Cardiology in the Young

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Effect of different dose regimens of everolimus in a series of neonates with giant cardiac rhabdomyomas

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Abstract

Everolimus is a mTOR inhibitor that has been increasingly used in high-risk cardiac rhabdomyomas in recent years. There are questions regarding the optimal dose and duration of therapy with everolimus for cardiac rhabdomyomas. The purpose of this study was to examine retrospectively the dosage-efficacy relationship in seven babies diagnosed with rhabdomyoma treated with different everolimus dose regimens retrospectively. Cardiac rhabdomyoma diagnosis was made in six of seven babies during the prenatal period. Indication of everolimus was an obstruction in six patients and supraventricular tachycardia which is resistant to antiarrhythmic drugs in the remaining one patient. The median age was 8 days (range; 2–105 days) at the time of starting everolimus. It was administered at a dose of 0.25 mg twice a day for two days a week in four patients; 0.1 mg/day in two and 0.4 mg/day in one patient. Serum everolimus level was kept between 5 and 15 ng/ml. All seven cases showed significant regression of cardiac rhabdomyoma within four weeks, and supraventricular tachycardia was controlled in two weeks after everolimus administration.

This study demonstrates that everolimus was effective in accelerating regression of the cardiac rhabdomyoma. Dose with 2 × 0,25 mg/day, 2 days a week, seems appropriate. However, lower doses such as 0.1 mg/day are also effective. But dose adjustment should be made according to serum level monitoring.

Cardiac rhabdomyoma is the most common cardiac tumour seen in fetuses and infants. It is accounting for >60% of all primary cardiac tumours in children.[1,2] It is highly associated with tuberous sclerosis complex, 80% of children with rhabdomyoma have findings of tuberous sclerosis complex.[3] Cardiac rhabdomyoma develops in utero and is often detected early on prenatal ultrasound or before the age of one year. It may involve the myocardium of both ventricles, the interventricular septum, and occasionally the atria, typically with well-described boundaries.[4] Most of them are asymptomatic in neonates and do not require treatment. Patients with haemodynamically critical cardiac rhabdomyoma may present with fetal arrhythmias, non-immune hydrops fetalis, respiratory distress, congestive cardiac failure, cyanosis, or sudden death. They often show spontaneous regression during childhood and need only close follow-up.[5] However, sometimes it is not possible to wait for spontaneous regression, especially when large masses cause intracardiac obstruction and become symptomatic by disrupting haemodynamics. If cardiac rhabdomyoma provokes haemodynamic problems, surgical treatment was the only option previously. In recent years, everolimus has been used as an alternative viable treatment option to surgery to accelerate regression of the mass. Everolimus is a serine-threonine kinase mTOR (mammalian target of rapamycin) inhibitor that has been increasingly used in high-risk cardiac rhabdomyomas in recent years.[6] Inhibition of mTOR activity leads to alteration of cell protein synthesis and thus prevention of cell proliferation, differentiation, growth, and migration. Its efficacy is good in rhabdomyoma associated with tuberous sclerosis, but there are uncertainties about the effective dose and duration of use. The purpose of this study was to examine the dosage-efficacy connection in seven babies diagnosed with rhabdomyoma treated with different everolimus dose regimens retrospectively.

Material and method

Seven patients who received everolimus treatment for significant cardiac rhabdomyomas in a single centre between 2017 and 2022 were evaluated retrospectively in the study. Significant cardiac rhabdomyoma is defined as the presence of either clinical symptoms or obstruction to the blood flow demonstrated by transthoracic echocardiogram. Prenatal and natal

