Cardiology in the Young

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Literature review of international mammalian target of rapamycin inhibitor use in the non-surgical management of haemodynamically significant cardiac rhabdomyomas

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Review Article

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Abstract

Cardiac rhabdomyomas represent the most common primary paediatric cardiac tumour and typically regresses over time in the majority of patients. Among those who are symptomatic, surgical resection or catheterisation procedures have traditionally proven effective. More recently, those invasive or challenging tumours have been successfully treated with mammalian target of rapamycin inhibitors, typically everolimus and sirolimus. This review outlines the current medical literature of the state-of-the-art medical treatment of these tumours. We specifically focus on dosing regimens, duration of therapy, and side-effect profiles of mammalian target of rapamycin inhibitors among this population. Although the majority of cases responded to mammalian target of rapamycin inhibition, standardised guidelines for dosing and duration of treatment remain to be defined.

Introduction

Cardiac rhabdomyoma is the most common primary paediatric cardiac tumour, often demonstrating mild atypical histologic features and lacking the capacity for metastasis.[1] Although histologically benign, the location within critical areas in the heart can lead to life-threatening complications. Symptoms of cardiac rhabdomyomas arise because of chamber or valve obstruction, arrhythmias, or cardiac failure resulting from extensive myocardial involvement. Traditionally, symptomatic lesions were treated by surgical excision or cardiac catheter interventions. However, more recently, novel new medical therapies with mammalian target of rapamycin inhibitors are being used, especially in children where surgical intervention is unsuitable or not possible. In this paper, we review the natural history of cardiac rhabdomyomas, previous treatments, and review the published cases to date using mammalian target of rapamycin inhibitors.

Natural history of cardiac rhabdomyomas

A cardiac rhabdomyoma is a hamartoma of developing cardiac myocytes which although benign in certain cases, due to their location and size, may lead to complications. The natural history of cardiac rhabdomyomas is one of spontaneous regression. Consequently, clinical and echocardiography monitoring is usually sufficient in the majority of cases except specific instances where intervention is warranted. Cardiac rhabdomyomas frequently occur in association in up to 50% of patients with tuberous sclerosis.[2] Similarly, anywhere between 50 and 90% of children diagnosed with cardiac rhabdomyomas demonstrate clinical or radiologic evidence of tuberous sclerosis. One paper,[3] describing 30 patients with cardiac rhabdomyomas, reported 83% of these patients had confirmed tuberous sclerosis. Another study[4] reported 31 of the 33 babies with cardiac rhabdomyomas having associated tuberous sclerosis: the majority had multiple lesions, and four babies presented with signs of left ventricular outflow tract obstruction and/or heart failure. Of these four, one required surgery, one died soon after birth due to multiple huge rhabdomyomas detected antenatally leading to severe heart failure, and in the other 2 obstructing masses reduced in size without requiring any intervention. In this same study, spontaneous regression of rhabdomyomas occurred in all 32 surviving patients. Bosi et al[5] reported 19 out of 33 patients with cardiac rhabdomyomas manifesting cardiac symptoms including arrhythmias, outflow tract obstruction, and atrioventricular valve regurgitation phenomena. Only 2 of the 33 patients required surgical resection of the left ventricular outflow tract obstructing tumours. Jóźwiak et al[6] studied 154 patients with tuberous sclerosis of whom 48% had cardiac rhabdomyomas. In the adolescent cohort, three of those patients who had had previous rhabdomyoma regression experienced re-growth of rhabdomyomas in teenage years, and three other patients had a de novo growth of rhabdomyomas in adolescence.

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Location of cardiac rhabdomyomas

Cardiac rhabdomyomas can arise anywhere throughout the heart; however, the most common areas include the intraventricular septum and ventricular cavities. The location determines everything from clinical symptoms and presentation to the need for intervention. In the majority of cases, rhabdomyomas are multiple. Sciacca et al[4] reported 205 rhabdomyomas among 33 patients at presentation. Ninety-four percent were in the ventricles, 2.9% in the right atrium, 1.9% close to valves, and 0.5% in the left atrium. Black et al[3] noted that 93% of patients had some involvement of the left ventricle. Bosi et al[5] reported 77 rhabdomyomas in 33 patients with all but one being located in the ventricles.

Currently established treatments

Given the natural history of the majority of cardiac rhabdomyomas is typically regression, a minority develop significant haemodynamic compromise requiring intervention. Traditionally, intervention comprises of either surgery or cardiac catheterisation (ductal stenting, balloon atrial septostomy). Among a series of 33 patients,[3] 23% (n = 7) required surgical intervention for left ventricular outflow tract obstruction without any complications. Ilina et al[7] reported successful patent ductus arteriosus (PDA) stenting in a baby with a large intracardiac rhabdomyoma causing tricuspid inflow obstruction leading to cyanosis and hypoxemia. PDA stent was performed on day 11 of life and allowed discontinuation of prostaglandin and discharged home. At follow-up at 7 months old, interestingly, the cardiac rhabdomyoma had not regressed in size as expected; however, relative to the size and somatic growth of the heart, it was no longer causing obstruction to right heart inflow. McMahon et al[8] reported a case of balloon atrial septostomy in a neonate with extensive right ventricular rhabdomyoma not amenable to surgical resection. This allowed decompression of the right heart and subsequent palliation with a Blalock Taussig shunt. Complete resolution of the rhabdomyoma was seen in a 5- year-old, and the child had successful coil occlusion of shunt and subsequent surgical closure of atrial septal defect.

