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Case Report

Sirolimus for management of complex vascular anomalies – A proposed dosing regimen for very young infants

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ABSTRACT

Neonates with vascular anomalies causing airway compromise and other complications require early initiation of medical therapy. Sirolimus has emerged as a safe and effective treatment, but standard recommendations for dosing start at seven months. Guidelines are needed for dosing in very young infants, who have reduced hepatic metabolism of sirolimus. We present our experience treating six neonates (mean age 14.8 days) with complicated vascular anomalies. Standard dosing caused supratherapeutic levels in this population. Our modified dosing regimen has resulted in safe therapeutic concentrations. Properly dosed, sirolimus is a viable and potentially lifesaving option for neonates with severe morbidity from vascular anomalies.

1. Introduction

Vascular anomalies are a heterogeneous group of diseases with derangements of blood vessel growth and/or structure. Based on the 2014 International Society for the Study of Vascular Anomalies guidelines, they are divided into two categories: vascular tumors (classified as benign, borderline and malignant) and vascular malformations (simple versus combined) [1]. Morbidity from these conditions due to growth, pain, coagulopathy, and organ dysfunction, is very common, especially when large in size. In rare instances, vascular anomalies can even result in death.

Larger congenital vascular anomalies are sometimes diagnosed on prenatal ultrasound. Infants with lesions involving the airway can be delivered by Ex-Utero Intrapartum Treatment (EXIT) procedure, securing the airway while the infant remains connected to a functional placenta [2]. However, after successfully stabilizing the infant in the perinatal period, treatment options for infants born with large vascular anomalies are limited. Sirolimus has recently emerged as a promising medical therapy for a number of vascular anomalies, but standard (Lexicomp) recommendations for dosing of sirolimus in vascular anomalies start at seven months of age [3–5].

2. Materials and methods

We performed a retrospective chart review of all infants under 6 months of age, treated with oral sirolimus for vascular anomalies of the airway or other sites. Initial sirolimus dose, frequency, and trough levels were reviewed. Clinical response and side effects were noted. All retrospective data collection was performed in accordance with the regulations of the UCSF Committee on Human Research.

3. Results

From 2013 to 2017, six infants under seven months of age were treated with sirolimus for complicated vascular anomalies. Four of the six had lymphatic malformations involving the airway, while two patients had kaposiform hemangioendotheliomas involving the chest and upper extremity. The results are summarized in Table 1. Individual cases are described in detail. In all subjects sirolimus oral solution was administered. Depending on the clinical status of the infant, the medication was administered PO, via nasogastric tube, or via Gtube. Doses in mg were drawn up and administered by oral syringe. For patients receiving sirolimus via NGT, the tube was flushed with formula or breastmik in the amount of 2–3 times the volume of drug.

All levels were measure using a validated, CLIA-approved chemiluminescent immunoassay.

3.1. Patient 1

Female term infant with a prenatally-diagnosed LM of the neck, face, and chest. She underwent sclerotherapy at one and two weeks of life. MRI at four weeks (Fig. 1A) showed a decrease in the size of mass,

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Table 1
Summary of clinical data on administration of sirolimus to neonates with complicated vascular anomalies.

Patient	Vascular Anomaly	Age at initiation	Goal trough ng/mL	Therapeutic Dose	Complications
1	LM neck	1 month	8–10	0.8 mg/m^2 daily	Hypertension
2	KHE w/KMP	6 days	10–15	Did not achieve stable dose prior to death	Expired due to complications of KMP
3	KHE w/KMP	3 weeks	8–10	0.3 mg/m^2 daily	Elevated triglycerides
4	LM neck	2 weeks	8–10	0.8 mg/m^2 every other day	None
5	LM neck	6 days	4–10	0.9 mg/m^2 every other day	None
6	LM neck	12 days	4–10	0.8 mg/m^2 every other day	None

