Cardiology in the Young

cambridge.org/cty

Very low-dose Everolimus therapy diminishes cardiac tumours in tuberous sclerosis complex disease

Stefan Rupp, Christian Jux and David Backhoff

Pediatric Heart Center, Department of Pediatric Cardiology, Intensive Care Medicine and Congenital Heart Disease, Justus-Liebig University, Giessen, Germany

Case Report

Cite this article: Rupp S, Jux C, and Backhoff D (2025) Very low-dose Everolimus therapy diminishes cardiac tumours in tuberous sclerosis complex disease. *Cardiology in the Young* **35**: 1716–1718. doi: 10.1017/S1047951125101650

Received: 28 March 2025
Revised: 19 May 2025
Accepted: 17 July 2025
First published online: 20 August 2025

Keywords:
Tuberous sclerosis complex; Everolimus; rhabdomyoma

Corresponding author: Stefan Rupp; Email: stefan.rupp@paediat.med.uni-giessen.de

Abstract

Tuberous sclerosis complex is syndrome that affects several organs. Cardiac manifestations include rhabdomyoma, which could lead to intracardiac obstruction of blood flow. In the present case, the so far lowest documented Everolimus blood level of 2–3 ng/ml led to tumour regression. Repeated Everolimus stopping and restarting for clinical reasons serves as a proof-of-concept for Everolimus therapy in tuberous sclerosis complex.

Introduction

Tuberous sclerosis complex is an autosomal inherited genetic syndrome with a highly variable phenotype that may affect several organ systems, including heart, brain, kidney, and skin.[1] Dysfunction of the proteins hamartin and tuberin, the products of the *TSC1* and *TSC2* genes, results in an upregulation of the mechanistic target of the rapamycin pathway and produces dysregulated of cellular growth.[2] Therefore, as a disease-modifying approach, mechanistic target of the rapamycin inhibitors like Everolimus became a viable and safe treatment option for angiomyolipoma associated with tuberous sclerosis complex.[3]

Cardiac manifestation of tuberous sclerosis complex includes rhabdomyoma, which could lead to arrhythmias or intracardiac obstruction of blood flow, especially during the first year of life. Everolimus has been used in a multitude of cases in neonates and children to regress cardiac tumours associated with tuberous sclerosis complex.[4,5,6,7]

Case report

We report on a female infant born at term, birth weight was 2710 g (small for date) with normal postnatal adaptation. On the fifth day of life, echocardiography was performed as a heart murmur was heard. The echocardiography revealed normal cardiac anatomy and function, but the presence of three cardiac tumours (two of which are shown in Figure 1a). One tumour was located just beneath the pulmonary valve (estimated volume 1300mm^3, Figure 1a,c) and led to severe right ventricular outflow tract obstruction (dp > 70 mmHg, Figure 1b). No arrhythmias were detected on repeated 24-hour Holter electrocardiogram and during home monitoring. Genetic evaluation confirmed the diagnosis of TSC-2 (duplication of 3589 base pairs of the Exon 11–14).

Because of the right ventricular outflow tract obstruction, a therapy with Everolimus was initiated in the first week of life (0.02mg/kg), resulting in blood Everolimus levels of 2–3µg/l. A rapid regression of tumour volume was seen during the following weeks, and therapy was stopped at an age of two months because attending doctors were worried about possible side effects of Everolimus (Figure 2). However, consequent echocardiography at an age of 1.5 months showed regrowth of the right ventricular outflow tract tumour and Everolimus therapy was restarted. Again, very low blood levels of Everolimus (2–3µg/l) led to immediate tumour regression. Everolimus was stopped for a second time at the age of 18 months, but regrowth of the tumour occurred, requiring a second restart of the Everolimus therapy. Altogether, low-dose Everolimus therapy was started/re-started five times in this patient (after birth, at the age of 1.5, 25, 36, and 60 months, respectively (Figure 2). After the latest start of therapy at the age of 5 years, the tumour remains very small (app. 10mm^3) without relevant right ventricular outflow tract obstruction. All echocardiographic images were performed in the outpatient clinic of the department by qualified investigators. No side effects of Everolimus were documented in this patient.

