Cardiology in the Young

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Giant left ventricular rhabdomyoma treated successfully with everolimus: case report and review of literature

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Review Article

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Abstract

Introduction: Intracardiac rhabdomyomas can cause severe ventricular dysfunction and outflow tract obstruction. *Case report:* A term newborn infant with antenatal diagnosis of giant left ventricle rhabdomyoma presented with cardiac failure and duct-dependent systemic circulation after birth. She was treated successfully with everolimus, showing decrease in tumour size and improvement in left ventricular ejection fraction. *Discussion:* Tumour regression rate was 0.32 cm^2/day and improved to 0.80 cm^2/day with the use of everolimus. Herein we report a newborn with inoperable giant left ventricular cardiac rhabdomyoma and significant regression of the tumour. To our knowledge, this is the largest left ventricular rhabdomyoma reported. A review of the literature was undertaken for comparison. *Conclusion:* Everolimus has proven to be efficacious in size reduction of cardiac rhabdomyomas in cases when surgical resection is not possible.

Rhabdomyomas are the most common cardiac tumours diagnosed in fetuses, neonates, and infants.[1,2] They resemble a hamartoma derived from embryonal myoblast and exhibit a fetal pattern of atrial natriuretic peptide immune reactivity and are associated with tuberous sclerosis complex in up to 60–96% of cases.[1,3] Rhabdomyomas are often detected early on prenatal ultrasound and trasplacentally transmitted maternal oestrogens are reported to be responsible for their growth in utero.[2] In the majority of cases, there is a spontaneous regression of the TSC-related rhabdomyomas.[3–5] Treatment for these tumours is reserved for those with life-threatening obstructive symptoms or arrhythmias refractory to medical therapy.[3,5,6] Surgical resection may be difficult when the tumours are multifocal, infiltrative, or giant.[6]

Mutations in two distinct tumour suppressor genes are found in more than 85% of cases of TSC.[1] These genes include tuberous sclerosis complex 1 (encoding hamartin) and tuberous sclerosis complex 2 (encoding tuberin), which function to regulate cell cycle and differentiation through a distinct cascade by inhibiting the mammalian target of rapamycin pathway.[6]

Everolimus is a serine–threonine kinase mammalian target of rapamycin inhibitor.[6] By targeting the mammalian target of rapamycin pathway, it particularly inhibits growth-driven cell proliferation.[6] Because these agents also inhibit lymphocyte and fibroblast proliferation, they are approved for clinical use as immunosuppressive and anti-proliferative agents.[7] Studies have confirmed the efficacy and safety of mammalian target of rapamycin inhibitors in the treatment of subependymal giant-cell astrocytoma and renal angiomyolipomas and hypothesised a broader disease-modifying effect for tuberous sclerosis complex.[8] Tiberio et al described for the first time the effect of everolimus on rhabdomyoma regression in a 7-year-old boy born with tuberous sclerosis complex and a large left-ventricular mass with poor ventricular function without evidence of inflow- or outflow-tract obstruction, who received treatment with everolimus for a subependymal giant-cell astrocytoma. At 13 months after receiving everolimus, a subsequent echocardiogram showed near-resolution of the previously unchanged ventricular rhabdomyoma.[7]

Herein we report a newborn with inoperable giant left ventricular cardiac rhabdomyoma and significant regression of the tumour after receiving treatment with everolimus. A review of the literature was also made for comparison.

Case report

A 40-year-old woman, gravida 1, was referred to our unit at 35.4 weeks of gestation for a fetal cardiac evaluation after the diagnosis of a cardiac tumour.

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Fetal echocardiography revealed a giant left ventricular tumour of 43 × 42 mm, occupying almost all the left ventricular cavity. The tumour severely impaired diastolic and systolic left ventricular function. Evidence of retrograde flow across the aortic arch predicted a duct-dependent systemic circulation and the need for intravenous prostaglandins after birth. Moderate pericardial effusion was also present (Fig 1). During counselling to the parents, clinical features of tuberous sclerosis were found in the father who was unaware of having a systemic disease.