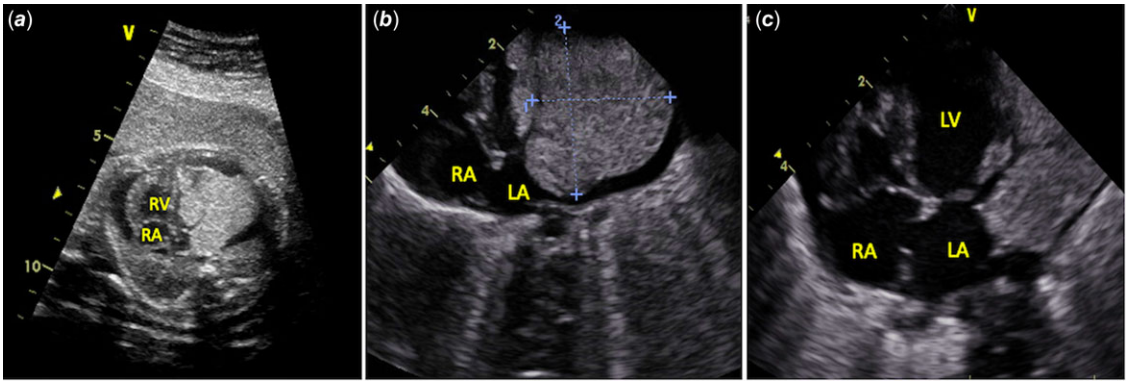

Figure 1. Case 1. (***a***) A four-chamber view of fetal echocardiography shows a giant left ventricle tumour occupying the left ventricle cavity, causing inflow obstruction. (***b***) A postnatal transthoracic echocardiography confirmed a 36 × 33 mm giant rhabdomyoma arising from the left ventricular myocardium and severely decreasing the ventricular volume. (***c***) The figure shows regression of the mass.

characteristics were recorded. Informed consent was obtained from parents after a detailed discussion about the risks and benefits of the medication. Initial thorough clinical examination, chest X-ray, electrocardiogram, and transthoracic echocardiogram were performed. The size of the tumour, number, location, haemodynamic interference, and cardiac function were noted. Baseline complete blood count, liver and renal function tests, and lipid profiles were done. Abdominal, cranial ultrasonography, and cranial MRI were performed for all infants to investigate for tuberous sclerosis. Neurology, oncology, ophthalmology, and dermatology consultations were requested. The indication for the administration of everolimus, time of initiation, dosage, duration of treatment, serum level, side effects, and outcome was recorded. The initial dosages of everolimus were determined based on previous reports.[6–8,10–19] Follow-up clinical examinations including electrocardiography and transthoracic echocardiogram were done two times a week for 2 weeks, then weekly for 4 weeks, and then biweekly to see the response. Sizes of the cardiac rhabdomyomas, gradients at the site of obstruction, and cardiac functions were noted on follow-up. Serum everolimus levels were also checked in the same way. Therapeutic serum levels were aimed to be kept between 5 and 15 ng/mL based on the work of Krueger et al.[7]

Results

Seven patients were included in the study. Cardiac rhabdomyoma was detected in six of seven babies during the prenatal period. One patient (case 2) was admitted due to a cardiac murmur on the postnatal 37th day. The mothers' mean age at pregnancy was 31.6 ± 4 years (median; 29.8, range; 21–34). The mean gestational age at diagnosis was 28.4 ± 6.0 weeks (median 28; range, 19–37). During the fetal period, two babies had supraventricular tachycardia (case 3,6). Fetal supraventricular tachycardia was brought under control with digoxin and flecainide combination therapy, and sinus rhythm was obtained and did not recur in the postnatal period in case 3. However, in case 6, intermittent short-term supraventricular tachycardia persisted throughout the fetal life due to drug incompatibility of the mother. Various degrees of growth in the size of rhabdomyoma were observed in all infants during the fetal follow-up period. Hydrops fetalis or death was not observed in the intrauterine period. No pregnancy termination was performed.