Novel treatments – mammalian target of rapamycin pathway

In the human body tuberous sclerosis proteins 1 and 2, also known as hamartin and tuberin, form a protein complex which is involved in control of cell growth and division and acts as a tumour suppressor. The TSC1/TSC2 protein complex controls mammalian target of rapamycin signalling (mammalian target of rapamycin) via its subset mammalian target of rapamycin complex 1. The production of these proteins is under the control of genes TSC1 and TSC2 (Fig 1).

The mammalian target of rapamycin signalling pathway serves as a central regulator of cell metabolism, growth, proliferation, and survival. The mammalian target of rapamycin protein is a serine-threonine kinase that belongs to the phosphoinositide 3-kinase-related kinase family. There are two subtypes of mammalian target of rapamycin, mammalian target of rapamycin complex 1 and mammalian target of rapamycin complex 2. Mammalian target of rapamycin complex 1 positively regulates cell growth and proliferation by promoting many anabolic processes, including biosynthesis of proteins, lipids, and organelles and by limiting catabolic processes such as autophagy (sequestration of intracellular components within autophagosomes and their degradation by lysosomes). Dysregulation of this pathway, e.g., mutations in

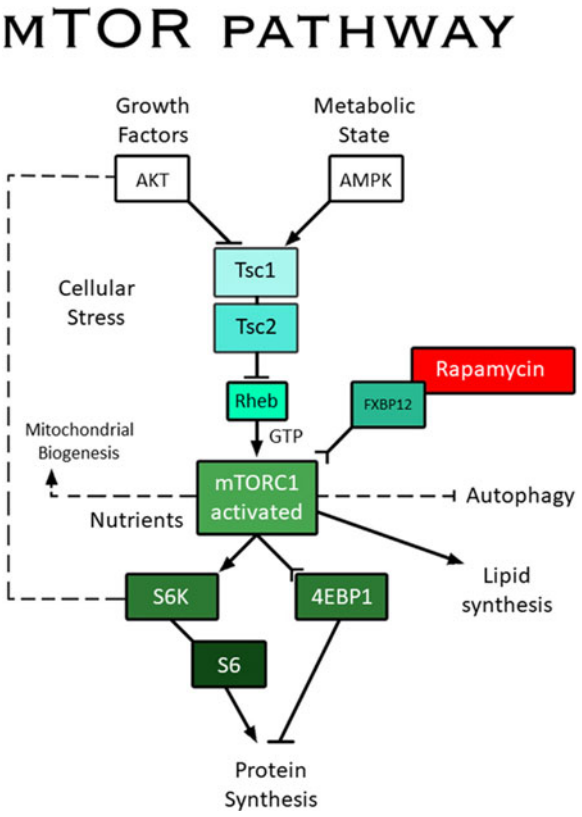

Figure 1. PRISMA flow diagram.

TSC1/TSC2 genes can therefore lead to unregulated cell growth and proliferation and thus tumour formation.

Since discovery of the mammalian target of rapamycin pathway, much interest has focused on the therapeutic use of rapamycin and rapalogs (rapamycin analogs). Initially, rapamycin was an anti-fungal drug and subsequently its immunosuppressive properties were noted and it came into use with organ transplant patients. In more recent times, it is being used in the treatment of tumours. Upon entering the cell, rapamycin binds to FK506-binding protein and interacts with the FKBP12-rapamycin binding domain of mammalian target of rapamycin, thus inhibiting mammalian target of rapamycin complex 1 functions. Of note, FKBP12-rapamycin cannot physically interact with or acutely inhibit mammalian target of rapamycin complex 2. Because of this mammalian target of rapamycin complex 1 is referred to as rapamycin-sensitive complex and mammalian target of rapamycin complex 2 as rapamycin insensitive.

Kotulska et al[9] demonstrated increased expression of mammalian target of rapamycin and decreased hamartin and tuberin in all six rhabdomyoma patients they studied. This study confirmed dysregulation of the mammalian target of rapamycin pathway in cardiac rhabdomyomas thereby raising the possibility of therapeutic use of mammalian target of rapamycin inhibitors. Numerous cases series and reports of mammalian target of rapamycin inhibitors, typically everolimus or sirolimus, have been published showing the success and complications associated with these treatments (Table 1).

Methods

The purpose of this review was to review all the published literature from 1990 to March 2020 on the use of mammalian target of

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Table 1 Summary of 90 patients, presentations, treatment and outcomes of mTOR inhibitor use