A 3040-g term female infant was born by caesarean section. The infant had Apgar scores of 6 and 8 at 1 and 5 min, respectively. She presented with signs of cardiac failure including respiratory distress, requiring orotracheal intubation and warranted transfer to neonatal ICU. Initial physical examination revealed rhythmic heart sounds without murmurs and symmetrical pulses in four extremities. Further evaluation reported preductal oxygen saturation of 88% and postductal oxygen saturation of 65%. Chest X-ray revealed severe cardiomegaly with clear lung fields. ECG demonstrated an incomplete left bundle branch block with a severe repolarisation disorder. Transthoracic echocardiogram confirmed the presence of a giant mass (47 × 40 mm) attached to the left ventricular wall, conditioning severe systolic and diastolic dysfunction. Two smaller tumours, sized 10 × 17 mm and 10 × 10 mm, located in the interventricular septum and the right ventricular free wall, respectively, were detected as well. Intermittent retrograde flow across the aortic arch was noted. A large patent ductus arteriosus of 7.3 mm with right to left shunt was present. Shortening fraction of the left ventricle was 15%. A moderate pericardial effusion with a maximum pool of 8 mm between pericardial leaves was also detected.

Prostaglandin E1 infusion was started at a dose of 0.05 mcg/kg/min on day 2 of life because of duct-dependent systemic circulation and decrease on patent ductus arteriosus diameter from 7.3 to 4.1 mm. Dobutamine was added on day 24 of life at a 10 mcg/kg/min dose and discontinued when digoxin was started on day 25 of life at a dose of 6 mcg/kg. Diuretics were used to prevent pulmonary oedema.

Abdominal ultrasonography was performed to discard associated anomalies of the urinary tract, showing bilateral renal cysts. Transfontanelle sonography revealed no alterations. Genetic evaluation confirmed the presumed diagnosis of tuberous sclerosis, with cardiac rhabdomyoma accounting for the major criteria and multiple renal cysts and confetti skin lesions accounting for two minor criteria. DNA extraction was performed for molecular testing, finding a pathogenic variant of tuberous sclerosis complex 2 gene on exon 34 that results in a premature stop codon and protein truncation. On day 36 of life, owing to unavailability, everolimus was started at a dose of 0.25 mg two times per day, only 2 days a week per nasogastric tube with no side effects encountered. Blood cell count, lipid profile, and hepatic and renal function tests were monitored weekly to avoid toxicity.

Tumour mass decreased significantly only after the start of everolimus, and ejection fraction also increased parallel to the tumour involution (Fig 2).

Mechanical ventilation was weaned according to cardiac conditions considering the risk of pulmonary oedema. On day 54 of life with enhancement of ejection fraction to 50%, she was successfully extubated to nasal ventilation and weaned to nasal cannula. With improvement in ventricular function, prostaglandin infusion was stopped. The patient was transferred to intermediate care on day 63 of life. A new transfontanelle sonography revealed a subependimary echogenic image located at the anterior horns of the right lateral ventricle, presumed to be a subependymal nodule. No seizures were recorded during hospital stay.

Sildenafil was started at day 72 to decrease pulmonary pressure. Supplemental oxygen was discontinued on day 76, and on day 79 of life she was discharged and continued treatment with everolimus; no adverse effects were reported.

On day 120 of life, a follow-up echocardiography was performed revealing a left ventricle rhabdomyoma of 22 × 29 mm with a normal ejection fraction. The patient was asymptomatic and tumour size regression was adequate, being unnecessary to restart everolimus. Radiologic, electrocardiographic, and echocardiographic evolution is shown in Figure 3.

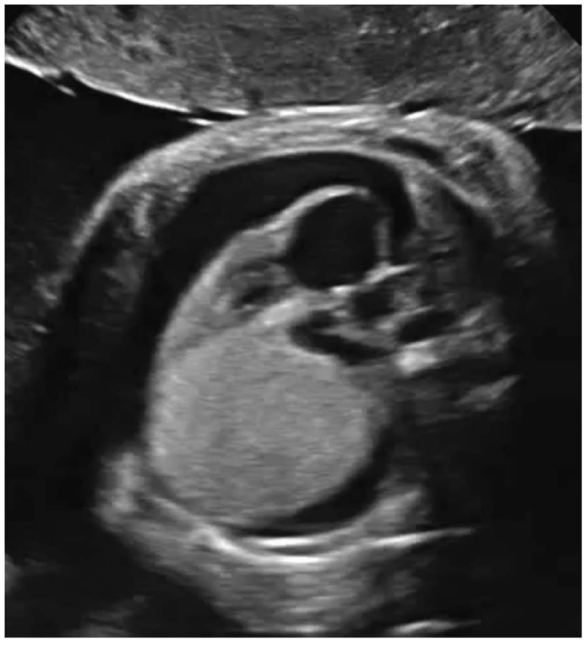

Figure 1. Giant left ventricular tumour on fetal echocardiography.