Postnatal follow-up

The gestation week at birth was between 33 and 39 weeks. The majority of patients were male (5/7). All babies were accepted as tuberous sclerosis complex-associated cardiac rhabdomyoma as a result of the investigations except case 1. Two cases were considered as materno-fetal tuberous sclerosis complex. The diagnosis of cardiac rhabdomyoma was confirmed by a transthoracic echocardiogram in all patients. In case 1, a transthoracic echocardiogram revealed a giant rhabdomyoma of 36 × 33 mm in size, originating from the left ventricular myocardium and significantly reducing the ventricular cavity, moderate mitral insufficiency, moderate pericardial, severe systolic, and diastolic dysfunction (Fig 1). Two smaller tumours, sized 10 × 17 mm and 10 × 10 mm, located at the interventricular septum and at the RV free wall, respectively, were detected as well. Case 2 was admitted on the postnatal 37th day, and a mass was detected in the interventricular septum (9 × 10 mm), and there was an additional mass (10.7 × 13.2 mm) close to the pulmonary valve leading to obstruction of the RVOT. In case 3, postnatal echocardiography revealed a giant mass (14 × 28 mm) originating from the interventricular septum and filling the RV. In addition, there were multiple masses in the LV apex and free wall. Case 4 had severe obstruction in LVOT with a mass at 15 × 19 mm in size. Case 5, postnatal echocardiography, revealed multiple masses, the largest one was 8 × 10 mm in size but did not cause any obstruction but he had multiple drugs (propranolol and flecainide)-resistant supraventricular tachycardia episodes. In the postnatal period, transthoracic echocardiography confirmed the giant mass (25 × 30 mm) causing significant obstruction to RV inflow which leads to duct-dependent pulmonary circulation in case 6. Moreover, he had multiple attacks of supraventricular tachycardia which was resistant to propranolol and flecainide therapies. There was pre-excitation in the superficial ECG. Patient 7 had multiple rahbdomyomas, the biggest one (21 × 27 mm) located at the left ventricular outflow tract. It was occluding the LV inflow and outflow tract, and the blood flow velocity at the LVOT was 4,2 m/sec.

Median age and weight were 8 days (range; 2–105 days) and 2975 g (range; 1950–5500), respectively, at the time of starting everolimus. The indication of the everolimus was obstruction in the inflow or outflow tract in five babies (cases 1,2,3,4,7), postnatal supraventricular tachycardia, and right ventricular inflow obstruction in one (case 6), and due to postnatal supraventricular

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tachycardia resistant to antiarrhythmic therapy without outflow tract obstruction in one (case 5). Everolimus was started with 0.25 mg two times per day twice a week in four babies (case 4–7), 0.1 mg daily in two babies (case 2,3), and 0.4 mg daily in one baby (case 1). Baseline characteristics, duration of treatment, and clinical response are summarised in Table 1.

The median duration of treatment was 8 weeks (range 4–12) for all patients. During this period, significant regression was observed in the cardiac rhabdomyoma in all patients (Fig 2). At the end of the 2nd and 4th weeks, the median reductions in the size of cardiac rhabdomyoma were 32.2% (range 21.4–47.2%) and 52.2% (range 37.0–66.3%), respectively (Fig 2). In case 6, also a balloon atrial septostomy was done because an interatrial shunt was insufficient to maintain haemodynamic stability. Everolimus treatment also controlled supraventricular tachycardias that were resistant to antiarrhythmic medication in two infants.

Everolimus was well tolerated. The median serum everolimus level was 9.3 ng/ml (range; 7.6–37.1), except for one patient who received high-dose everolimus therapy. The drug level was kept within the target range with current therapy in all other. There were no complications or side effects related to the drug administration or systemic involvement in the four babies. Hypertriglyceridaemia was detected in two patients (cases 2 and 7). In case 2, serum triglyceride levels showed fluctuations although everolimus serum levels were between 5 and 15 ng/ml. Serum triglyceride levels showed peaks between 400 and 560 mg/dl during treatment. Triglyceride levels were decreased by reducing the dose of everolimus and initiating omega-3 acids. In case 7, hypertriglyceridaemia is treated by lowering the dose of everolimus. One of the seven babies died (case 1). He was considered surgically inoperable because of the huge size of the mass. He received high-dose everolimus treatment, and although there is a significant reduction in the size of the mass, he succumbed to pneumonia on the 25th day of the treatment. The patient's WBC count was 22,900/mm^3, the neutrophil count was 13.700/mm^3, the PLT count was 87/mm^3, and CRP was 12.9 mg/dl (<0.5). The baby also had high serum everolimus concentration above the recommended therapeutic level (37.1 ng/ml).