	Case	Location of CR	Presenting issue	Other treatment	Drug used	Patient age starting txn	Dose	Drug level aim	Duration of txn	Response	Side effects	Reference
1	Initial	Mass in LVOT (diameter 1.3 cm^2) with extensive intramural components. LVOT gradient 66 mmHg. Smaller RV masses with mild RVOTO	Poor suck, de-saturations, hypotonia worsening LVOTO (80 mmHg)	PGE2, Dopamine	Everolimus	7 days	0.5 mg BD twice /week	0.4–2.6 ng/mL	1 month	Reduction in LVOT mass diameter + resolution of LVOTO	Elevated serum triglycerides (560 mg/dL)	[10]
	Recurrence	Significant regrowth of all cardiac masses after 10 days of stopping txn	Louder murmur	–	Everolimus	(approx 7 weeks)	0.5 mg BD twice /week	(0.4–2.6 ng/mL)	6/12 + 1.5/12 of tapering dose	Marked decrease in size of cardiac masses	Elevated serum triglycerides, normalised with starting omega 3. IVS thickening (6 mm to 12 mm), normalised on D/C of drug	
2	Initial	Giant tumour engulfing RV with severe TR and RVOTO. Smaller tumours in LV	PGE2 dependant from birth	PGE2, Ductal Stent and balloon atrial septostomy	Everolimus	3 weeks	3 mg/m^2 Dosing freq not specified	4–5 ng/ml	3 months	Substantial decrease in tumour size, no RVOTO	Hyponatremia requiring NaCl supplementation	[11]
	Recurrence	Dramatic increase in size of CR in RV after 2 weeks of stopping txn	–	–	Everolimus	(approx 4 months)	not specified	(Not specified)	until 1 year old	Rapid regression in CR size	–	
3		8 CRs: 2 in RV, 2 in mitral papillary muscle, 3 in IVS, 1 on TV with assoc TR. RVOTO	Cyanosis, Low sats (85–90%)	PGE2, Frusemide	Everolimus	not specified	0.25 mg QDS for 4 doses then reduced to 0.25 mg BD twice/week	5–15 ng/ml	2.5 months	×2 RV CRs had disappeared. RVOTO and inflow obstruction resolved. Trivial TR	Elevated serum triglycerides. Normalised with omega 3	[12]
4		Large CR almost filling whole LV and protuding into LVOT- 21 × 37 × 21 mm. Smaller CR in RV below pulmonary artery – no RVOTO	LVOTO	PGE2	Everolimus	2 days	1.5–2 mg/m^2 OD. D/C × 4/7 due to high levels then restarted at 1 mg/m^2	5–15 ng/ml	19 days	LV CR reduced to a vol of 5 ml and dimensions of 10 × 28 × 13 mm. RV CR significantly reduced in size	Nil	[13]
5		Multiple CRs in IVS, subpulmonic area, left AV junction, mitral papillary muscles, RV anterior wall, LV posterior wall	Refractory SVT	Flecanide, sotolol, adenosine, amiodarone, propranolol, Cardioversion.	Everolimus	10 days	0.25 mg BD twice/week	Not specified	4 weeks	After 8 days reduction in freq and duration of SVT. After 15 days – CRs began to shrink visibly on echo	Nil	[14]
6		Giant CR (40 × 35 × 40 mm) over apical and free wall of LV incl left coronary artery. Several smaller CRs	Ventricular extrasystoles. Severely reduced LV vol and function (EF-35%)	PGE2	Everolimus	1 week	1.5 mg/m^2 initially-titrated down over time to 1 mg/m^2	5–15 ng/ml	10 weeks	>80% reduction in size of main CR	Mild mucositis. Slight increase in serum TG levels (139 mg/dL)	[15]

(*Continued*)

Table 1 (*Continued*)

	Case	Location of CR	Presenting issue	Other treatment	Drug used	Patient age starting txn	Dose	Drug level aim	Duration of txn	Response	Side effects	Reference
7		LV Inflow tract CR – 24 × 21mm, LV outflow tract CR-22/20 mm with mild obstruction, CR @cardiac apex-16/ 18 mm, RA CR – 10 × 10 mm, multiple tiny masses in RV and LV-free wall	Cyanosis, Low sats (85%)	Frusemide, Amiodarone	Everolimus	2 days	0.25 mg BD twice/ week – adjusted depending on level	5–15 ng/ml	3 months	Significant reduction in tumour size	Not specified	[16]
8		Large LV apical mass, smaller LV masses	–	Digoxin	Everolimus	5 years	Not specified	2.3–7.1 ng/ml	13 months	Near resolution of previously unchanged ventricular CR	Not specified	[17]
9		Massive intrapericardial CR with invasion into LV, IVS, mitral papillary muscles. Large pedunculated RVOT CR w mild obstruction	Initially tachypnea and severely depressed LV function. Circulatory collapse DOL 8	High freq ventilation, dopamine, milrinone, epinephrine, calcium gluconate	Everolimus	Not specified (neonate)	0.5 mg daily	Not specified	Ongoing (>10 months)	Significant regression of left tumour size. Normal LV EF (63%). RVOT tumour barely visible	Not specified	[18]
10	Patient 1	6 CRs: Largest in RV (16 × 11 mm) with severe inflow obstruction, LV Lat wall (8 × 15 mm), mitral papillary muscle muscle (7 × 5 mm), smaller ones attached to apex and septum. Note: also double outlet right ventricle, pulmonary atresia, ventricular septal defect	PGE2 dependant from birth	PGE2	Everolimus	20 days	0.1 mg daily	5–15 ng/ml	34 days	Significant reduction in RV CR, near disappearance of LV CR	Nil	[19]
	Patient 2	LV CR ×2 (7.3 × 2.8 mm, 27.2 mm), RV CR ×3 (8.3 × 6.8 mm, 4 mm, 6 mm), RA CR- 6 mm	Not specified	Not specified	Everolimus	4 days	0.1 mg daily	5–15 ng/ml	81 days	Reduction in largest LV CR. Complete regression of smaller LV CR, RA and RV CRs	Nil	
	Patient 3	3 large non obstructive CRs: apex of RV (11 × 6 mm), ×2 in LV (3.6 × 5.7 mm, 6.6 × 5.2 mm)	Nil haemodynamic significance	–	Everolimus	9 days	0.1 mg OD initially. Increased to 0.5 mg OD @4/12 due to low serum levels. Increased to 0.75 mg OD @7.5/12 due to low serum levels	5–15 ng/ml	Not specified	RV and LV CRs undetectable by 1 month and day 147, respectively	Mouth ulcers – required 1 week of txn at 4 months old	
11		Multiple CRs. Largest in LVOT- 15 × 12 mm with a gradient of 70 mmHg and vel of 4.2 m/s	Murmur	PGE2	Sirolimus	10 days	0.5 mg OD. Reduced to 0.4 mg OD on day 7 due to high serum levels	not specified	24 days	LVOT CR reduced dramatically in size (5 × 4 mm)	Nil	[20]
12		Base of IVS, moderator band and RVOT, at time of treatment just 1 at moderator band	Refractory atrial tachycardia. 2nd degree AV block	Digoxin, propranolol, quinidine	Sirolimus	3 years	1 mg/m^2 BD. Increased to 2 mg/ m^2 after few months to be in target range	5–15 ng/ml	Not specified	Resolution of atrial tachycardia after 14 days txn	Slight increase in cholesterol	[21]