Discussion

The main treatment of symptomatic cardiac tumours is surgical resection. However, this may be difficult when the tumours are multifocal and infiltrative.[6,8] Furthermore, surgery for cardiac tumours carries an acceptable mortality risk (6.25% in Ying et al series).[9] The use of everolimus has proven to be efficacious by

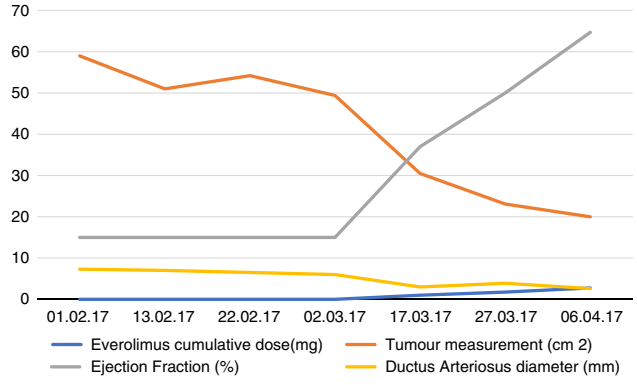

Figure 2. Clinical evolution showing tumour size decrease and improvement on ejection fraction with everolimus treatment.

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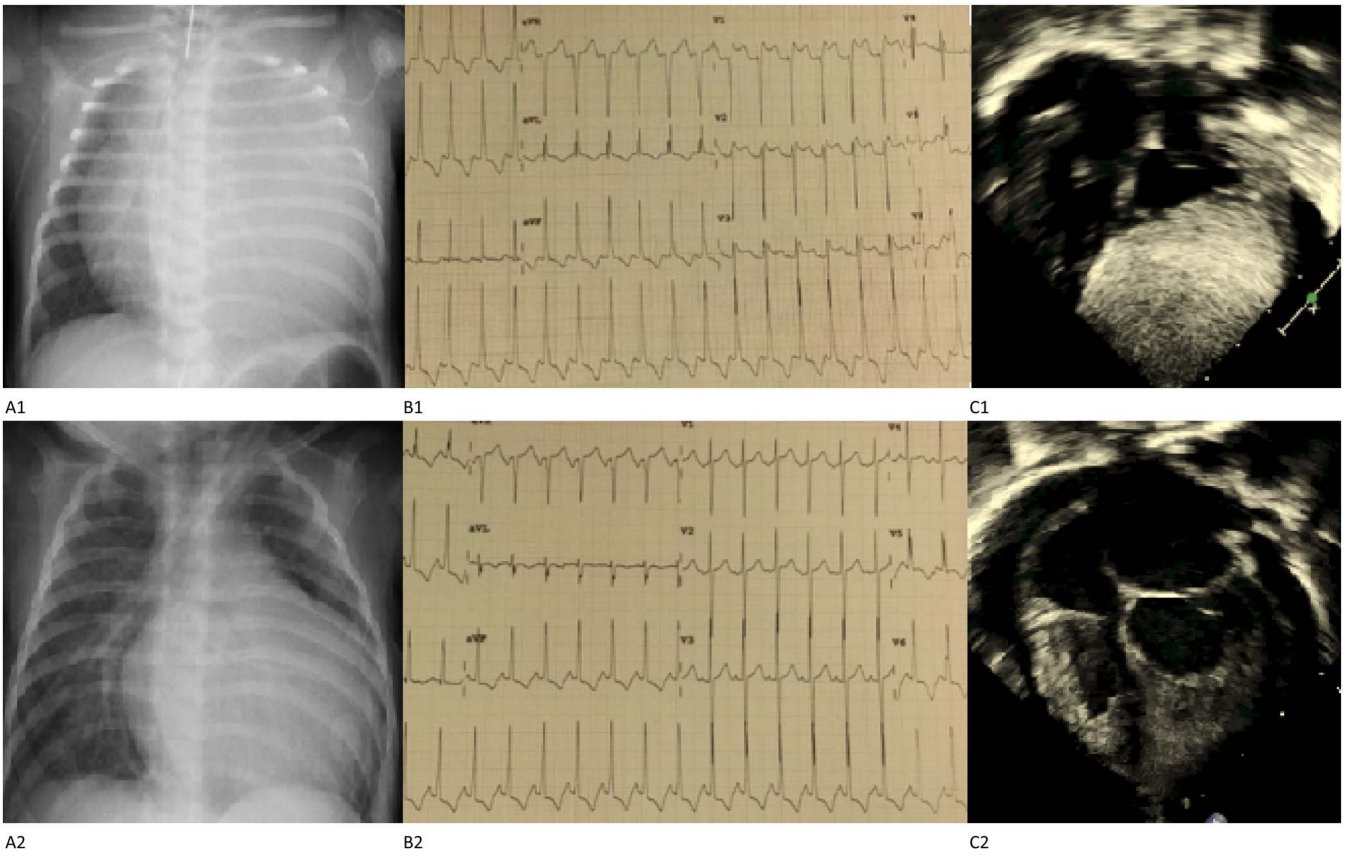

