

Sirolimus for the Treatment of Complicated Vascular Anomalies in Children

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Background. Vascular anomalies comprise a diverse group of diagnoses. While infantile hemangiomas are common, the majority of these conditions are quite rare and have not been widely studied. Some of these lesions, though benign, can impair vital structures, be deforming, or even become life-threatening. Vascular tumors such as kaposiform hemangioendotheliomas (KHE) and complicated vascular malformations have proven particularly difficult to treat. **Procedure.** Here we retrospectively evaluate a series of six patients with complicated, life-threatening vascular anomalies who were

treated with the mTOR inhibitor sirolimus for compassionate use at two centers after failing multiple other therapies. **Results.** These patients showed significant improvement in clinical status with tolerable side effects. **Conclusions.** Sirolimus appears to be effective and safe in patients with life-threatening vascular anomalies and represents an important tool in treating these diseases. These findings are currently being further evaluated in a Phase II safety and efficacy trial. *Pediatr Blood Cancer* 2011;57:1018–1024. © 2011 Wiley-Liss, Inc.

Key words: vascular anomalies; vascular malformations; kaposiform hemangioendothelioma; Kasabach–Merritt phenomenon; lymphatic malformation; rapamycin; sirolimus

INTRODUCTION

Vascular anomalies comprise a heterogeneous group of disorders. While the vast majority of these follow a benign course, complicated vascular anomalies can cause disfigurement, chronic pain, and organ dysfunction with significant morbidity and mortality. Optimal care of these rare complicated patients requires expertise from multiple medical specialties, including surgery, radiology, dermatology, hematology-oncology, and pathology. Despite the potential severity of complications, uniform guidelines for treatment and response measurement in children and young adults with these diseases are lacking. The most recent classification system, adopted by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996, divides these lesions into two broad categories: vascular tumors and vascular malformations, as illustrated in Figure 1 [1].

Vascular malformations are anomalies which occur during the morphological development of the vascular system. These lesions are present at birth and persist without intervention, generally growing with the child, although they can be exacerbated by trauma, infection, or hormonal changes. The classification of these lesions is based on malformed vascular channels involving capillaries, veins, arteries, lymphatics, or combinations of these.

Venous malformations and combined lesions with a venous component predispose to venous stasis and localized intravascular coagulopathy (LIC) [2]. Risk of these complications is increased in diffuse or multifocal lesions, with higher likelihood of significant consumptive coagulopathy. Chronic LIC can result in phlebolith formation and pain.

Lymphatic malformations, particularly those of the microcystic type, and combined malformations such as lymphatico-venous or capillary lymphatico-venous malformations, can lead to significant disfigurement from soft tissue hypertrophy and skeletal overgrowth, bony abnormalities, and/or infection. Diffuse lymphatic malformations can involve the bone, mediastinum, pleura, pericardium, liver, spleen, and/or gastrointestinal tract. Bony lesions can result in osteolysis, often known as “disappearing bone” or Gorham disease [3]. Depending on the location of the malformation and the organs involved, lymphatic malformations can result in chylous pericardial or pleural effusions with

significant organ compromise, and/or in skin blebbing that predisposes to recurrent cellulitis and serious infections.

Treatment of vascular malformations has been largely based on symptoms. Capillary malformations are often treated with laser therapy. Venous malformations have been treated with compression garments and low-molecular weight heparin [4], with improvement in pain and swelling symptoms. Venous malformations have also been treated with sclerotherapy and in some cases surgical excision and debulking. Lymphatic malformations of the macrocystic type can also be treated with sclerotherapy, but extensive malformations may require surgical debulking as well. Medical treatments for lymphatic malformations have included interferon alone [5] or in combination with bisphosphonates for bony disease [3], and there are a multitude of other case reports with various other agents such as cyclophosphamide [6,7]. There is no established standard of care and to date there have been no prospective clinical trials.

