Everolimus for the Treatment of Tuberous Sclerosis Complex–Related Cardiac Rhabdomyomas in Pediatric Patients

Nagib Dahdah, MD

Cardiac rhabdomyoma (cRHM), a benign, smooth-muscle hamartoma, occurs predominantly in infants and children; approximately 75% of affected children are aged ≤1 year, and 33% are aged ≤1 month.[1,2] cRHM is the most common type of primary cardiac tumor identified in pediatric patients, accounting for >60% of all primary cardiac tumors in this population,[2-4] with an estimated incidence of 0.02%-0.08% of live births.[2,5] It is also the most common cardiac tumor of the fetus.[2]

In 60%-80% of cases, cRHM is associated with tuberous sclerosis complex (TSC),[4] an autosomal dominant disease in which abnormal cellular proliferation and differentiation result in the development of hamartomas.[6] Although patients may remain asymptomatic and clinically well, these hamartomas may ultimately cause organ dysfunction in multiple locations, including the brain, heart, skin, kidneys, lungs, and liver.[7,8] TSC has an overall incidence of 1:6000-1:10 000 live births and a population prevalence of 1:20 000.[7,9] In >85% of patients, the origin of TSC is an inactivating mutation in the genes encoding either hamartin (*TSC1*) or tuberin (*TSC2*).[10,11] In healthy persons, these genes act together to inhibit mammalian target of rapamycin (mTOR), which is involved in the regulation of cell growth, proliferation, differentiation, and metabolism.[6,8,10,11] Inactivating *TSC1* or *TSC2* mutations eliminate this mTOR inhibition, resulting in the TSC phenotype and the development of hamartomatous lesions.[6,8]

cRHMs are rarely observed in patients without TSC and are usually the presenting manifestation, often detected in utero.[2,7,12,13] They are located primarily in the ventricles (**Figure 1**), where they may interfere with ventricular function, but can occur in the atria as well.[4,8,14,15] Moreover, multiple cRHMs commonly occur; almost all fetuses with multiple cRHMs are found to have TSC.[4,12,16] Although most patients with cRHMs are asymptomatic, in some patients the cRHMs are either sufficiently large or in a location that causes cardiac compromise, reflected in dysrhythmias, intracardiac blood flow obstruction, or congestive heart failure.[4,5,8] Arrhythmias, both bradycardia and tachycardia, are issues of varying significance in TSC, occurring in 16%-47% of cases with cRHMs (**Figure 2**),[4] and are more prevalent in patients with TSC compared with the general population. Patients with larger cRHMs are more likely to experience arrhythmias.[17] The mechanisms underlying bradycardia in TSC are thought to be sinus and atrioventricular node dysfunction, and those underlying tachycardia include atrial, accessory atrioventricular connection reentrant, and ventricular tachycardia.[12] These symptoms are usually associated directly with the location of specific tumors.[12] cRHMs can lead to loss of functional myocardium and predispose patients to left ventricular and papillary muscle dysfunction, which can cause low cardiac output and congestive heart failure. Arrhythmia due to cRHMs is a major cause of fetal and neonatal death.[2] Fetal arrhythmias are frequently associated with hydrops, a prognostic indicator of poor outcome.[18] In addition, arrhythmia that persists postnatally is associated with increased risk of sudden neonatal and infant death.[18]

There is a high rate of spontaneous regression of cRHMs in utero and after birth, likely owing to a reduction in the effects of maternal estrogen and postnatal loss of mitotic potential of rhabdomyoma cells. Many cRHMs will have regressed by birth, and complete resolution of tumors frequently occurs during early childhood.[4,15,19,20] Currently, surgical resection is the usual treatment for cardiac tumors with severe obstruction and hemodynamic compromise or with hemodynamically significant arrhythmias that are unresponsive to antiarrhythmic medications.[12]

Despite the generally good outcome and tumor regression, cRHMs can be fatal, and intervention may be required either immediately upon presentation or during early childhood.[1,12,21] In fact, cRHM-related hemodynamic compromise and congestive heart failure are the most frequent causes of death among pediatric patients with TSC aged <10 years.[12] Furthermore, growth or appearance of new cRHMs may occur during puberty.[11] There remains a clear unmet need among young patients with cRHM who could benefit from expedited tumor regression to prevent cardiac symptoms and ultimately mitigate or resolve the potentially serious and life-threatening sequelae of their condition.