Figure 3. (A1) Chest X ray before treatment with everolimus showing severe cardiomegaly. (B1) ECG showing incomplete left bundle branch block with a severe repolarization disorder. (C1) Four chamber view echocardiogram demonstrating the presence of a giant rhabdomyoma (47 x 40 mm) attached to left ventricular wall. (A2) Chest X ray after treatment with everolimus showing improvement in cardiomegaly. (B2) ECG showing improvement in the repolarization pattern. (C2) Four chamber view echocardiogram after everolimus treatment revealing a significant decrease in rhabdomyoma dimensions.

enhancing rhabdomyoma size regression rate without significant adverse effects.[6]

The study of Kotulska was the first to show mammalian target of rapamycin pathway dysregulation and an increased expression of proapoptotic Bax protein in cardiac rhabdomyoma associated with tuberous sclerosis complex.[10] The authors also looked for the possible mechanism of cardiac rhabdomyoma regression and postulated that it depends on apoptosis regulation abnormalities associated with mammalian target of rapamycin pathway disruption.[10] To date, several cases of cardiac rhabdomyomas treated successfully with everolimus have been described (Table 1).[1,2,4,6,7,9,11–21] However, the United States Food and Drug Administration has not approved the treatment of cardiac rhabdomyomas with mammalian target of rapamycin inhibitors.[1]

We report a case of a giant rhabdomyoma of the left ventricle, causing severe left ventricular dysfunction and leading to a duct-dependent systemic circulation. Before treatment, the size regression rate was 0.32 cm^2/day, and increased to 0.80 cm^2/day after everolimus. Aw et al reported an rhabdomyomas size regression rate 11.8 times faster with everolimus than historic controls, and a reduced dose of 4.5 mg/m^2/week was sufficient to obtain recommended therapeutic level.[6]

Everolimus undergoes complete hepatic metabolism through CYP 450 3A4. This metabolic pathway is immature in preterm and full-term newborns in the neonatal period,[8] for which liver function should be monitored. The various rapamycin analogues differ in hepatic metabolism, in which everolimus is 2.7-fold lower than sirolimus. Nonetheless, sirolimus systemic clearance is half that of everolimus, giving everolimus faster steady-state levels after initiation and faster elimination after discontinuation.[22] CYP3A-dependent sirolimus metabolite formation changes in an age-dependent manner as described by Emoto et al,[23] with rapid increase of sirolimus clearance over time in neonates and in infants, indicating a developmental change. In our review of literature, hypertriglyceridaemia and mild mucositis were the most commonly reported adverse effects of mammalian target of rapamycin inhibitors, which disappeared after discontinuation of the drug and were not dose dependent. Doses of everolimus ranged from 0.1 mg daily to 3 mg/m^2 body surface, achieving regression of the cardiac rhabdomyoma. Mass regrowth was observed in some cases, for which everolimus was restarted. Rebound growth was not associated with dose or duration of treatment. Dosage regimens for sirolimus range from 0.1 mg/kg/day to 0.5 mg daily, reporting cardiac rhabdomyoma regression. It is noteworthy that dose had to be tapered owing to supratherapeutic serum levels – above 20 ng/ml – in all cases, without adverse effects reported.[12,19,20] In the case reported by Lee et al, sirolimus reached a level of 42.1 ng/ml in a preterm infant with an initial dose of 0.25 mg daily. Steady-state serum level of sirolimus at 10–20 ng/ml was achieved under 0.12 mg once daily, which corresponded to 0.1 mg/kg/day, suggesting this to be a reasonable dose to start treatment with sirolimus.[20]