Vascular tumors are broadly divided into hemangiomas and other, often more complicated, tumors. These vascular tumors are

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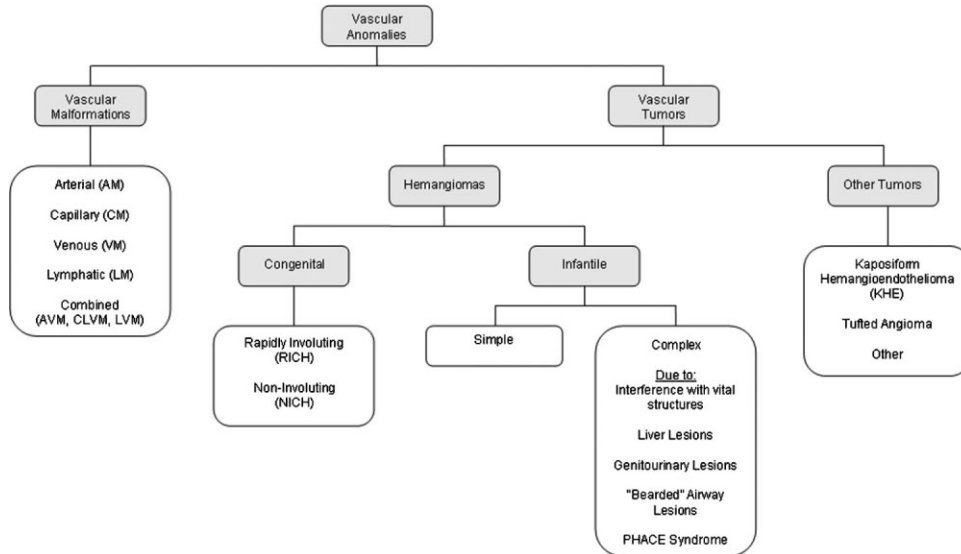


Fig. 1. Classification of vascular anomalies. This figure reflects the most recent classification of vascular anomalies established by ISSVA in 1996, and adapted from Adams and Wentzel [37].

thought to be the products of endothelial proliferation [8]. Congenital hemangiomas are fully formed at birth and either rapidly involute (rapidly involuting congenital hemangioma, or RICH) or do not (non-involuting congenital hemangioma, or NICH). In contrast, the more common infantile hemangiomas appear some time after birth, usually within the first 2 months of life. These proliferate for approximately a year, eventually stabilize, and then slowly involute, often with complete resolution.

Other vascular tumors, such as kaposiform hemangioendotheliomas (KHE) and tufted angiomas, are infiltrative lesions that invade skin, subcutaneous fat, and muscle planes. KHEs, and to a lesser extent tufted angiomas, can cause a coagulopathy called Kasabach–Merritt phenomenon (KMP), which carries a mortality rate of 14–24% [9,10]. This involves platelet trapping resulting in profound thrombocytopenia, an enlarging lesion, and a consumptive coagulopathy with significant hypofibrinogenemia. While not all KHE lesions or tufted angiomas result in KMP, it is the KMP that is directly responsible for the significant morbidity and mortality associated with these disorders. A number of treatments have been tried but none have been uniformly effective and none have been validated in prospective clinical trials. Steroids are often used as first line therapy with varying results [11,12]. Vincristine is generally used as second-line therapy once steroid treatment has proven insufficient [13,14]. Interferon has also been used but has significant potential neurological side effects, particularly in infants [15,16]. Other chemotherapeutic agents such as cyclophosphamide and actinomycin have even been tried, with variable responses [17,18].

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase regulated by phosphoinositide-3-kinase (PI3K) (Fig. 2). mTOR acts as a master switch of numerous cellular processes, including cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth [19]. Mutations in the tuberous sclerosis complex tumor suppressor proteins TSC1 and TSC2, which are upstream of the mTOR protein in the signaling pathway, result in the human diseases tuberous sclerosis and lymphangioliomyomatosis (LAM) [20]. Sirolimus treatment for these lesions has

resulted in significant reductions in size [21,22]. Sirolimus and other mTOR inhibitors are predicted to be similarly effective agents in other disorders in which the mTOR growth control pathway is affected.