13	Patient 1	2 CRs: 1 at apex filling one half of LV chamber, second in RV free wall	Reduced LV compliance (E/A reversal)	Digoxin, frusemide	Everolimus	not specified (neonate)	0.334 mg/m^2 OD. After 1 week 0.427 mg/m^2 OD. After 2 weeks 0.558 mg/m^2 OD. Day 50 reduced to 0.241 mg/m^2 OD. Day 80 reduced to 0.12 mg/m^2 OD	3–7 ng/ml	3 months	Significant reduction in CR size. Slow increase in size of CR after stopping txn but with somatic growth no ill effect	Reduction in height, weight, occipital frontal circumference < 3rd centile	[22]
	Patient 2	Large LV CR occluding LV inflow, mitral valve orifice and LV outflow	Respiratory distress requiring intubation haemodynamic compromise	Intubation, dopamine, adrenaline, PGE1	Everolimus	not specified (neonate)	0.316 mg/m^2 OD. Day 14 increased to 0.613 mg/m^2 OD. Day 28 increased to 1.2 mg/m^2 OD. Day 35 reduced to 0.6 mg/m^2 OD. Final dose 0.35 mg/m^2 0D	3–7 ng/ml	6 months	Significant reduction in size of CR (appeared as small nodule attached to lateral papillary muscle in LV). Normal blood flow through aortic valve and mitral valve	Nil	
	Recurrence	16 days after stopping txn – significant increase in size of CR	Mild MR	–	Everolimus	(6.5 months)	0.125 mg OD (0.35 mg/m^2 OD)	(–)	Not specified	Tumour regressed to small nodule and remained that way	Nil	
	Patient 3	Large CR (SA = 2.6 cm^2 in PLAX and 4.1 cm^2 in parasternal long axis). LVOTO, compression between main pulmonary artery and aorta pushing them apart	Premature ventricular contractions	Digoxin	Everolimus	2 days	0.658 mg/m^2 OD. Day 5 reduced to 0.33 mg/m^2 OD. Day 32 increased to 0.51 mg/m^2 OD	3–7 ng/ml	4 months	Significant reduction in size of tumour (PLAX = 0.8 cm^2)	Reduction in height and weight <15th centile	
	Recurrence	Increased size of CR (2.97 cm^2) with associated LVOTO	–	–	Everolimus	(5 months)	0.125 mg OD (=0.379 mg/m^2 OD)	(–)	4 months	Reduction in size of CR	Nil	
14		8 CRs: 2 in RV, 2 in LV septal wall, 2 in LV free wall, 1 in subpulmonic region, ×1 lateral to pulmonary valve	Asymptomatic – treatment given for SEGA	–	Everolimus	Not specified	Not specified	Not specified	Not specified	Resolution of all CRs at 1 month f/u	Nil	[23]
15		Not specified	Initially cardiogenic shock. Subsequent frequent NSVT on holter	Sugical debulking of biggest tumour. Amiodarone, Nadolol	Everolimus	10 months	0.08 mg/m^2 OD, Twice per week for 3–4 months. 0.35 mg OD twice per for about 11 weeks	Trough 8–10 ng/ml	6 months	Significant reduction in size of rhabdomyomas. Increase arrhythmia burden with everolimus/amiodarone therefore nadolol added and VT controlled	Adenovirus + pneumonia – required to half everolimus for 3 weeks. Increased VT burden on everolimus	[24]
16	Patient 1	Not specified	Not specified	Flecanide and propranolol	Everolimus	14 days	0.3 mg OD twice/ week	Not specified	Not specified	Reduction in CR size	Nil reported	[25]
	Patient 2	Not specified	Not specified	Antiepileptics	Everolimus	5 months	1 mg OD	Not specified	Not specified	Reduction in CR size	Transient anemia	
	Patient 3	Not specified- CR and SEGA	Not specified	Propraolol, antiepileptics	Everolimus	7 days	Not specified	Not specified	Not specified	Reduction in CR size and SEGA size	Recurrent infection, increase in cholestrol, TG and lactate dehydrogenase, reduction in phosphate	

(*Continued*)

Table 1 (*Continued*)

