Effect and Complications of Everolimus Use for Giant Cardiac Rhabdomyomas with Neonatal Tuberous Sclerosis

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Am J Perinatol Rep 2019;9:e213–e217.

Abstract

Most cardiac rhabdomyomas with tuberous sclerosis (TS) are asymptomatic and spontaneously regress. However, some cases require surgical intervention due to arrhythmia and severe obstruction of cardiac inflow or outflow. We report herein a neonatal case of giant cardiac rhabdomyomas with TS and insufficient pulmonary blood flow from the right ventricle. Lipoprostaglandin E1 was necessary to maintain patency of the ductus arteriosus. We used everolimus, a mammalian target of rapamycin inhibitor, to diminish the cardiac rhabdomyomas. After treatment, the rhabdomyomas shrank rapidly, but the serum concentration of everolimus increased sharply (maximum serum trough level: 76.1 ng/mL) and induced complications including pulmonary hemorrhage, liver dysfunction, and acne. After the everolimus level decreased, the complications resolved. Everolimus may be a viable treatment option for rhabdomyomas, but its concentration requires close monitoring to circumvent complications associated with its use.

Keywords
- complication
- everolimus
- rhabdomyoma
- tuberous sclerosis

Tuberous sclerosis (TS) is caused by loss-of-function mutations of the *TSC1* or *TSC2* gene.[1] *TSC1* and *TSC2*, respectively, encode hamartin and tuberin, which combine to suppress the mammalian target of rapamycin (mTOR) signaling pathway.[2,3] The mTOR signaling pathway regulates cell proliferation and vascularization.[4] In patients with TS, the mTOR signaling pathway is abnormally activated due to diminished hamartin or tuberin function, leading to hamartomatous cell growth and other symptoms.[2,3] Cardiac rhabdomyoma is one of the features of TS in the neonatal and early infantile periods. In half of rhabdomyoma cases, the rhabdomyomas spontaneously regress in childhood.[5]

Everolimus is an mTOR inhibitor. Its effectiveness against subependymal giant cell astrocytomas,[3,6] renal angiomyolipomas,[7] and epilepsy[8] in patients with TS has been documented.

There are some reports of cardiac rhabdomyoma treatment using everolimus,[9–17] but none describes the serious complications associated with its use. We report herein a neonate with TS and giant cardiac rhabdomyomas occupying the right ventricular cavity, impeding ventricular function, and decreasing pulmonary blood flow. Lipoprostaglandin E1 (lipo-PGE1) was required to maintain patency of the ductus arteriosus. Everolimus administration successfully reduced the tumor size although the clinical course was complicated by a pulmonary hemorrhage attributed to the adverse effects of everolimus.

Case Report

A 43-year-old woman was referred for fetal echocardiography at 21 gestational weeks due to multiple intracardiac

received
November 8, 2018
accepted
March 5, 2019

DOI https://doi.org/10.1055/s-0039-1692198.
ISSN 2157-6998.

tumors. Although the fetus had cardiac enlargement with a cardiac thoracic area ratio of 67% at 35 gestational weeks, the fetus developed neither arrhythmia nor hydrops.

A male infant was born at 38 weeks' gestation by scheduled cesarean section due to a previous cesarean section. The birth weight was 2,029 g, the heart rate was 138 beats per minute, the respiratory rate was 20 breaths per minute, the blood pressure was 60/37 mm Hg, and oxygen saturation was 90% without any respiratory support at neonatal intensive care unit admission. A systolic heart murmur (grade 4/6) and peripheral coldness were found. There was no skin lesion, and the blood test showed no abnormalities.

The largest intracardiac tumor, 35 mm × 21 mm in size, occupied the right ventricular cavity (►**Fig. 1a**), resulting in decreased right ventricular output. Echocardiography showed scant antegrade blood flow via the pulmonary valve and significant pulmonary regurgitation caused by backward blood flow from the ductus arteriosus. The right atrium was dilated, and a right-to-left shunt through the foramen ovale was detected. Stenosis of the left ventricular outflow tract due to the tumor was observed, and the flow velocity of the ascending aorta increased (1.5 m/s), but the systemic blood pressure remained normal. Since the pulmonary blood flow was dependent on the ductus arteriosus, we started lipo-PGE1 (5 ng/kg/min) soon after birth to maintain patency of the ductus arteriosus.