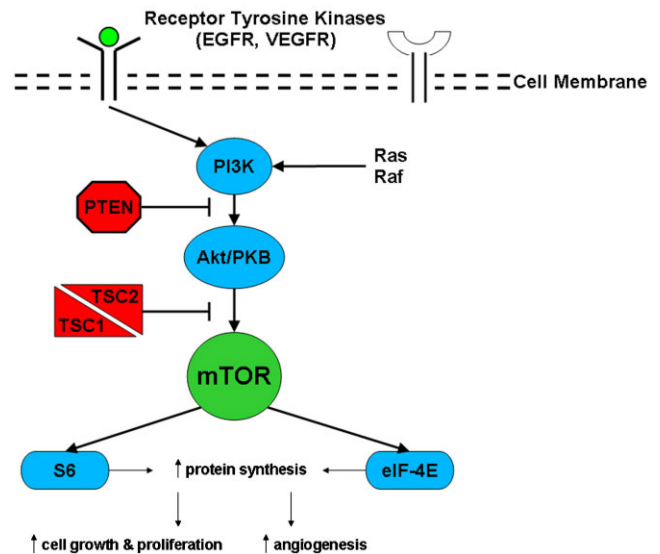


Fig. 2. mTOR pathway. Extracellular growth factor signals are transmitted through receptor tyrosine kinases to phosphoinositide-3-kinase (PI3K). Signals are transferred through Akt/protein kinase B (PKB) to mammalian target of rapamycin (mTOR) which in turn activates protein synthesis, resulting in cell proliferation and increased angiogenesis. The tumor suppressor proteins PTEN and TSC1 and 2 exert negative effects upon this pathway upstream of mTOR. Activation of mTOR results in upregulation of protein synthesis through activation of ribosomal protein S6 (via phosphorylation of its activator S6-kinase 1) and release of eukaryotic translation initiation factor 4E (eIF4E), a critical component of the 40S ribosomal subunit, from its binding protein. Sirolimus directly inhibits mTOR, thereby preventing downstream protein synthesis and subsequent cell proliferation and angiogenesis.

Several other members of the PI3K/mTOR pathway have also been implicated in the generation and propagation of vascular anomalies. Vascular endothelial growth factor (VEGF) is a key regulator in lymphangiogenesis and angiogenesis, and acts as both a potential upstream stimulator of, and a downstream effector in, the mTOR signaling pathway. Akt, just upstream of mTOR, has been found to be over-expressed in the endothelial cells of cutaneous vascular malformations in a murine model [23]. Mutations in PTEN, an important tumor suppressor protein in the mTOR signaling pathway, have been identified in both fast flow vascular anomalies and in slow flow lesions with associated overgrowth [24]. Therefore, it has been postulated that mTOR inhibitors such as sirolimus could be beneficial in the treatment of these lesions.

In fact, one case report has been published describing the treatment of Proteus syndrome, resulting from an identified PTEN germline mutation, using oral sirolimus [25]. That particular patient had multiple hamartomas which resulted in respiratory and gastrointestinal dysfunction with tachypnea, poor feeding, and hypoalbuminemia. He was started on sirolimus at age 26 months, with clinical improvement in 2 months. After 17 months on therapy, sirolimus was discontinued; within 12 weeks he had respiratory issues and was restarted on sirolimus with no plans to discontinue it again. More recently, a single case report describing the use of sirolimus to treat a life-threatening and treatment-refractory KHE was published [26].

Sirolimus, also known as rapamycin, is currently the only FDA-approved mTOR inhibitor, indicated for prevention of kidney allograft rejection in adults and children 13 years or older, but is commonly used to manage organ rejection in younger children. In renal transplantation, sirolimus has been well tolerated at a trough level of 15–20 ng/ml, with some hyperlipidemias [27]. In one study of liver and small bowel transplants, 77% of patients tolerated the drug without incident [28]. Forty-nine children were treated with sirolimus in a pediatric renal transplant study, with the main toxicities being hyperlipidemia, mucositis, and poor wound healing [29].

This case series represents a retrospective evaluation of six patients with complicated vascular anomalies. All patients had failed multiple surgical and/or medical therapies, were facing debilitating or life-threatening complications of their disease, and were treated with oral sirolimus for compassionate use.

METHODS

A retrospective review was performed on six cases of complicated vascular anomaly treated with sirolimus after failing multiple other treatments. Five patients were treated at Cincinnati Children's Hospital Medical Center (CCHMC), while one (patient 5) was treated at Children's Hospitals of Minnesota in consultation with Dr. Denise Adams at CCHMC. The case series, with review of the medical record, was approved by the Institutional Review Board. All patients began treatment with sirolimus between July 2007 and February 2010. Treatment regimen: all patients were treated with the liquid formulation of sirolimus for ease of titration. Initial dosing was 0.8 mg/m² per dose, administered twice daily at approximately 12-hr intervals. Subsequent dosing adjustments were made in order to maintain a goal drug trough level of 10–15 ng/ml. Pneumocystis prophylaxis with co-

trimoxazole or pentamidine was also started given the potential risk of immunosuppression.

