. Moreover, over-centimetric lesions and localizations at risk of hydrocephalus were present in cases 1 and 2, respectively.

All patients showed good tolerance to sirolimus. In particular, the most frequent toxicity was fever, without evidences of infection, which occurred in 2 patients, followed by constipation and hypercholesterolemia in 1 patient each. According to CTCAE version 3.0, all side effects were grade 1, except for fever (grade 2). As regards the serological level of sirolimus, 15 controls were performed. Dose adjustment was necessary a median of 2 times for each patient. No significant overdose was documented.

All children underwent at least 2 echocardiograms. BCR on CRs was complete response in 2 patients ([Fig. 1](#)) and partial response in the other one; in this case the tumor shrinkage was more than 50% of the baseline ([Fig. 2](#)). The median time to BCR in all patients was 1.9 months (range 0.8–4.7 months). In those with complete response, the median time to BCR was 3.3 months. There were no arrhythmic or obstructive cardiac complications in all patients during the follow-up.

All patients underwent at least one control of SEGAs with MR scan. The best response on SEGAs was stable disease in all patients, without dimensional/numerical progression or tumor shrinkage. However, there was an improvement in seizure control in all convulsant patients.

Discussion

Cardiac involvement in TSC is often predominant in the fetal period and first years of life with spontaneous involution in subsequent years. In our series we observed a substantial efficacy of sirolimus on CRs. All patients were affected by multiple and large-sized CRs. In one case, these tumors were associated with arrhythmic complications. Despite important cardiac involvement, after sirolimus therapy, we saw 2 complete responses and 1 partial response (with tumor debulking of more than 50%). The median time to BCR was 1.9 months (range

0.8–4.7 months). Moreover, in those who achieved a complete response the median time to BCR was 3.3 months. This time span seems to be too short to be due to natural spontaneous regression of CRs.

Sirolimus may have a role in promoting natural regression of CRs. This activity of the drug may be crucial in neonates or infants with CRs and cardiac complications. In fact, a more rapid reduction of the tumor volume could improve prognosis, allowing better control in life-threatening arrhythmias or relieving severe intracardiac obstructions, thus avoiding the need for surgical resection. Single case reports and short series have been published on the use of mTOR inhibitors in infants with similar features [11–14].

Also in our series, 1 patient experienced improvement in seizure control, with a complete response. SEGA size remained stable in all patients. Benefits on SEGAs have already been demonstrated with everolimus in over 100 pediatric and adult patients (age of patients was generally over 3 years and up to 34 years) [10, 11] and with sirolimus in a series of children older than 36 months [7].

Given recent suggestions, prospective clinical trials are needed, in particular to evaluate cardiac activity in newborns and infant patients.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

All authors declare that there is no conflict of interest regarding the publication of this paper.

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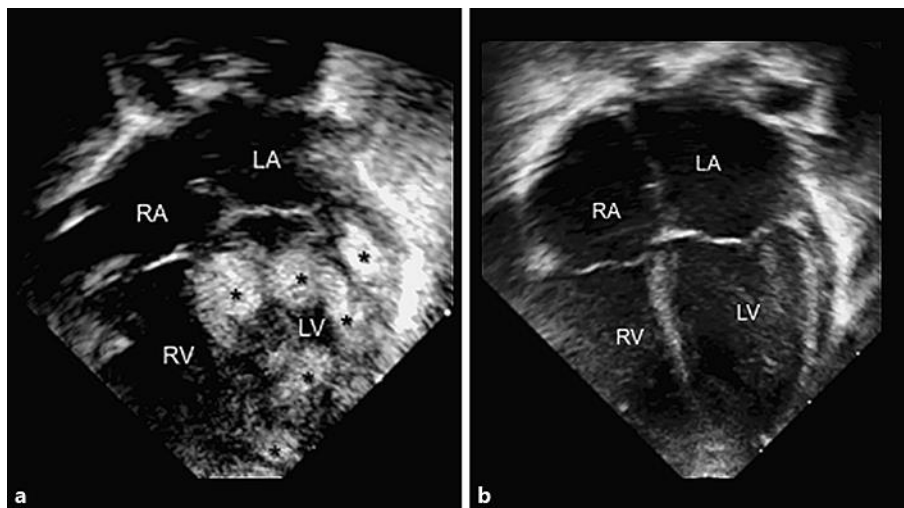


Fig. 1. A complete response to sirolimus therapy. **a** At baseline echo evaluation, patient 1 had at least 6 evident lesions involving left ventricle walls and the interventricular septum (shown with *). **b** After 1.9 months, a complete response was achieved. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium.

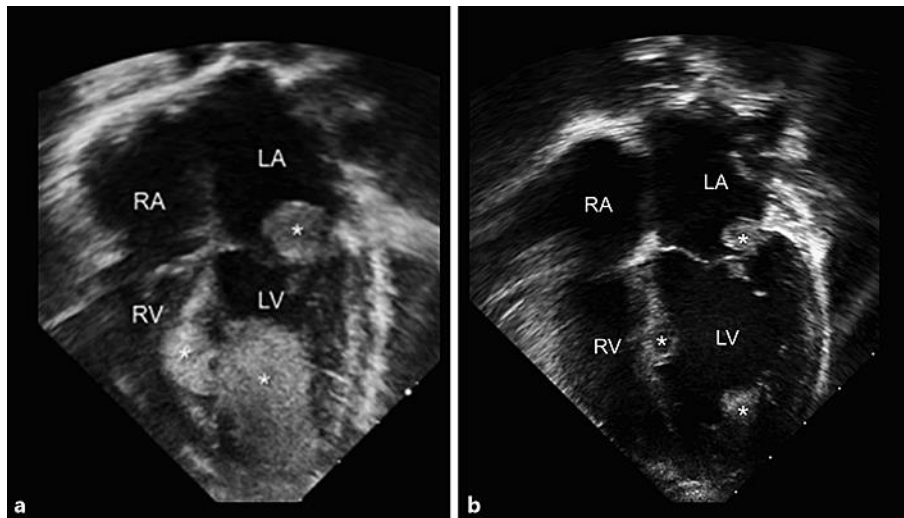


Fig. 2. A partial response to sirolimus therapy. **a** At baseline echo evaluation, patient 3 had at least 3 evident lesions (shown with *). Two of these lesions were in critical points: on the left atrioventricular valve, and in the left ventricle with filling of part of the ventricular chamber. **b** After 4.7 months, a partial response with tumor debulking greater than 50% was achieved. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium.

Table 1. Clinical features of individual patients regarding tuberous sclerosis

Patient	Gene mutations	Cardiac rhabdomyomas	Cardiac disorders	SEGAs	Refractory epilepsy	Renal angiomyolipomas	Renal disorders	Retinal hamartomas	Optical disorders	Skin fibroids
1	NA	P	–	P	–	–	–	–	–	P
2	TSC2	P	–	P	P	–	–	P	–	–
3	TSC2	P	P	P	P	–	–	P	P	–

P, present; NA, not available; TSC2, tuberous sclerosis complex 2 gene.