Target levels have been described for sirolimus and everolimus. Sirolimus and everolimus were initially developed to treat fungal infections and cancer and to prevent organ transplant rejection. As a result, robust knowledge around dosing and

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Table 1. Characterization of patients with cardiac rhabdomyomas treated with mTOR inhibitors.

First author, year	Patient GA and BW	Echographic data at diagnosis	Clinical presentation	EKG findings	mTOR inhibitor dose and adjuvant therapy	Adverse effects	Reported evolution	Tuberous sclerosis features	Follow up
Tiberio, 2011[7]	7 years	Large LV apical mass with smaller masses in the ventricular and apical septum			Digoxine everolimus		Near-resolution after 13 months.	SEGA at 5 years	Free of cardiovascular symptoms
Demir, 2012[11]	Term 3400 g	8 RDM. One was highly mobile and obstructed RV Flow.	Cyanosis soon after delivery		PGE_1, furosemide, prophylactic trimethoprim-sulfamethoxazole. Everolimus 0.25 mg every 6 h 2 day per week	Serum TGL level 398 mg/dl	After 2.5 months, haemodynamic instability of the patient improved	Hypopigmented skin lesions	Symptom-free for 2 months
Breathnach, 2014[12]	38 W	Multiple intracardiac tumours including a large 15 × 12 mm tumour obstructing LV outflow tract	Single first heart sound, III/VI harsh systolic ejection murmur		PGE_1, sirolimus 0.5 mg once daily, prophylactic co-trimoxazole	TGL level 5.32 mmol/L Sirolimus level 26 ng/ml on day 7, dose reduced to 0.4 mg daily	On day 5 of treatment, LVOT tumour started to decrease, marked reduction by day 24 (5 × 4 mm)	Subependymal nodules in both lateral ventricles, infantile spasm at 3 months of age, mutation of C to T at position 4375 (R1459X) on exon 33 of the TSC2 gene	Tumours increased slightly in size after discontinuation of sirolimus, gradient across LVOT remained stable at follow-up at 8 months of age
Dogan, 2014[9]	Term 3550 g	Multifocal echogenic masses, 3 in LV, 1 in RA	II-III/VI systolic ejection murmur, hepatomegaly, mild cyanosis	WPW	Everolimus 0.25 mg^2 times per day, 2 days per week		Improvement at 6 weeks of age	Subependymal nodules	Symptom-free for 15 months
Miczoch, 2014[4]	37 W 2550 g	Giant obstructing the RVOT			Everolimus 3 mg/m^2		Regression after 4 weeks of treatment	Mutation TSC2 gene, small cortical tubers and nodules	Two weeks after cessation cardiac RDM increased markedly. Everolimus was restarted and rapid regression was observed
Wagner, 2015[13]	Term 2955 g	Largest mass almost filling the entire ventricle 21 × 37 × 21 mm	III/VI murmur		PGE_1, everolimus 1.5–2 mg/m^2			Prenatal MRI subependymal nodules, de novo TSC2 mutation	Everolimus stopped after 19 days of treatment, no rebound growth
Oztunc, 2015[14]	38 W	Multiple cardiac masses	SVT Ejection murmur	WPW	Adenosine, amiodaron, propranolol, sotalol, flecainide, Everolimus 0.25 mg twice a day, 2 days a week		Regression after 15 days of everolimus	Multiple tubers, TSC1 gene mutation	At 6 months after discharge, no recurrent tachycardia, small residual masses
Choudry, 2015[15]	Term 3650 g	8 RDM from 3 to 12 mm, 4 in RV, 4 in LV			Everolimus			Infantile spasms, subependymal nodules, renal AML	Resolution of all intracardiac masses at 1 month
Hoshal, 2015[1]	35 W 2535 g	Large pedunculated RVOT tumour with mild obstruction to flow. LV systolic function severely depressed, EF 20%	Systolic murmur	Biventricular hypertrophy	Dopamine, epinephrine, milrinone, calcium gluconate, blood products for coagulopathy. Everolimus 0.5 mg daily		Regression of RVOT tumour after 2 months	Subependymal nodules	Thriving, continued to receive everolimus
Colaneri, 2016[16]	35 W 2000 g	Giant tumour (4 × 3 × 4 cm) on LV		Ventricular extrasystoles	PGE_1, everolimus 0.25 mg daily	Mild mucositis, TG slightly elevated	Regression after 10 weeks	Renal AML Splice-site mutation (intron 29) of tuberine gene	Symptom-free and progression-free for 9 months
Bornaun, 2016[2]	38 W 3500 g	Mass located LVOT was 1.3 cm^2	Respiratory distress, systolic ejection murmur	Marked ST depression and LVH	Dopamine, PGE_1, everolimus 0.25 mg twice a day, twice a week. Omega 3	TG levels 560 mg/dl, thickening of IV walls	Resolution of LVOT obstruction after 1 month	Subependymal hamartomas TSC1 mutation hypopigmented skin lesions	Regrowth 10 days after cessation of therapy, everolimus restarted
Shigemitsu, 2016[17]		Largest RDM on RV, 30 × 36 mm	Circulatory collapse		Milrinone, everolimus 1 mg/m^2 day		On day 19, heart failure improved	Subependymal nodules, multiple retinal hamartomas	
Kayalil, 2017[18]	Term, 2800 g	LV mass (3.5–4 cm diameter)	Systolic ejection murmur hepato-splenomegaly		Everolimus 0.25 mg every 6 hours twice a week		After 20 days of everolimus, surgical resection was offered		Patient died. Final pathologic diagnosis was fetal-type RDM (no spider cells) without evidence of TSC