RESULTS

Patient Characteristics

A total of six patients are described here in the order in which they were treated. One patient had a diagnosis of KHE with KMP, one patient had a capillary lymphatico-venous malformation, and four patients had a confirmed diagnosis of diffuse microcystic lymphatic malformation involving bone and pleural effusions. Gender was equally distributed between male and female patients, and the mean age at time of treatment initiation was 7 years and 3 months (age range 7 months to 14 years, 9 months). Most of the patients had been heavily pretreated, all with at least one other medical therapy, and most with at least one surgical or interventional procedure performed prior to sirolimus; total number of prior interventions ranged from 2 to 5. While some patients had shown a minimal response to other therapies prior to initiation of sirolimus therapy, these were insufficient and all patients continued to experience significant morbidities with risk of mortality. Patient 1 had ongoing coagulopathy requiring multiple blood products, and was in high-output heart failure. Patients 2, 4, and 5 had significant chest tube output, requiring ongoing hospitalization and increasing their risks of infection. Patient 3 had continuing bloody Jackson-Pratt (JP) drain output several months post-operatively despite multiple attempts at sclerotherapy; he required frequent red blood cell transfusions and suffered multiple bouts of cellulitis resulting in several hospitalizations and necessitating continuous intravenous antibiotic coverage. Patient 6 was in respiratory failure, requiring ventilatory support, unable to be extubated despite having multiple chest tubes in place with copious chylous drainage. A brief clinical summary of the patients appears in Table I.

Response

All six patients had significant responses to sirolimus. The patient with KHE (Fig. 3) had rapid improvement in platelet count and fibrinogen level, and clinical improvement of her high-output heart failure, such that she was subsequently stable enough to undergo stenting of her left lower extremity after failed embolization. In the four cases with diffuse microcystic lymphatic malformations, all of whom had chylous pleural effusions at the start of sirolimus therapy, chest tube output decreased substantially over a short period of time, such that all of them were able to have their chest tubes removed (Fig. 4). The patient in respiratory failure, patient 6, was extubated 15 days after starting sirolimus. In the patient with a capillary lymphatico-venous malformation (patient 3), initiation of sirolimus allowed for drain removal after prolonged drainage post-operatively from a debulking procedure. Furthermore, addition of sirolimus allowed the taper of vincristine and/or steroids, such that all but one patient (patient 5, who was only on sirolimus for a short time) was maintained for the majority of the treatment course on sirolimus as a single agent. Details of the treatment courses appear in Table II.

The average time to response was 25 days, but ranged from 8 to 65 days. Four of these six patients are now off of sirolimus, two for longer than 1 year, with no recurrence of their symptoms.

TABLE I. Demographics and Diagnoses of Patients Treated With Sirolimus for Complicated Vascular Anomalies

Patient	Age gender	Diagnosis	Affected locations	Previous treatment(s)
1	10 months female	Kaposiform hemangioendothelioma with Kasabach–Merritt phenomenon	Abdomen, back, chest, left leg, pelvis, retroperitoneum	Steroids, vincristine, cyclophosphamide, interferon, bevacizumab, embolization
2	6 years male	Diffuse microcystic lymphatic malformation	Pleural effusion, mediastinum, paraspinal, bone lesions, cutaneous (chest/back/shoulder)	Interferon, celecoxib, thorascopic decortication, pleurodesis, chest tubes
3	6 years male	Capillary lymphatico-venous malformation	Lung, liver, left lower extremity, pelvis/buttocks, retroperitoneum	LMWH, interferon, ibuprofen, surgical debulking, sclerotherapy
4	14 years female	Diffuse microcystic lymphatic malformation	Chylous pleural effusion, mediastinum, spleen, bone lesions	Chest tube, pleurodesis, ligation of the thoracic duct, celecoxib
5	14 years female	Diffuse microcystic lymphatic malformation	Bilateral pleural effusions, pericardial effusion, bone lesions	Chest tubes, interferon, celecoxib
6	7 months male	Diffuse microcystic lymphatic malformation	Bilateral chylous pleural effusions, bone lesions T11–L4, liver, intraabdominal, spleen	VATS x2, pleurodesis, ligation of thoracic duct, pericardial window, chest tubes

LMWH, low-molecular weight heparin; VATS, video-assisted thoracoscopic surgery.

