Introduction: Tuberous sclerosis complex (TSC) is characterized by the growth of benign tumors in multiple organs, caused by the disinhibition of the mammalian target of rapamycin (mTOR) protein. Recent reports on Everolimus, an mTOR inhibitor, are encouraging with size reduction of renal angiomyolipomas and subependymal giant cell astrocytomas, and rhabdomyomas (RHM). We herein report the efficacy of everolimus on large RHM in neonates compared to historic controls from our center. Methods: Cases recently treated with Everolimus were reviewed and compared to historic controls. For comparison, the largest dimension of the largest RHM from each patient was measured and reported as a percentage compared to the earliest echocardiography study. Babies who underwent the first echocardiography imaging within 1 month of life were eligible. Results: Studies from 4 Everolimus treated cases were compared to 10 controls. Treatment was started at 6.5 days (range 2-20) with an Everolimus initial posology of 0.1 mg po die, leading to a therapeutic serum level (5-15 ng/mL). Therapy was maintained for a median of 73 days (range 34-138) without significant side effects. Compared to historic controls, Everolimus -treated patients (Figure) had a RHM size regression rate 11.8 times faster than historic controls (linear regression slope -0.0285 vs. -0.0024; p<0.001). Following medical therapy, 2 cases were operated for congenital heart disease, without requirement of RHM resection, 1 had a near-obstructive sub-aortic tumor shrink to non-consequential size. In addition, there was no rebound in size following Everolimus discontinuation. The latter had RHM disappeared, but is still on medication to maintain efficacy on significantly reduced cerebral tumors. Conclusion: According to this early clinical experience, Everolimus is safe and efficacious for accelerated RHM size reduction in the neonate. Since long term effects on the newborn remain unknown this approach should be used with caution only in selective cases.