A magnetic resonance imaging of the brain showed cerebral white matter radial migration lines, a cortical tuber, and a subependymal nodule. Multiple retinal nodular hamartomas were also observed. TS was diagnosed based on these three major findings (brain, retina, and heart).[1]

Volume reduction of the cardiac rhabdomyomas was crucial to maintain pulmonary blood flow. We decided to use everolimus to reduce the cardiac rhabdomyomas rapidly. We started once daily oral everolimus administration on day 4. The initial dosage of 0.4 mg/d (2.8 mg/m^2/d, 0.2 mg/kg/d) was decided based on previous reports.[3,18] The target trough level was set at 5 to 15 ng/mL.[6] Echocardiography at day 7 demonstrated a decrease in the tumor size in the right ventricle and an increase in the antegrade blood flow via the pulmonary valve. We terminated lipo-PGE1.

We experienced a serious complication at day 6, 3 days after the initiation of everolimus administration, when the patient's respiratory condition worsened and mechanical ventilation was started. Continuous bloody tracheal aspiration indicated a pulmonary hemorrhage, and the laboratory data revealed severe coagulopathy with a prothrombin time–international normalized ratio (PT-INR) of 2.4 and fibrinogen value of 52 mg/dL, as well as elevated liver enzymes. We decided to stop everolimus on day 7 after the fourth administration. After a single infusion of fresh-frozen plasma, the coagulopathy improved (PT-INR 1.6 and fibrinogen 158 mg/dL) at day 9. Acne, which appeared on the bilateral cheeks at day 8, was treated with topical quinolone medication and improved after 2 weeks. Hyperlipidemia, hyperglycemia, and stomatitis were not observed.

Echocardiography at day 16 showed closure of the ductus arteriosus, confirming that biventricular circulation was achieved. The patient was weaned from mechanical ventilation on the same day.

With general improvement in the patient's condition, we tried to restart everolimus in the hope of further reducing the tumor size. At day 10, everolimus was administered at a lower dose of 0.1 mg/d. However, we discontinued everolimus again after we obtained the serum drug concentration measurement for day 7 showing a trough level of 76.1 ng/mL, which significantly exceeded the target level. At day 25, everolimus was administered at a dose of 0.025 mg/d, which resulted in a re-elevation of the liver enzymes. After everolimus was terminated altogether, the liver enzyme levels normalized again. Changes in the serum everolimus concentration and liver enzymes are shown in ►**Fig. 2**.

Echocardiography at days 20 (►**Fig. 1b**) and 42 (►**Fig. 1c**) showed regression of the giant tumor in the right ventricle. The patient was discharged at day 54.

Discussion

Everolimus was effective as a treatment of the giant cardiac rhabdomyomas with TS in our case; the drug reduced the tumor size rapidly, increased pulmonary blood flow, and

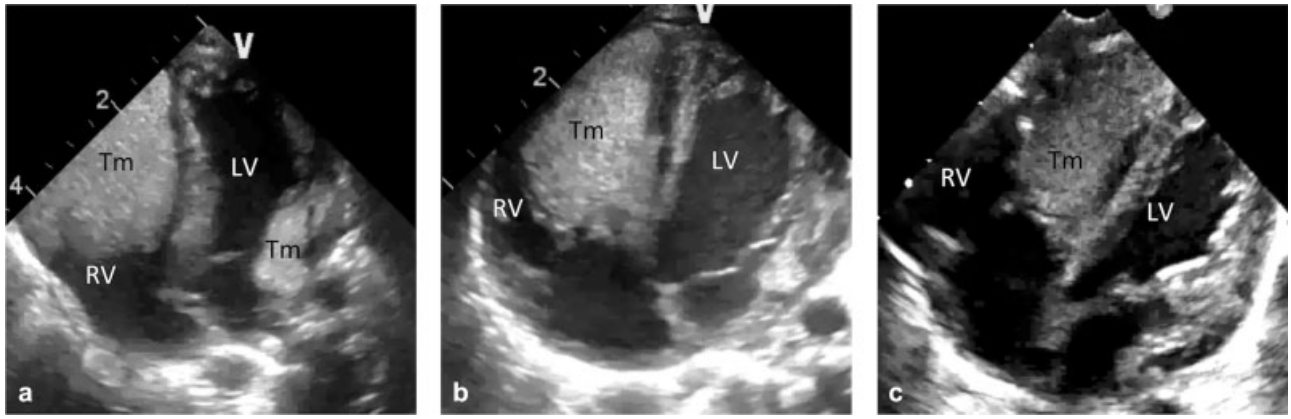

Fig. 1 Figures show view of four chambers on echocardiography. (a) The patient at birth. Multiple tumors were found in both ventricles. The largest rhabdomyoma occupied most of the right ventricular cavity (size: 35 × 21 mm). (b) The patient at day 20. The largest rhabdomyoma showed regression (size: 28 × 15 mm). (c) The patient at day 42. The largest rhabdomyoma significantly regressed (size 24 × 11 mm). LV, left ventricle; RV, right ventricle; Tm, tumor.