	Case	Location of CR	Presenting issue	Other treatment	Drug used	Patient age starting txn	Dose	Drug level aim	Duration of txn	Response	Side effects	Reference
	Patient 4	Not specified	Not specified	Propraolol, anti epileptics	Everolimus	7 days	0.05 mg every second day	Not specified	Not specified	Reduction in CR size	Infantile acne, increase in phosphate and cholinesterase	
	Patient 5	Not specified	Refractory arrhythmia	Flecanie, metoprolol, amiodarone, digoxin, anti epileptics	Everolimus	3 months	0.1 mg BD	Not specified	Not specified	Reduction in CR size and control of refractory arrhythmia achieved	Recurrent upper respiratory tract infection, transient neutropenia	
	Patient 6	Not specified	Not specified	Digoxin, anti epileptics	Everolimus	2 days	1.5–2 mg/m^2 daily	Not specified	Not specified	Reduction in CR size	Increase in TG/ cholesterol, transient lymphopenia	
	Patient 7	Not specified	Not specified	Anti epileptics	Everolimus	2 days	0.25 mg daily	Not specified	Not specified	Reduction in CR size	Nil reported	
17		×1 large CR on LV free wall, ×1 CR on RV free wall, ×1 CR in IVS, multiple small CRs in right and left ventricular myocardium	Reduced LV function on echo	Nil	Sirolimus	1 week	not spec	Not specified	4 weeks	Reduction in size of all CRs and normalisation of LV function	Nil	[26]
18		47 × 40 mm CR LV free wall, 10 × 17 mm CR in IVS, 10 × 10 mm CR in RV free wall	Resp distress at birth requiring intubation. Severe systolic and diastolic dysfunctions	Intubation, PGE2, Dobutamine, diuretics	Everolimus	Day 36	0.25 mg BD twice/ week	Not specified	84 days	Reduction in tumour size (biggest reduced to 22 × 29 mm) and restoration of normal ejection fraction	Nil	[27]
19	Patient 1	25 × 25 × 33 mm CR at apex encroaching into LV and RV cavity. ×3 small non-obstructive tumours (location not specified)	Nil issue	Nil	Sirolimus	Not specified (neonate)	0.1 mg/kg OD (0.36 mg)	5–15 ng/ml	4 weeks	Reduction in size of large CR to 12% of original size	Nil (slight increase in size post stopping sirolimus but no haemodynamic issues)	[28]
	Patient 2	22.1 × 14.5 × 8 mm CR LV lat wall, 10.6 × 9.6 × 9.7 mm CR in LVOT. Multiple other small CRs in RV and LV	Nil specified	Nil specified	Sirolimus	Not specified (neonate)	0.1 mg/kg BD initially. Reduced to 0.05 mg/kg BD at 12 days due to high levels. Reduced to 0.03 mg/kg OD 1 month later	5–15 ng/ml	Not specified	Reduction in size of CRs, LV lat wall CR = 10 × 9 × 7 mm, LVOT CR = 6 × 5 × 5 mm	Nil	
20		IVS CR 35 × 28 mm	Cardiac arrest ×2. Severely impaired function	Nil specified	Everolimus	Not specified (neonate)	0.1 mg OD	Trough 5–8 ng/ml	Not specified	Reduction in size of CR to 21 × 11 mm	Nil reported	[29]
21		13.2 mm and 5.1 mm CRs in LV free wall, 5.1 × 3.6 mm CR in LVOT/ IVS, RV free wall CR	Respiratory distress, cardiac arrest. (28/40)	Intubation, cardiopulmonary resuscitation, dobutamine	Sirolimus	18 days	Initially 0.25 mg OD. Day 14 reduced to 0.12 mg/day due to high serum levels	10–20 ng/ml	2.5 months	Reduction in size of all CRs: LVOT CR reduced to 2.3 × 1.9 mm, IVS to 8.7 mm. Clinical improvement – d/c home at 2 months old	Nil reported (Given prophylactic co-trimoxazole for duation of sirlimus therapy)	[30]

22	51 patients	Median maximum diameter of tumor was 8.7 (5.9–11.3) mm	Not specified	Not specified	Sirolimus	Median age = 15 months (7–35 months).	Started at 1 mg/(m(2)·d)	5–10 μg/L	Not specified	CRs disappeared in 51% cases, reduced by more than 50% in size in 29%, reduced by less than 50% in size in 12%, had no change/progressed in 8%	10 reported adverse events : 9 – dyslipidemia, ×1 canker sore	[31]
23		Multiple CRs in both ventricles with largest in RV cavity measuring 35 × 21mm and causing near functional pulmonary atresia and LVOTO	Murmur, cool peripheries, sats-90%	PGE2	Everolimus	Day 4	Initially 0.2 mg/kg OD × 4/7. Stopped due to complications. Day 10: one dose of 0.1 mg. Stopped again due to high serum level. Day 25 dose of 0.025 mg given but stopped due to high LFTs	5–15 ng/ml	6 doses	Some reduction in CR size while on treatment	Stopped after 4 doses due to severe respiratory deterioration, pulmonary haemorrhage, coagulopathy and deranged LFTs – treated with fresh frozen plasma. Day 8 developed acne requiring topical quinilone – resolved 2 weeks later	[32]
24		Multiple. X1 CR in RV free wall 40 × 37 × 30 mm, ×1 in LV basal septum/LV cavity 28 × 16 × 14 mm, muliple small tumours in both atria and ventricles, ×1 CR on septal leaflet of TV 5 mm	Hypotension, then acidosis and NSVT	Epinephrine, vasopressin, amiodarone	Everolimus	Not specified (neonate)	Initially 0.3 mg/m^2 OD. At 6/12 old increased to 0.6 mg/m^2 OD	Not specified	>6 months (not specified)	Reduction in size of CRs and subependymal nodules + complete involution of renal tumours	Nil reported	[33]
25	Patient 1	RVOT – 24 mm	Resp distress	Not specified	Everolimus	7 days	Daily divided dose of 4.5 mg/m^2/week	Not specified	60 weeks	Reduction in size of CRs	Varicella at 6 weeks of txn so had to stop txn for 4 weeks	[34]
	Patient 2	Superior vena cava /RA junction – 13 mm	Resp distress	Not specified	Everolimus	6 days	Daily divided dose of 4.5 mg/m^2/week	Not specified	32 weeks	Reduction in size of CRs	Nil reported	
	Patient 3	LVOT – 12 mm	Resp distress	Not specified	Everolimus	90 days	Daily divided dose of 4.5 mg/m^2/week	Not specified	8 weeks	Reduction in size of CRs	Nil reporter	
	Patient 4	RV cavity – 28 mm	Resp distress	Not specified	Everolimus	3 days	Daily divided dose of 4.5 mg/m^2/week	Not specified	16 weeks	Reduction in size of CRs	Nil reporter	
	Patient 5	RV cavity – 36 mm	Resp distress	Not specified	Everolimus	1 day	Daily divided dose of 4.5 mg/m^2/week	Not specified	8 weeks	Reduction in size of CRs	Nil reporter	