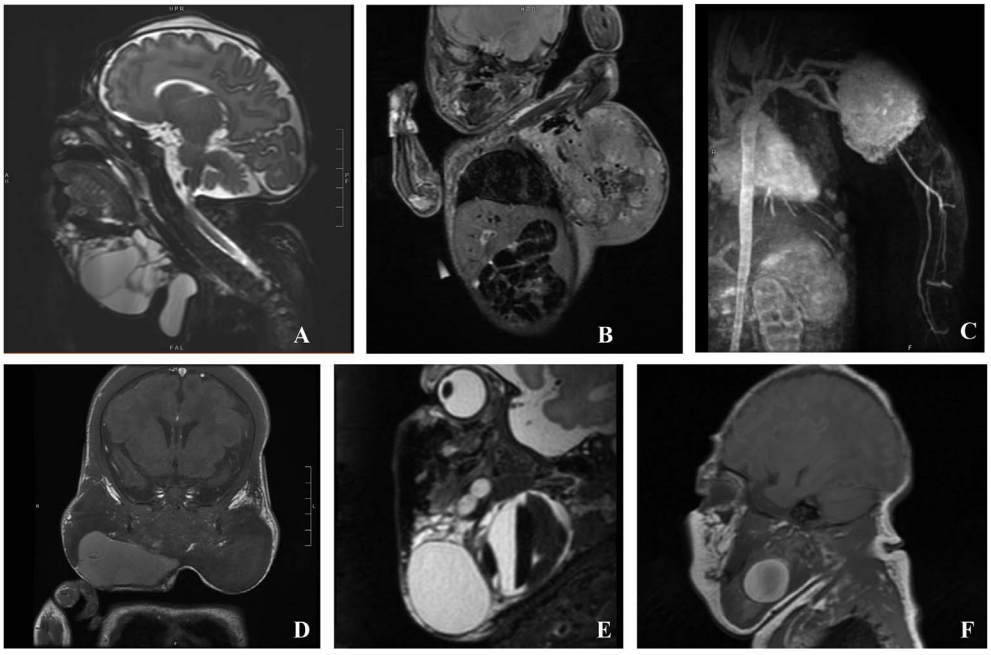

Fig. 1. A-F. Representative radiographic images of vascular anomalies from each patient.

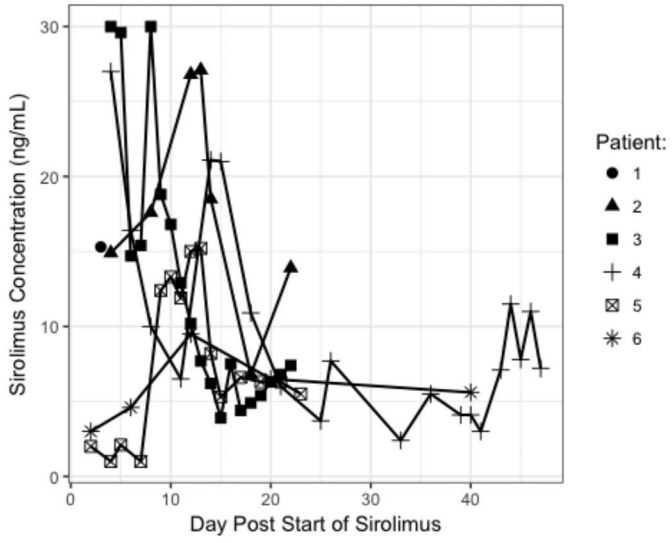

Fig. 2. Trough values for each patient, from initiation to steady state. Patients 1–3 were initiated on sirolimus based on pediatric recommendations, and patients 4–6 started at lower doses in response to observation of supratherapeutic troughs in Patients 1–3.

but laryngoscopy revealed increased swelling within the airway. On DOL 30, sirolimus was initiated at a dose of 0.8 mg/m^2 every 12 hours. The first trough after dose 6 was supratherapeutic (> 30 ng/mL), and she was found to have elevated systolic blood pressures and neutropenia. The dose was titrated down to 0.8 mg/m^2 once daily by two months of age, with goal trough 10 ng/mL (Fig. 2). MRI at 2 months showed marked improvement in the innumerable loculated cystic lesions infiltrating the neck soft tissues, floor of mouth, parapharyngeal and masticator spaces bilaterally. Direct fiberoptic exam also demonstrated improvement in the airway disease.

3.2. Patient 2

Chest wall kaposiform hemangioendothelioma (KHE). Male born via C-section at 38 weeks with a prenatally diagnosed chest wall mass. At birth the large, firm, heterogeneous, violaceous mass extended from the left nipple to the lateral edge of the scapula (12 × 15 × 8 cm). The infant had evidence of Kasabach-Merritt Phenomenon (KMP) with platelets of 13,000/μl, INR of 3.8, fibrinogen of 31 mg/dL, hematocrit of 29.8%. MRI revealed a large hyperintense mass centered in the left lateral chest wall with a large feeding artery from a branch off of the left axillary artery (Fig. 1B). On day of life (DOL) 4, embolization was performed with no improvement in the consumptive coagulopathy. Sirolimus was initiated on DOL6 at a dose of 0.8 mg/m^2 every 12 hours, and methylprednisolone was started on DOL7. After the sixth dose of sirolimus, his serum level was 15 ng/ml, suggesting that this dosing regimen would likely result in supratherapeutic levels above 15 ng/mL at steady state (Fig. 2). However, he suffered several severe complications including intraparenchymal cerebral hemorrhage, high output cardiac failure and pulmonary hemorrhage, and expired on DOL9. Postmortem pathology of the mass was consistent with KHE.

3.3. Patient 3

Left upper extremity KHE. Male born via vaginal delivery at term, with a large, vascular anomaly covering 75% of the left upper arm