The median follow-up period was 8.5 months (range 6–36) after discontinuation of the treatment. Recurrence of right ventricular outflow tract obstruction was noted after discontinuation of everolimus in case 2. Everolimus was restarted in this baby at the same dose when the velocity of the RVOT reached 4.3 m/s. It regressed within 2 weeks, and the obstruction was resolved. Tumour rebound did not occur in the other babies.

Discussion

The findings of this study demonstrate that everolimus treatment is effective in tumour regression in patients with cardiac rhabdomyoma who needs rapid tumoral mass reduction if appropriate serum levels are provided. Cardiac rhabdomyoma tends to grow due to maternal hormones in the fetal period and even in the early neonatal period and has a tendency to regress later on.[9] However, spontaneous regression may not be seen in all cases. In addition, sometimes in certain situations, patients cannot wait for spontaneous regression due to haemodynamic compromises and faster solutions may be obligatory. Although most patients with cardiac rhabdomyoma are asymptomatic, in some patients, cardiac rhabdomyoma can reach a size that will cause life-threatening haemodynamic problems such as cardiac inflow/outflow obstructions ending up with heart failure or cause tachycardia resistant to drugs.[2,5,6,10] Haemodynamics may even become ductus-dependent in some cases due to severe obstruction caused by the tumour as in our case 6.[12] In such cases, the surgical option is the first solution that comes to mind, but surgical removal of the masses is difficult and has a high risk, and it is not always possible because of the multiple masses in different locations and their infiltrative nature. Therefore, everolimus has been used as an alternative viable treatment option to surgery in these cases to accelerate regression of the mass. Despite the current lack of high-quality data from randomised or large cohort studies, mTOR inhibitors have been already used in the treatment of cardiac rhabdomyoma in patients with tuberous sclerosis complex, especially for symptomatic or large cardiac rhabdomyoma often as an alternative to surgical treatment.[6,13,14] Aw F et al. compared the rate of cardiac rhabdomyoma size reduction between a small group of patients treated with mTOR inhibitors and a historical control group.[15] They observed that patients treated with everolimus had a cardiac rhabdomyoma regression rate 11.8 times faster than controls.

As seen in most case-based studies in the literature, there is not yet a standard protocol for everolimus in the treatment of cardiac rhabdomyomas. Although the dose of everolimus varied among the reports, there was a general consensus that serum trough levels should be kept within the therapeutic range of 5–15 ng/mL.[6,8,17,19] The doses of everolimus varied from 0.05 to 1 mg and were implemented in different dosing schedules from daily dosing to two days per week in the other studies. Generally, doses of 4.5 mg/m^2/week (about 0.1 mg/day) or 0.25 mg two times per day, 2 days per week, have been used.[6] There are also researchers who recommend a dose of 0.1 mg in newborns.[17] In most of the studies reporting the information about targeted everolimus level, it is 5–15 ng/mL.[6,8] In case 1, we used the higher dose of 0.4 mg/day, since the patient was in a critical situation. Although cardiac rhabdomyoma regressed rapidly on the 10th day and the baby was relieved haemodynamically, pneumonia developed in the follow-up. Because of this unfavourable experience, the 2nd and 3rd babies were successfully treated with a lower dose of 0.1 mg daily. In the next four babies, a 2 × 0.25 mg regimen was used two days a week due to ease of use. Both everolimus protocols were found to be effective, safe, and tolerable. According to our experience, keeping serum everolimus levels around 5–15 ng/ml will increase the safety margin of the drug. It should be kept in mind that similar doses may result in different serum levels in different patients. Dose adjustment should be made according to serum level monitoring. A low initial dose regimen (0.1 mg once daily) may be considered a safer approach in newborn babies, followed by titration according to serum level monitoring.