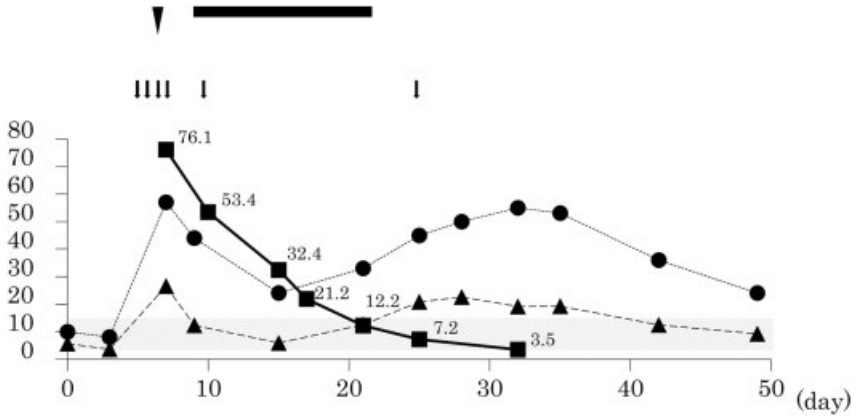

Fig. 2 Figure shows the administration and the serum concentration of everolimus, serum AST and ALT levels, and major complications. Squares indicate the trend in the everolimus trough level (ng/mL). The numbers next to the squares indicate the everolimus trough level. Shaded areas indicate the target everolimus trough level (5–15 ng/mL). Triangles and circles indicate the trend in AST/10 (U/L) and ALT (U/L), respectively. Arrows indicate the day of everolimus administration, and the arrowhead indicates the day on which pulmonary hemorrhage occurred. Square bar indicates the duration of acne. The high serum trough level of everolimus may be related to the pulmonary hemorrhage, acne, and liver dysfunction seen in this patient.

rendered surgical intervention unnecessary. Several reports have demonstrated the effectiveness of this drug (►**Table 1**).[9–17] Cardiac rhabdomyomas with TS usually spontaneously regress in childhood.[5] Therapeutic intervention is not needed unless arrhythmia or severe intracardiac obstruction occurs.[19] In cases of refractory arrhythmia or severe obstruction of blood flow, surgery for tumor resection or single ventricular hemodynamics is necessary during the neonatal period.[20] Given the effectiveness of everolimus in rapidly reducing the size of rhabdomyomas, the drug may be a viable treatment option for giant cardiac rhabdomyomas in patients with TS.

The appropriate dosage of everolimus has not been determined. Previous studies have set the everolimus target trough level at 5 to 15 ng/mL.[9,10,12–17] The package insert recommends monitoring the serum drug concentration from 2 weeks after commencing administration or changing the dosage. In our case, everolimus was administered at a dose of 0.2 mg/kg once daily starting at day 4. The serum everolimus concentration, measured immediately before the administration of the 4th dose at day 7, was 76.1 ng/mL, which was much higher than the target trough level. Our measurement of the serum drug concentration, which we made much earlier than recommended by the package insert, indicated that the initial dose should have been lower. Although the half-life of the drug is reportedly 25 to 43 hours,[21] the estimated half-life in our case was 84 to 128 hours, far exceeding the reported values. Our case underscores the fact that meticulous monitoring of the serum everolimus concentration is essential.

Our patient developed pulmonary hemorrhage coinciding with the elevation of the serum everolimus concentration. Everolimus reportedly damages not only tumor vessels but also normal blood vessels[22] and can lead to pulmonary hemorrhage.[23] A recent in vivo study suggested that mTOR inhibitors may interact with the *STAT1* gene, causing amplification of cellular apoptosis and augmenting lung injury.[24] Coagulopathy, which developed in our patient, is another possible complications. In the present case, in addition to increased pulmonary blood flow due to lipo-PGE1, tumor shrinkage caused by everolimus increased the pulmonary blood flow. All these factors contributed to the pulmonary hemorrhage.