AV = atrioventricular; BD = twice per day; CR = cardiac rhabdomyoma; D/C = discontinuing; IVS = interventricular septum; LFT = liver function tests; LV = left ventricle; LV EF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; LVOTO = left ventricular outflow tract obstruction; NSVT = non-sustained ventricular tachycardia; OD = once per day; PGE2 = prostaglandin E2; PLAX = parasternal long axis; RA = right atrium; RV= right ventricle; RVOT = right ventricular outflow tract; RVOTO = right ventricular outflow tract obstruction; SEGA = subependymal giant cell astrocytoma; SVT = supraventricular tachycardia; TG = triglyceride; TR = tricuspid regurgitation; TV = tricuspid valve; VT = ventricular tachycardia.

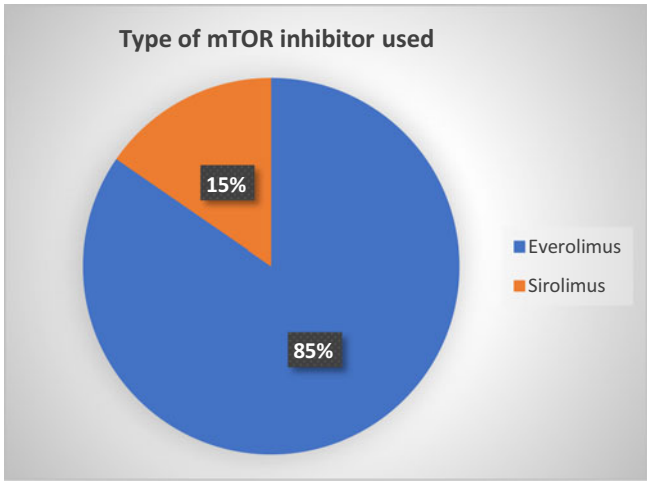

Figure 2. Study design for George *et al* trial.

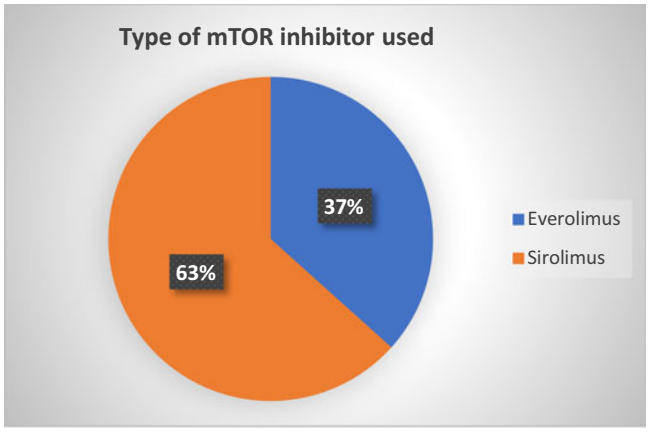

Figure 3. Choice of mammalian target of rapamycin inhibitor (including Chinese paper[31]).

rapamycin inhibitors in treatment of cardiac rhabdomyoma. We conducted a PubMed search for any literature using the key words cardiac rhabdomyoma, mammalian target of rapamycin inhibitors, everolimus, and sirolimus. We excluded cases of antenatal treatment of mothers with mammalian target of rapamycin inhibitors. Any articles/papers with overlapping data were not included twice. Using these criteria, we included all the published data (Table 1) outlining location, number of cardiac rhabdomyomas, clinical symptoms, associated treatments, type of mammalian target of rapamycin inhibitor used, age at commencement of therapy, dose and dosing range, duration of therapy, effect of treatment, and side effects or complications.

Results

In total, 25 published papers met inclusion criteria reporting on 90 patients (Table 1). In general, these were all case reports or small case series, apart from one large case series published from China.[31] However, specific details on each patient in the series were not given in the publication, and so for the purpose of some of our analysis, this paper was excluded, leaving a total of 39 patients in 24 publications (see Table 1).

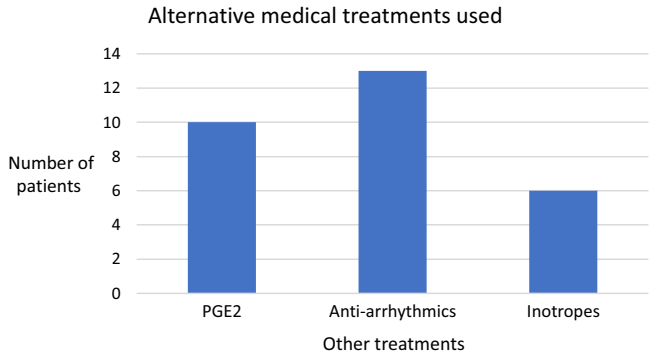

Figure 4. Alternative medical treatments used (excluding Chinese paper[31]).

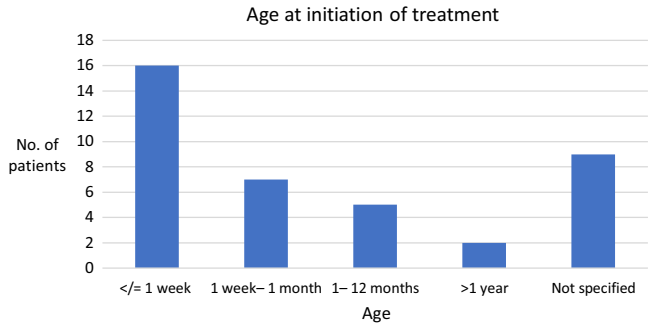

Figure 5. Age at initiation of mammalian target of rapamycin inhibitor treatment (excluding Chinese paper[31]).