Discussion

Mechanistic target of the rapamycin inhibitors have been shown to be beneficial for the treatment of several clinical manifestations of tuberous sclerosis complex, including epilepsy, facial angiofibromas, cardiac rhabdomyomas, and lymphangioleiomyomatosis.[8] Based on

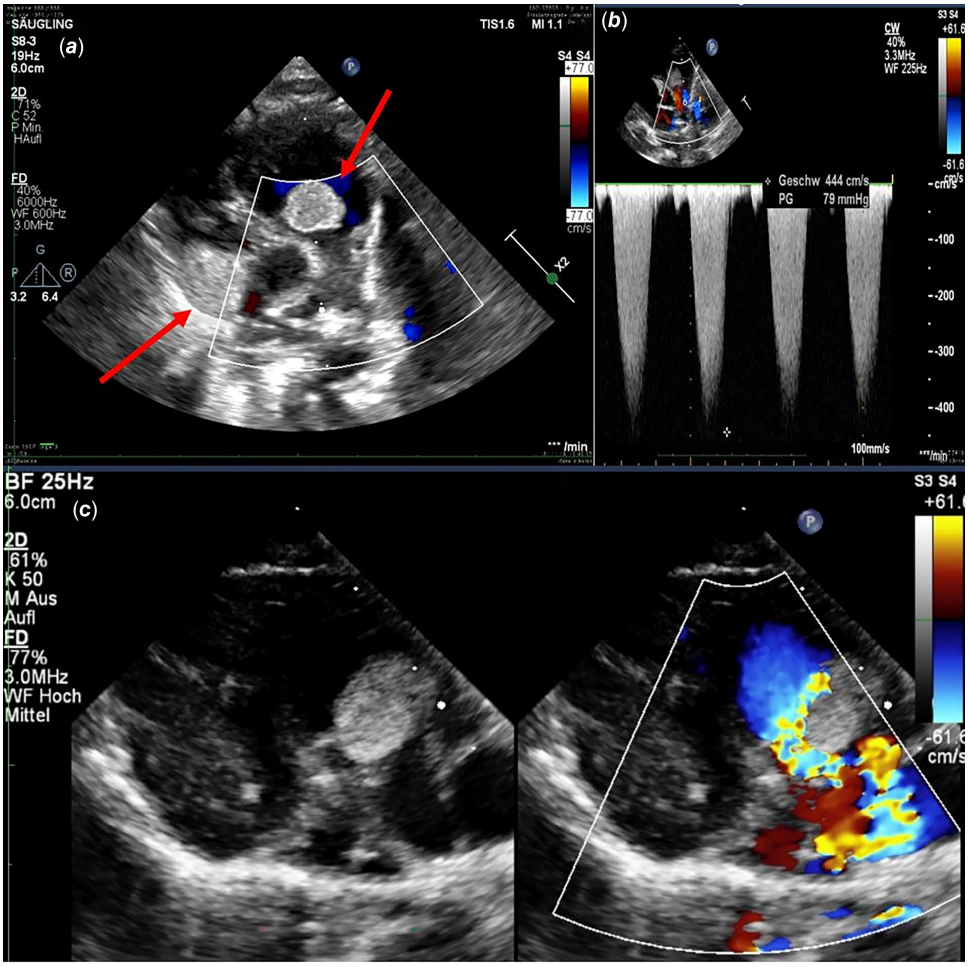

Figure 1. Echocardiographic images documented at day 4 of life. (***a***) Parasternal short axis shows two tumours marked with a red arrow: one attached to the left atria, the second in the right ventricular outflow tract, resulting in a dynamic outflow tract obstruction with a peak gradient > 70 mmHg (***b***). (***c***) The tumour is shown simultaneously without on the left and with colour Doppler ultrasound on the right in a modified long axis.

previous case reports of regression of intracardiac tumours, Everolimus therapy was initiated in the present case. In previous reports, Everolimus was effective with serum levels of 5–15 ng/mL.[5,6] Two reports describe that a low-dose therapy with Everolimus and a level of 3–7 ng/mL[4,7] was sufficient to reduce tumour size. In the present case, we showed that an even lower Everolimus level of 2–3 ng/ml was enough to diminish tumour size. This effect was proven unintentionally as starting/restarting was performed five times in this patient.

Ongoing very low-level Everolimus therapy might also have beneficial effects in cardiac or other tissues, because this directly targets the constantly upregulated mechanistic target of the rapamycin pathway and might lead to a more normalised mechanistic target of the rapamycin pathway activation, while side effects like stomatitis or systemic infections might be lower than reported.[9] Prospective studies are needed to address if longer very low-dose therapy might have beneficial effects for tuberous sclerosis complex patients.

https://doi.org/10.1017/S1047951125101650 Published online by Cambridge University Press