Aw, 2017[6]	31 W 980 g	2 RMD of RV + VSD, DORV with pulmonary valve atresia and hypoplastic pulmonary artery			Everolimus 0.1 mg daily		Significant reduction of RV RDM, surgical repair at 4.3 months, no need for RDM resection		Total regression recorded at 21 months
	34 weeks 1670 g	2 RDM, first attached to IV septum (7.3 × 2.8 mm), second located more anteriorly towards LV outflow tract (27.2 mm)			Everolimus 0.1 mg daily				Progressive increase in RDM size. Child remained asymptomatic
	34 weeks	Multiple RDM, largest near apex of RV (11 × 6 mm), two in the LV (3.6 × 5.7 mm and 6.8 × 5.2 mm)			Everolimus 0.1 mg daily		On day 22, echo showed 50% reduction of subaortic mass	SEGA	Patient remains on everolimus to mantain efficacy on cerebral SEGA
	38 weeks	Cardiac RDM in LV attached to IV septum (9 × 4.3 mm)			Everolimus 0.1 mg daily	Mouth ulcers	LV RDM undetectable 138 days after initiation of therapy.	SEGA	Progressive increase in RDM at day 112 without flow acceleration
Weiland, 2017[19]	–	Tumour located at the apex, encroaching on the LV and RV cavities, measured 25 × 25 × 33 mm in orthogonal planes. Also 3 smaller non-obstructive tumours			Sirolimus 0.1 mg/kg daily (steady-state target level of 5–15 ng/ml)	Sirolimus levels at 4 weeks was 22.5 ng/ml, discontinued sirolimus	11 days after starting therapy, echocardiogram showed a 74% reduction in the tumour volume	Missense mutation in the TSC2 gene	Follow-up 9 months after sirolimus was stopped, RDM showed interval size increase, remains less than one-third of original volume, unobstructive
	–	Multiple tumours in RV and LV. One larger tumour involving lateral wall of LV (22.1 × 14 × 8 mm), LVOT mobile mass (10.6 × 9.6 × 9.7 mm)			Sirolimus 0.1 mg/kg every 12 hours (steady-state target level of 5–15 ng/ml)	Sirolimus levels at 12 days 24.3 ng/ml, dose halved	Repeat echocardiogram showed tumour volume of LVOT reduction to one quarter the original volume, LV free wall volume decreased by >50%	Novel pathologic variant in the TSC2 gene	Follow-up 1 month later showed continued improvement in tumour size. Sirolimus level 12.1 ng/ml
Lee, 2017[20]	28 W 1170 g	Multiple RDM, largest (13.2 mm) in LV free wall, a 4.9 × 3.3 mm RDM in subaortic IVS, a 5.1 mm RDM in LV free wall. LVOT obstruction 80%	Cyanosis, SaO_2 75–80%. II/VI systolic murmur		Sirolimus 0.25 mg daily starting on the 18 DOL, prophylactic co-trimoxazole. Achieved steady-state target level of 10–20 ng/ml	Sirolimus levels at 14 days 42.1 ng/ml, dose tapered to 0.12 once daily	On 22nd day of treatment, marked reduction in size (3.7 × 3 mm) of RDM located in IVS. Obstruction in RV inflow tract disappeared at 43 days of treatment	Mother and brother disgnosed with TSC	Patient was discharged at 2 months of age, stopped sirolimus after 2 weeks of discharge. Symptom-free for 7 months
Chang, 2017[21]	38 W 2800 g	Large, high echogenic cardiac tumour occupying apical half chamber of LV (2.9 cm^2), small tumour in RV			Everolimus 0.0625 mg/day, aiming to achieve serum levels 3–7 ng/ml Weekly escalation	Everolimus serum level unexpectedly rose to 20 ng/ml, tapered dose to 0.0625 mg/day. Fever, cough, respiratory distress, everolimus withheld	After the third week, echocardiography revealed a remarkable reduction of tumour size	Genetic studies for TSC1 and TSC2 negative	Discharged on the 17th day of therapy. By day 50th of therapy, LV tumour had reduced to 0.29 cm^2 surface area. Slow increase in tumuor size, cardiac output remained adequate
	37 W 2880 g	Large, high echogenic tumour with three lobes in the basal area of LV. LV inflow, mitral valve orifice, and LV outflow completely occluded by tumour	SaO_2 85%		Everolimus 0.0625 mg/day, PGE_1, dopamine, bosmin, phenobarbitalphenytoin	Low serum levels of everolimus owing to drug–drug interaction with anticonvulsants	On 35th day, echocardiogram displayed a remarkable regression of the tumour and blood flow through both the mitral and aortic valves became satisfactory	Genetic studies for TSC1 and TSC2 negative	Patient discharged on 74th day of therapy. At 6 months of age, the remaining tumour appeared as a small nodule. At 16 days after discontinuation of everolimus, tumour size redounded to a surface area of 1.35 cm^2 with mild degree of mitral regurgitation. Everolimus reinstituted
	37.5 W 2720 g	High echogenic tumour exerting compression on the LVOT and extending outwards to the septum between AO and MPA. Surface areas of 2.6 cm^2 in long-axis view and 4.1 cm^2 in short-axis view		Isolated VPC	Everolimus 0.125 mg/day digoxin	On 5th day of therapy, everolimus serum level was 16.12 ng/ml, dose was reduced to 0.0625 mg	3 months later, echocardiography revealed marked shrinkage of tumour (0.8 cm^2 in long-axis view)	Genetic studies for TSC1 and TSC2 negative	Follow-up echocardiograms revealed steady regrowth of tumour. Compression effect of LVOT also recurred. Everolimus was reinstituted at 0.125 mg/day