Each paper reported either a reduction in size or complete resolution of cardiac rhabdomyomas. In three, patients-specific improvement in rhythm control (re-entrant tachycardia, atrial tachycardia) was also reported. Interestingly, one paper[24] reported a significant increase in ectopic burden and non-sustained ventricular tachycardia with use of everolimus despite a reduction in size of cardiac rhabdomyoma and so concomitant therapy with nadolol was required.

There are two mammalian target of rapamycin inhibitors in use, sirolimus and everolimus. Excluding the Chinese series, 85% of patients (n = 33) were treated with everolimus and 15% (n = 6) with sirolimus (Fig 2). Interestingly, all 51 patients in the Chinese series were treated with sirolimus. Therefore, when this paper is included in analysis, 37% (n = 33) of patients were treated with everolimus and 63% (n = 57) with sirolimus (Fig 3).

Given the known haemodynamic and arrhythmic complications associated with rhabdomyomas, it is unsurprising that patients required other concomitant medical therapies, prior to, or in combination therapy with mammalian target of rapamycin inhibitors. Ten patients were reported to have required prostaglandin E2, 13 patients were treated with anti-arrhythmic agents, and six patients needed inotropic support (Fig 4).

There was a wide range of ages at which therapy was initiated with the majority being within the first week of life (n = 16). Nine papers did not specify the age of commencement of therapy. Seven patients were treated with mammalian target of rapamycin inhibitors between 1 week and 1 month of age, five patients between 1 month and 12 months of age, and two patients started treatment after 1 year of age (Fig 5).

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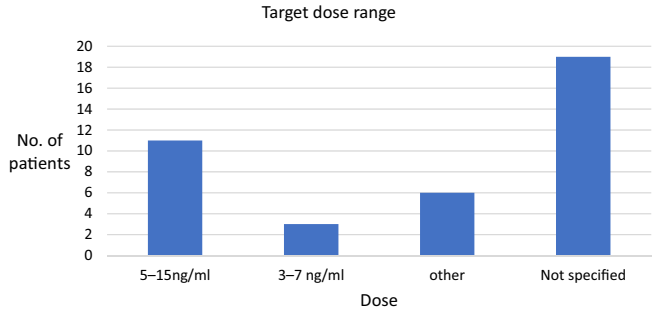

Figure 6. Target dose range for mammalian target of rapamycin inhibitor levels.

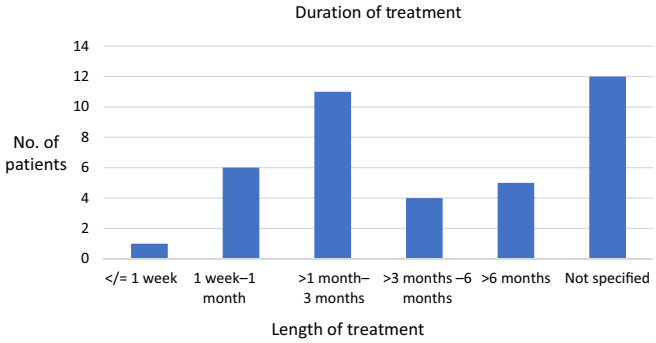

Figure 7. Duration of treatment with mammalian target of rapamycin inhibitors.

The dose of mammalian target of rapamycin inhibitor varied considerably between reports. Some used set doses, others dose per kg or body surface area (BSA). There was significant differences in frequency of dosing; once vs. twice per day, daily, every other day or twice per week. Some centres used a target range to guide their dosing. The most commonly used range was 5–15 ng/ml (n = 11); however, a large proportion did not report their target range (n = 19). Other target ranges used include 5–10 ng/ml, 3–7 ng/ml, 4–5 ng/ml, and in one paper[(6)] 0.4–2.6 ng/ml (Fig 6).

Furthermore, there was a significant variation in the duration of mammalian target of rapamycin treatment between the different centres. However of those centres who reported a duration of therapy, the majority were treated for 1–3 months (n = 11). In one case, 32 only 6 doses were given in total due to serious adverse effects leading to discontinuation of therapy. In five cases, children received therapy for longer than 6 months (Fig 7).

The side-effect profile of any novel therapy is critically important. Of the 90 patients overall, 15 (17%) were reported to have dyslipidaemia (raised cholesterol or triglycerides), the most commonly reported side effect. Five cases of systemic infection were reported. One case report[24] described a patient who developed adenovirus pneumonia while on treatment which necessitated halving of mammalian target of rapamycin inhibitor dose for 3 weeks. Another case series[25] reported two patients with recurrent upper respiratory tract illnesses while on therapy. One child[34] developed varicella infection during treatment and so mammalian target of rapamycin inhibitor therapy was held for 4 weeks. Other side effects reported included mucositis/mouth ulcers (n = 3), infantile acne (n = 2), reduced growth (n = 2), and deranged full blood count/urea and electrolytes including anaemia, neutropenia, and lymphopenia (n = 6). Of the 90 patients reviewed, 64 (71%) reportedly showed no adverse effects (Figs 8 and 9).