Among the reported cases who get treatment, information in terms of how fast the tumour shrinks and how long it takes varies. Generally, 3–4 weeks after everolimus treatment, 30–50% reduction in dimensions was observed.[6,14,19] However, the optimal duration of mTOR inhibitor treatment is still unknown. We aimed to use it for at least 4 weeks if there were no side effects. Therapy with mTOR inhibitors resulted in a significant clinical improvement or resolution of cardiological symptoms in 30 out of 33 children with symptomatic cardiac rhabdomyoma (90.9%).[6] Likewise, we observed a significant reduction in mass in all cases. Sometimes, treatment modalities can be combined as in our case number 6. Since a huge cardiac rhabdomyoma occluded the inflow of the right ventricle, percutaneous balloon atrial septostomy was performed to provide preload, and, simultaneously, PGE1 was administered to supply pulmonary blood flow until the mass regressed and allowed right ventricular filling.

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Table 1. Detailed clinical characteristics of all patients.

	Age at diagnosis	Sex	TSC	Location of significant cRHM	Largest size before treatment (mm)	Time of treatment (days)/ weight(g)	Everolimus dosage	Max. Everolimus serum level (ng/ml)	Duration of treatment (weeks)	Adverse effects	Follow-up time (month)	Outcome
Case 1	21 GW	F	No	Lateral wall of LV	33 × 36	2/1950	0.4 mg/day	37.1	4	Pneumonia	–	cRHM regressed Dead
Case 2	Postnatal-37 days	F	Yes	Outflow of RV	10.7 × 13.2	105/5500	0.1 mg/day	12.6	8	Serum TG level 592 mg/dl	6	cRHM Regressed
Case 3	34 GW	M	Yes	Outflow of LV	14 × 28	6/2975	0.1 mg/day	7.6	12	–	25	cRHM Regressed
Case 4	32 GW	M	Yes	Outflow of LV	15 × 19	4/3200	0.25 mg twice a day, 2 days a week	9.3	10	–	36	cRHM regressed
Case 5	28 GW	M	Yes	Apex of LV	8 × 10	8/2900	0.25 mg twice a day, 2 days a week	8.9	6	–	10	cRHM Regressed SVT controlled
Case 6	25 GW	M	Yes	Inflow of RV	25 × 30	6/2800	0.25 mg twice a day, 2 days a week	8.5	5	–	6	cRHM Regressed SVT controlled
Case 7	22 GW	M	Yes	Outflow of LV	21 × 27	3/3300	0.25 mg twice a day, 2 days a week	11.3	10	Serum TG level 268 mg/dl	7	cRHM Regressed

*cRHM, cardiac rhabdomyoma; F, female; GW, gestational week; LV, left ventricle; M, male; RV, right ventricle; SVT, supraventricular tachycardia; TG, triglyceridemia; TSC, tuberous sclerosis complex.