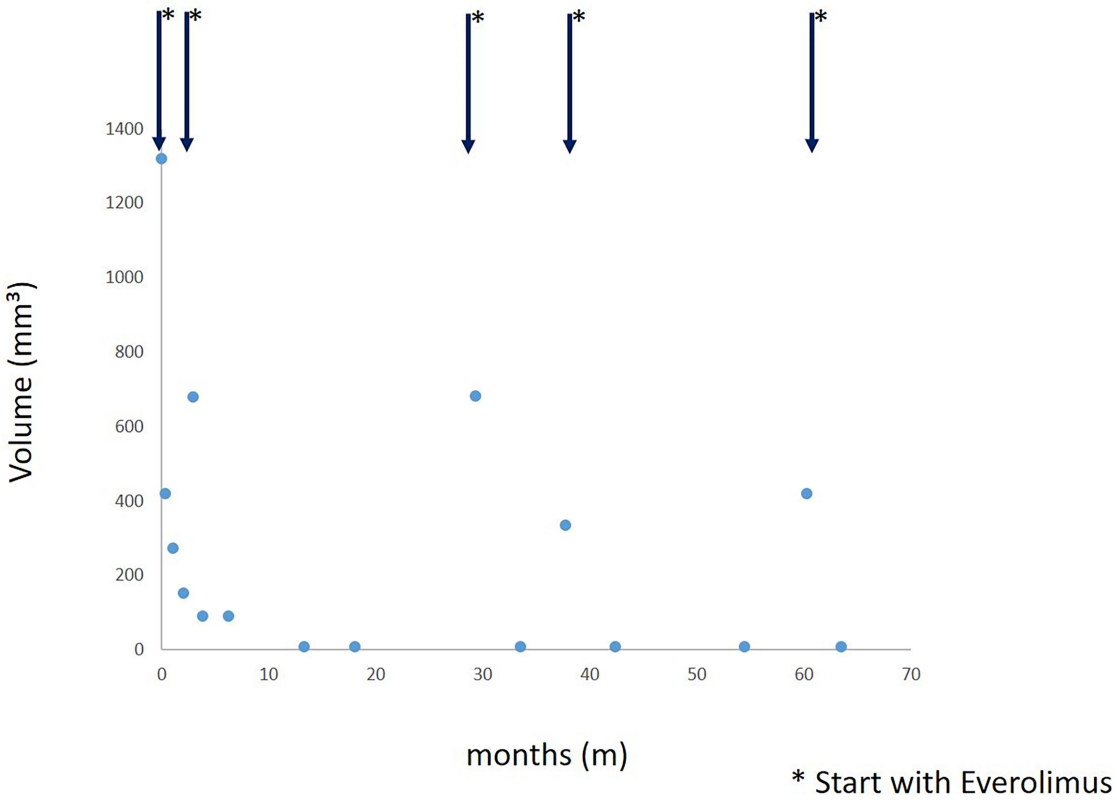

Figure 2. The size of the tumour in the first 5 years of the patient. The * marks the starting/restarting of the therapy with Everolimus.

Acknowledgements. None.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. The authors declare none.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees (Justus-Liebig-University).

References

1. Davis PE, Filip-Dhima R, Sideridis G, et al. Presentation and diagnosis of tuberous sclerosis complex in infants. Pediatrics 2017; 140(6): e20164040.
2. Crino PB. Evolving neurobiology of tuberous sclerosis complex. Acta Neuropathol 2013; 125: 317–332.
3. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013; 381: 817–824.
4. Nespoli LF, Albani E, Corti C, et al. Efficacy of everolimus low-dose treatment for cardiac rhabdomyomas in neonatal tuberous sclerosis: Case report and literature review. Pediatr Rep 2021; 13: 104–112.
5. Dhulipudi B, Bhakru S, Rajan S, Doraiswamy V, Koneti NR. Symptomatic improvement using Everolimus in infants with cardiac rhabdomyoma. Ann Pediatr Cardiol 2019; 12: 45–48.
6. Aw F, Goyer I, Raboisson MJ, Boutin C, Major P, Dahdah N. Accelerated cardiac rhabdomyoma regression with Everolimus in infants with tuberous sclerosis complex. Pediatr Cardiol 2017; 38: 394–400.
7. Garg A, Gorla SR, Kardon RE, Swaminathan S. Rapid involution of large cardiac rhabdomyomas with Everolimus therapy. World J Pediatr Congenit Heart Surg 2021; 12: 426–429.
8. Capal JK, Franz DN. Profile of everolimus in the treatment of tuberous sclerosis complex: an evidence-based review of its place in therapy. Neuropsychiatr Dis Treat 2016; 12: 2165–2172.
9. Hatano T, Endo K, Tamari M. Efficacy and safety of low-dose everolimus treatment for renal angiomyolipoma associated with tuberous sclerosis complex. Int J Clin Oncol 2021; 26: 163–168.

https://doi.org/10.1017/S1047951125101650 Published online by Cambridge University Press