Discussion

As previously highlighted, cardiac rhabdomyomas are generally benign with little clinical impact and a tendency to spontaneously regress over time. However for the small number which cause haemodynamic compromise, intervention, or treatment is required. Mammalian target of rapamycin inhibitors are a novel treatment modality indicated in symptomatic cardiac rhabdomyomas which are not amenable to surgical resection or intervention. Having examined the series of published cases using mammalian target of rapamycin inhibitors for haemodynamically significant rhabdomyomas, these agents are clearly efficacious with all cases showing reduction in size or full resolution of cardiac rhabdomyoma.[10–23,26–30,32,33] However, these drugs are not without risk, and standardised dosing and treatment duration regimens remain to be defined. From the published case reports to date, there is no general consensus on dose of mammalian target of rapamycin inhibitors (variations from 0.1 mg OD to 0.25 mg BD twice per week to 0.5 mg BD twice per week). Also there is wide variation in the duration of treatment (19 days to 1 year). Several case reports mentioned a rhabdomyoma growth rebound on sudden cessation of treatment and recommended tapering the dose of mammalian target of rapamycin inhibitor in order to avoid this. There have been no studies to date comparing everolimus to sirolimus; however, if we look at data from studies of these drugs in relation to transplant/immunosuppression, we learn more. One study in 2010[35] looked at 409 patients post renal transplant; 220 of whom received everolimus vs 189 of whom received sirolimus. The study showed that although the overall incidence of discontinuations due to side effects was higher in the everolimus group, the frequency of severe side effects was similar in both. Another group[36] looked at heart transplant recipients with renal impairment who were randomised to either everolimus or sirolimus showing everolimus had less impact on lipids than sirolimus. Mammalian target of rapamycin inhibitors have many side effects including hypertriglyceridaemia, immunosuppression, and sepsis. Careful monitoring for these side effects is essential and in certain cases other therapies may be initiated, e.g., omega 3 fatty acids.

The ORACLE trial[37] is the first large randomised control PROTOCOL trial looking at the use of everolimus in cardiac rhabdomyomas associated with tuberous sclerosis. It is a phase II, prospective, randomised, placebo-controlled, double-blind, multicentre protocol trial. They plan to recruit 40 children with symptomatic cardiac rhabdomyoma secondary to tuberous sclerosis. The patients will be randomised to receive oral everolimus or placebo for 3 months. The primary outcome is 50% or more reduction in the tumour size related to baseline. As secondary outcomes, they have included the presence of arrhythmias, pericardial effusion, intracardiac obstruction, adverse events, progression of tumour reduction, and effect on heart failure. They are using a dosing regimen of 4.5 mg/m^2 BSA as start dose and a target range of 5–15 ng/ml. This study will hopefully clarify the efficacy, optimal dosing, and side-effect profile of everolimus.

Conclusion

Mammalian target of rapamycin inhibitors have a valuable role in the treatment of haemodynamically significant cardiac rhabdomyomas which are either inoperable or surgically challenging.

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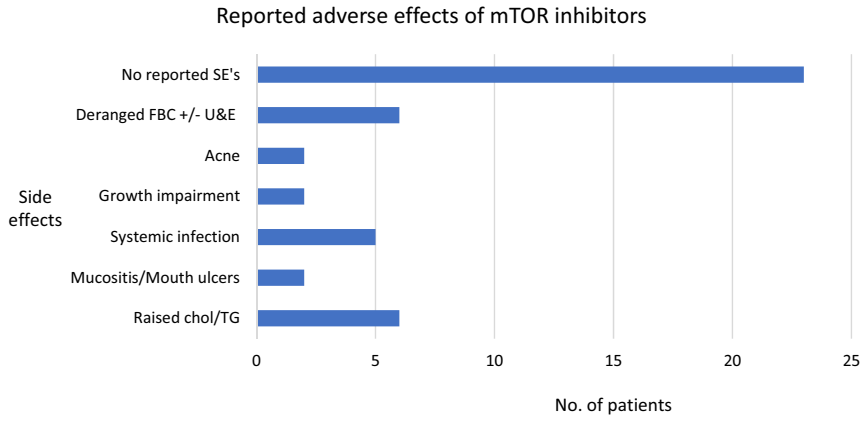

Figure 8. Reported adverse effects of mammalian target of rapamycin inhibitors (excluding Chinese data, total patients n = 39). FBC = full blood count; U&E = urea and electrolytes.

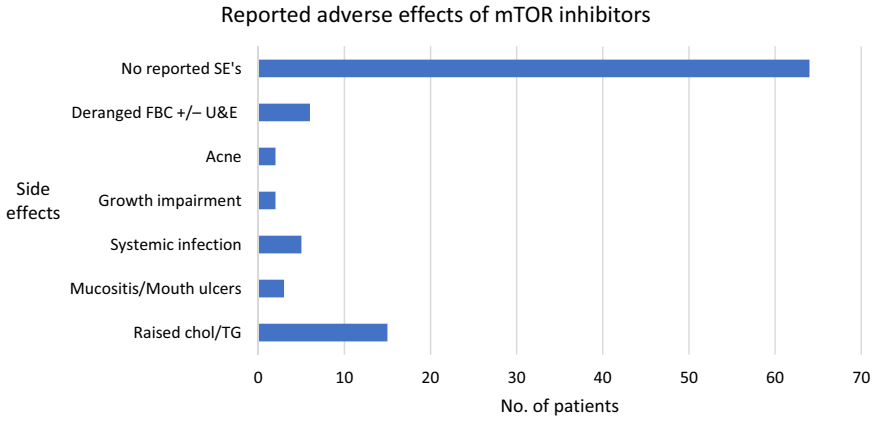

Figure 9. Reported adverse effects of mTOR inhibitors (including Chinese data, total patients n = 90). FBC = full blood count; U&E = urea and electrolytes.

To date, there have only been case reports with regard to use of these medications. The ORACLE study will hopefully provide further data on the efficacy, dosing, and side-effect profile of everolimus. However, further trials will be warranted to compare sirolimus and everolimus and potential other therapies for use in this clinical setting.

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Conflicts of interest. None.

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