The emerging recognition of the involvement of mTOR in cRHMs provides a potential target for therapy. mTOR inhibitors have demonstrated efficacy in other TSC-associated tumors, including subependymal giant cell astrocytomas (SEGAs), slow-growing brain tumors found in up to 20% of patients with TSC,[22-26] and renal angiomyolipomas, found in up to 80% of these patients.[27-30] However, the observation of lesion regrowth following discontinuation of mTOR inhibition has led to the suggestion that this therapy may need to be continuous.[30-32]

cRHM	Cardiac rhabdomyoma
mTOR	Mammalian target of rapamycin
SEGA	Subependymal giant cell astrocytoma
TSC	Tuberous sclerosis complex

From the Division of Pediatric Cardiology, CHU Sainte-Justine, University of Montreal, Quebec, Canada

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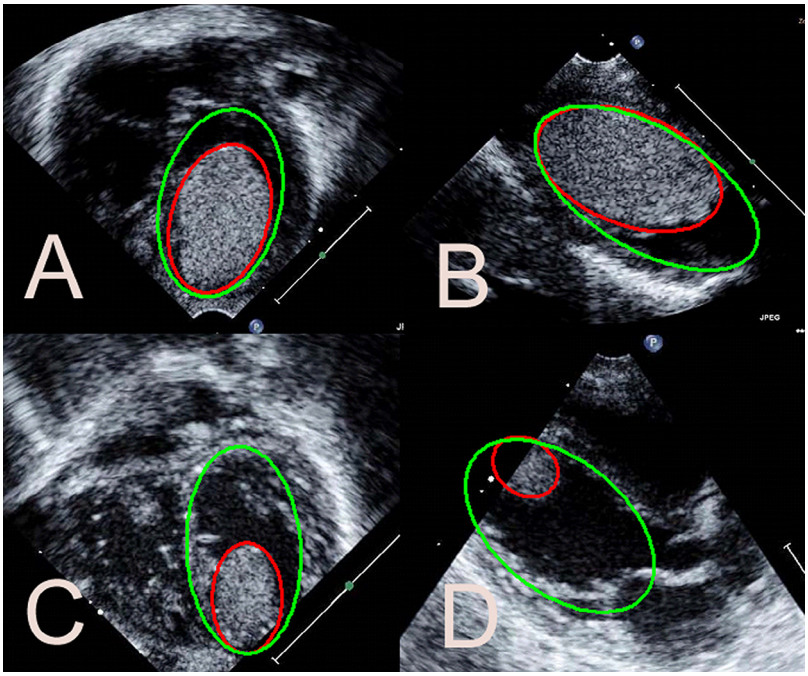

Figure 1. Large cardiac rhabdomyoma in a newborn occupying a significant volume of the left ventricle at birth in the apical 4-chamber view (**A**) and long axis view (**B**). At 1 month following everolimus therapy, the rhabdomyoma had shrunk significantly in size (same views, respectively, **C** and **D**). The green shapes approximately delineate the left ventricular cavity, and the red shapes delineate the rhabdomyoma.

Everolimus is an mTOR inhibitor approved by the US Food and Drug Administration for the treatment of pediatric and adult patients with TSC-associated SEGAs that require intervention but for which curative resection is contraindicated, and in adult patients with TSC with renal angiomyolipomas that do not require immediate surgery.[33] The aim of this review is to provide a consolidated discussion of published case studies to explore the clinical benefit and safety profile of everolimus for the treatment of cRHMs in infants and preschool children.

Case Studies

A literature search of PubMed for case studies of young patients administered everolimus off-label for the treatment of TSC-related cRHMs yielded 15 cases reported in 14 articles.[5,8,20,34-44] Some overlap existed among the articles, with some of the same cases reported in several articles.[8,34,38,42] Four cases had both SEGA and cRHMs; in 3 of these cases, everolimus was administered to treat the SEGA, and the cRHMs were treated incidentally.[8,35,38,39]

The patient history for each case (n = 15) is summarized in **Table I** (available at www.jpeds.com). The majority of patients were male (n = 9/15; the sex was not reported in 1 case[44]). The presence of cRHMs was established prenatally in 13 patients, at 2 days postnatally in 1 patient, and at 2 weeks postnatally in 1 patient.[35,37] Among the patients for whom genetic findings were available (n = 6), 5 had a *TSC1* or *TSC2* mutation (3 with a *TSC2* mutation and 2 with a *TSC1* mutation); in 1 patient, no known TSC gene mutation was found.[38] Family histories of TSC were reported for 9 patients; 5 patients had a parent with a diagnosis of TSC, and 4 patients had no family history of TSC. Two patients with healthy parents expressed de novo *TSC1/2* mutations (1 novel *TSC1* mutation and 1 novel *TSC2* mutation). In all but 1 case, everolimus was initiated within 1-20 days after birth (or reported simply as "newborn"); in the remaining case, the child was aged 5 years at the start of everolimus treatment.[8]

Only approximately one-half of the patients were symptomatic before administration of everolimus, although all patients had evidence of multiple cRHMs located in various regions of the heart. Functional problems associated with cRHMs included heart failure; heart murmur; reduced left ventricular volume, left ventricular ejection fraction, and left ventricular end diastolic volume; low oxygen saturation; ventricular inflow/outflow obstruction; valve regurgitation; and tachycardia. Everolimus treatment for each case is summarized in **Table II** (available at www.jpeds.com). 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, based on the work of Krueger et al.[25] The total duration of everolimus treatment ranged from 15 days to 13 months (and was at least 1 month for 1 case in which the total duration was not reported[35]). In all cases, treatment with everolimus appeared to cause rapid and dramatic cRHM regression or resolution; symptomatic patients became asymptomatic, with marked tumor responses often demon-

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