Everolimus can adversely affect liver function and lead to decreased metabolism of the drug. In our patient, an elevation of aspartate transaminase and alanine transaminase was evident at day 7 when the serum everolimus concentration peaked, and acne was also observed. As summarized in ►**Table 1**, complications reported in neonates include mouth ulcers, hyperlipidemia, etc. Liver dysfunction and acne were listed among the possible complications in the package insert in 2018, in which the incidence rates of liver dysfunction and acne were 1 to 10%. Half the Japanese population lack the activity of CYP3A5, the enzyme involved in everolimus metabolism.[21,25] Although we did not assess enzyme activity in our patient, the extremely high concentration of everolimus and the prolongation of its half-life might be related to the lack of CYP3A5 activity.

The toxic and therapeutic levels of the serum everolimus concentration also require clarification. Complications, such as mouth ulcer and hyperlipidemia, have been documented in patients with concentrations of everolimus below the target trough level of 5 to 15 ng/mL.[9,11,15] In contrast, there were no complications in a case reported by Shigemitsu et al[13] despite a maximum trough level of 21 ng/mL.

Follow-up after the cessation of everolimus treatment is also important. Some studies reported tumor regrowth after stopping everolimus administration.[11,12] It is also necessary to follow the long-term growth and development of pediatric patients who have received everolimus. There are as yet no reports on the long-term prognosis of neonates or young children who have received this treatment.[26]

In conclusion, everolimus may be a viable treatment option for giant cardiac rhabdomyomas in patients with TS. When administering the drug to neonates, the patient should be closely observed for possible side effects, and the serum drug level should be routinely monitored.

Table 1 Cases of everolimus use for cardiac rhabdomyoma with tuberous sclerosis

Case	GA (wk)	BW (g)	Maximum tumor diameter (mm)	Start of everolimus treatment (d)	Drug dosage	Calculated dosage (mg/kg/wk)	Everolimus trough level (ng/mL)	Complications	Outcomes	Reference
1	38	3,350	8	1	0.1 mg/d	0.21	10.2	Mouth ulcer, suspected infection	50% reduction in size of largest RHM, with some RHM disappearing after 36 d	Aw et al (2017)[9]
2	Term	3,550	24	2	0.5 mg/d, twice a week	0.28	7.8	NA	Significant reduction of RHM over 2 mo	Doğan et al (2015)[10]
3	38	3,500	20	7	0.5 mg/d, twice a week	0.29	2.6	Hyperlipidemia	Significant reduction of RHM over 4 wk, but treatment resumed as RHM increased again 10 d after discontinuation of treatment. After 7 mo, treatment was tapered and discontinued	Bornaun et al (2016)[11]
4	36	1,670	27.2	4	0.1 mg/d	0.42	11	None	Significant reduction of RHM over 20 d. RHM increased again after stopping everolimus but was asymptomatic	Goyer et al (2015)[12]
5	37	2,930	36	19	1 mg/m^2/d	0.48	21	None	Rapid regression within a few weeks	Shigemitsu et al (2016)[13]
6	Term	3,400	25	0	1 mg/d, twice a week	0.59	83.5	Hyperlipidemia	Remarkable reduction of RHM over 2.5 mo. Two out of six RHM disappeared	Demir et al (2012)[14]
7	30	980	16	20	0.1 mg/d	0.71	13.7	Fever, respiratory deterioration	BT shunt operation was done at 88 d of life. Afterward, two-ventricle repair was done with no need for RHM resection	Mohamed et al (2014)[15]
8	35	2,000	40	1 wk	0.25 mg/d	0.88	16	Mucositis, hyperlipidemia	80% reduction in size of major RHM over 10 wk	Colaneri et al (2016)[16]
9	Term	2,955	37	2	0.4–0.45 mg/d	1.07	108	Hyperlipidemia, lymphopenia	Giant LV RHM continued to shrink (21 × 37 × 21 mm–10 × 28 × 13 mm) over 3 wk	Wagner et al (2015)[17]
10	38	2,029	35	4	0.4 mg/d	1.38	76.1	Pulmonary hemorrhage, acne, liver dysfunction	After 4 everolimus doses, tumors shrank. Actual right ventricle volume and right ventricle output increased, and biventricular circulation was established	Our case

Abbreviations: BT, Blalock–Taussig; BW, birth weight; GA, gestational age; LV, left ventricle; NA, not applicable; RHM, rhabdomyoma.
Note: Everolimus dosage was assumed to be 0.45 mg/d in case 9.

Ethical Approval

All the procedures involving human participants were performed in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments. The approval of the ethics review committee and parental consent to use everolimus were obtained. Parental written informed consent was obtained for this report.

Funding

No financial assistance was received to support this study.

Conflict of Interest

All the authors declare that they have no conflict of interest.

Acknowledgment

We thank Mr. James R. Valera for his assistance with editing this article.

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