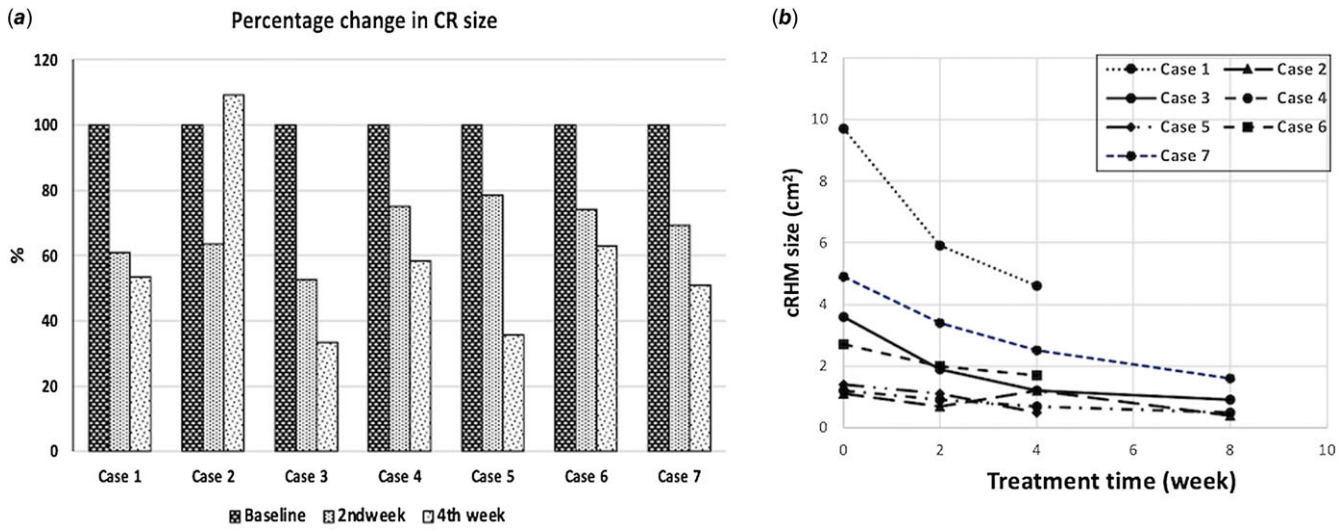

Figure 2. (***a***) Figure showing the percentage change in tumour size relative to baseline during treatment. (***b***) The figure shows the cardiac rhabdomyoma size (cm^2) following initiation of everolimus in the 2nd and 4th weeks.

Arrhythmias including bradycardia or tachycardia occur in 16–47% of cases with cardiac rhabdomyoma and are more prevalent in these patients compared with the general population.[1,2,19] Patients with larger cardiac rhabdomyomas are more likely to experience arrhythmias. Arrhythmias due to cardiac rhabdomyomas is a major cause of fetal and neonatal death, and it is usually associated directly with the location of specific tumours. A few cases are reporting the comorbidity of tuberous sclerosis complex, cardiac rhabdomyomas, and pre-excitation, and its prevalence is not fully known.[20,21] Van Hare et al. suggested that accessory pathways in patients with rhabdomyoma arise from the intracardiac tumour or are closely related to it.[22] Similarly, three cases presented with supraventricular tachycardia and Wolff Parkinson White syndrome were detected in one of them. The utility of mTOR inhibitors for treating cardiac rhabdomyoma-related arrhythmias has yet to be addressed. Limited case reports indicate that everolimus has been successful in this regard.[23,24] In our study, case 3 with fetal supraventricular tachycardia responded to transplacental antiarrhythmic therapy. The other two babies (case 5 and 6) were resistant to antiarrhythmic therapy in the postnatal period, and supraventricular tachycardia was controlled with everolimus therapy.

Information on the follow-up period after discontinuation of everolimus administration is limited. The finding that in some of these cases, rebound growth of cardiac tumour occurred following the withdrawal of everolimus suggests that continuous use of everolimus is necessary for some patients.[19] However, in the meta-analysis of Sugalska et al., rebound was observed in 17.1% of cases after cessation of treatment, and treatment was restarted in 7.3% of them.[7] Aw F et al. observed an increase in cardiac rhabdomyoma size in three of four patients after discontinuation of everolimus .[15] However, everolimus was not restarted in these patients as regrowth did not cause haemodynamic problems. In our case series, after cessation of treatment rebound that requires re-treatment was observed in only one patient (14.2%). Moreover, no supraventricular tachycardia attack was observed after discontinuation in babies given everolimus treatment for supraventricular tachycardia.