AML = angiomyolipoma; AO = ascending aorta; BS = body surface; BW = birth weight; DOL = day of life; DORV = double-outlet right ventricle; EF = ejection fraction; GA = gestational age; IV = interventricular; LA = left atrium; LV = left ventricle; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; MPA = main pulmonary artery; mTOR = mammalian target of rapamycin; RA = right atrium; RDM = rhabdomyomas; RV = right ventricle; RVOT = right ventricular outflow tract; SEGA = subependymal giant-cell astrocytoma; SVT = supraventricular tachycardia; TG = triglyceride; TSC = tuberous sclerosis complex; VPC = ventricle premature contractions; VSD = ventricular septal defect; W = weeks; WPW = Wolf–Parkinson White

treatment-related side effects existed years before these drugs were first used to treat tuberous sclerosis complex.[22] Toxicity occurs in tuberous sclerosis complex patients with overall reduced frequency and severity compared with oncologic patients, possibly because these agents are monotherapies for tuberous sclerosis complex patients, whereas in other oncologic and transplant settings they are frequently combined with chemotherapy or immunosuppressant regimens. Furthermore, for cancer treatment, dosing is closer to the maximum tolerated dose, whereas in tuberous sclerosis complex dosing strategies seek to identify the minimum effective dose, thus avoiding side effects associated with higher doses.[22] In our case report, everolimus levels were not measured owing to unavailability. However, liver and renal function, lipid profile, and blood cell count were closely monitored. It is important to note that most commonly reported adverse effects have not been dose dependent.