Everolimus is primarily metabolised by the liver cytochrome P450 enzymes. This metabolic pathway is immature in preterm and full-term newborns in the neonatal period, for which liver function should be monitored. The elimination half-life of everolimus is 29.7 hours in children and adults and also is prolonged to a mean of 79 hours in patients with hepatic impairment.[25,26] It is not known in preterm and newborn babies. Although previous studies, mostly large randomised EXIST studies, proved the acceptable safety profile of mTOR inhibitors in children with tuberous sclerosis complex, some side effects of everolimus treatment have been reported.[8,27,28] The most common side effects were dyslipidaemia (mostly hypertriglyceridaemia), recurrent infections, mouth ulcer, transient lymphopenia /neutropenia, liver dysfunction, transient anaemia, and electrolyte abnormalities.[6,15,17] Therefore, complete blood count and liver function tests, blood biochemistry including electrolyte, triglyceride levels, and serum drug concentration should be checked during follow-up. Although most of the adverse effects were reported as mild and the severity of side effects is mostly dosage-dependent, pulmonary haemorrhage was reported as the most serious side effect.[26] In our series, the baby who was given a higher dose than the other babies died due to pneumonia on the third week of everolimus therapy. But it has not been fully clarified whether the pneumonia was a side effect of everolimus or a coincidence. Some authors ceased mTOR inhibitors treatment when adverse events occurred, others implemented treatment, for example, omega-3 acids for hypertriglyceridaemia or prophylactic treatment with antifungal drugs or antibiotics.[20] We did not observe any side effects other than hypertriglyceridaemia. Hypertriglyceridaemia was observed although everolimus levels were at the target level in our patients. Triglyceride levels were controlled by reducing the dose of everolimus and omega-3 acids. High levels of drug serum levels were observed even at low everolimus doses. It should be kept in mind that similar doses may result in different serum levels in different patients. Dose adjustment should be made according to serum level monitoring.

Although there are no long-term data on everolimus use specifically in children being treated for tuberous sclerosis complex-related cardiac rhabdomyoma, the data reported to date suggest that long-term treatment with everolimus in young patients does not affect growth and physical maturity, but more longitudinal data are needed, through child-bearing age, to establish this lack of influence.[27]

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Almost all of the experience with everolimus therapy belongs to use in the postnatal period. Transplacental everolimus treatment can be life-saving, especially in rhabdomyomas that cause haemodynamic problems and even hydrops due to both obstruction and tachyarrhythmia in the fetal period. Recently, a few case-based experiences have been shared regarding its use as transplacental in the fetal period. However, the dose of everolimus to be used in this period and the appropriate maternal serum levels are unknown. Fakhari et al. reported that they used transplacental sirolimus in three fetuses and rhabdomyomas gradually decreased in all of them.[28] They also noted no severe adverse events occurred during the treatment period.

Limitation

The small number of cases stands out as the most important limitation. Studies on the half-life of the drug, especially in newborn infants, will be instructive. More data are needed in terms of the long-term side effect profile of the drug. In addition, randomised multicentre studies are needed to better understand the efficacy of everolimus independent of natural spontaneous regression.

Conclusion

This series demonstrates that everolimus was effective on accelerating regression of the cardiac rhabdomyoma in neonates and one infant. Different everolimus protocols have been experienced in literature. Dose with 2 × 0,25 mg/day, two days in a week, or doses as low as 0.1 mg daily are also effective. There is no need for higher doses in terms of effectiveness; it should be noted that the possibility of side effects will increase if used. If serum levels are kept between 5 and 15 ng/ml, it will be better tolerated and the possibility of side effects will be much less. Serum everolimus levels should be checked regularly, even at low doses, for a safer treatment protocol.

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Conflict of interest. None.

Ethical standards. 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.

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