In the first published case reporting regression of a cardiac rhabdomyoma in a patient receiving everolimus, Tiberio et al[7] described a therapeutic range of 5–15 ng/ml. The patient achieved everolimus serum levels of 2.3–7.1 ng/ml, showing near-resolution of ventricular rhabdomyoma.[7] Target sirolimus levels in the initial period after transplant range from 10 to 15 ng/ml, decreasing to 5–10 ng/ml over the medium to long term.[12] Breathnach et al aimed for a level of 20 ng/ml in their report, which showed a significant effect on tumour regression. However, initial dosage of 0.5 mg once daily was reduced to 0.4 mg once daily owing to sirolimus level of 26 ng/ml on day 7 of treatment.[12]

As described above, everolimus has a wider therapeutic range, and its use in tuberous sclerosis complex as monotherapy reduces the frequency and severity of toxicities.[12,22] Multiple dosing regimens have been described, and lower doses compared with the one described by Tiberio et al – for which no toxicity was reported – have been found to achieve regression of cardiac rhabdomyomas.

When compared, both agents similarly inhibit cell proliferation and T-cell immunologic activity, and both are efficacious in preventing organ rejection.[22] Comparative pharmacokinetics suggest that everolimus is more readily absorbed and exhibits greater oral bioavailability compared with sirolimus owing to selective intestinal cell efflux for which sirolimus alone is a substrate.[22] The more robust clinical trial experience with everolimus combined with regulatory approvals by the FDA and the European Medicines Agency provide the most compelling reason favouring everolimus over sirolimus to treat subependymal giant-cell astrocytoma and other tuberous sclerosis complex disease manifestations at this time.[22]

As rhabdomyomatous tissue can generate myocardial electrical potential and act as an accessory pathway, arrhythmias may develop with an incidence of 14–16%.[3,13] Resolution of arrhythmia was observed before tumour size regression in the majority of cases, with 2 weeks being the fastest rate.

Prenatal cardiac rhabdomyomas can be diagnosed from the 20th week of gestation, with a tumour growth spurt occurring between 22 and 32 weeks.[24] In this period, arrhythmia and non-immune hydrops may cause fetal death.[24] In fetuses with a tumour size greater than 20 mm, hydrops and dysrhythmia are significantly associated with neonatal morbidity.[24]

In older patients with tuberous sclerosis complex, the sequelae left by cardiac rhabdomyomas may lead to increased risk of sudden cardiac death.[24] It is important to remember that mammalian target of rapamycin inhibitors have proven to be a systemic therapy, which is rather important in a multisystem disease such as tuberous sclerosis complex. Unfortunately, little is known about the long-term effects of mammalian target of rapamycin inhibitors in patients with tuberous sclerosis complex who started everolimus early in their childhood.[24]

A potential use of mammalian target of rapamycin inhibitor therapy could be in pregnant women, for *in utero* treatment of cardiac rhabdomyomas. Successful pregnancies in women undergoing everolimus treatment have been reported without teratogenic manifestations in the neonate.[1] However, hyperglycaemia and hyperlipidaemia could be fetal risk factors that should be considered.[1] This is the largest cardiac rhabdomyoma of the left ventricle reported, presenting with an accelerated response to everolimus and no significant adverse effects.

Conclusion

Mammalian target of rapamycin inhibitors have proven to be efficacious in the size reduction of cardiac rhabdomyomas in cases in which surgical resection is not possible owing to extensive intramural myocardial involvement or tumour size. The more robust clinical trial experience with everolimus provides the most compelling reason favouring everolimus over sirolimus to treat tuberous sclerosis complex disease manifestations. Although several dosage regimens have been used, doses as low as 0.1 mg daily and 0.1 mg/kg/day for everolimus and sirolimus, respectively, have been reported to be effective. Monitoring serum levels for dosage tapering are recommended, although adverse effects are presumably dose-independent. Treatment with mammalian target of rapamycin inhibitors has proven to be well tolerated; however, little is known about the long-term effects of this treatment started in the neonatal period.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951118000598

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