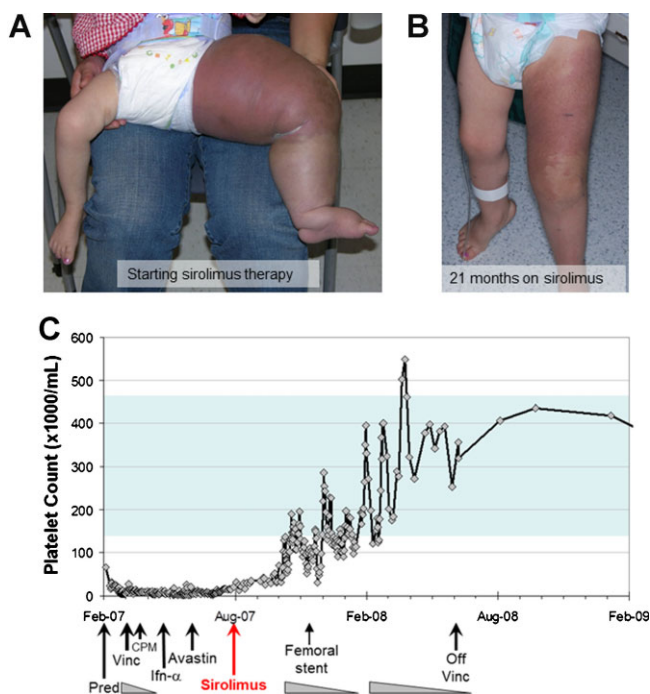


Fig. 3. Response to sirolimus in patient 1. Initially started on sirolimus at the age of 10 months for a treatment-refractory KHE with KMP, this patient had an excellent and sustained response to sirolimus with improvement in the appearance and size of her lesion (A,B) and in her platelet count (C), with resolution of her high-output cardiac failure. In (A) a photograph demonstrates the appearance of her leg shortly after starting sirolimus. In (B) 21 months later, she had decreased coloration, substantially decreased circumference, and excellent function. In (C) her platelet counts are graphed as correlated with treatments. She required steroid pulses twice after starting sirolimus for respiratory issues related to (1) her cardiac failure and (2) RSV and influenza A infections.

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Side Effects

Side effects observed in these patients were consistent with the previously reported sirolimus experience in children. Observed effects included Grade II–III mucositis ($n = 3$), Grade I hypercholesterolemia ($n = 2$), Grade II headache ($n = 1$), Grade II–III elevation of AST and ALT ($n = 2$), and Grade III neutropenia ($n = 1$). Only one (patient 5) discontinued sirolimus due to side effects. Elevation of liver enzymes improved with dose adjustment. The neutropenia in patient 6 was not clearly attributable to sirolimus as his absolute neutrophil count (ANC) appeared to vary with supportive intravenous immunoglobulin (IVIg) infusions, and so may have been due to an antibody-mediated phenomenon.

It is noteworthy that no infections occurred, definitely attributable to sirolimus, despite the fact that several of the patients had multiple risk factors for infection with lymphatic lesions and chest tubes and/or central lines in place. Patient 1 contracted both respiratory syncytial virus (RSV) and influenza A while an inpatient, and was placed on a steroid burst for respiratory symptoms. A short time later, while on both steroids and rapamycin, she was diagnosed with a central line infection. She also developed a bacteremia 7 months off sirolimus. Patient 3 experienced three episodes of cellulitis while on sirolimus, but none were more severe than he had experienced prior to starting the drug, and the frequency of infections was actually decreased during this time as compared to previously. Patient 5 was diagnosed with a central line infection prior to starting sirolimus but did not have any confirmed infectious complications later in his course.

DISCUSSION

Our experience suggests that sirolimus is a reasonable treatment for children and young adults with complicated vascular anomalies, even when they have proven refractory to a number of other treatments. Response rates were excellent, with six of six patients with highly refractory disease showing significant

TABLE II. Results of Rapamycin Treatment in Six Patients With Complicated Vascular Anomalies

Patient	Duration of rapamycin Therapy	Time to initial response: description of initial response	Side effects	Results
1	27 months	4 days: normalization of fibrinogen; 10 days: rise in platelet count	Mouth sore (Grade II), hypercholesterolemia (Grade I)	Normalization of platelet count, normalization of fibrinogen, resolution of high-output cardiac failure, improvement in size and appearance of lesion
2	28 months	14 days: removal of chest tube	None	Resolution of pleural effusions, removal of chest tube, decreased size of lymphatic malformation, improvement in cutaneous discoloration, stabilization of bony lesions, improvement in pain scale score
3	27 months ^a , tapering	6 weeks: removal of JP drain	Headaches (Grade II), mouth sore (Grade II)	Removal of drains after debulking surgery, cessation of weeping from malformation, no longer red cell transfusion-dependent, improvement in lymphatic blebs, decreased leg circumference
4	14 months	8 days: removal of chest tube	Increased ALT/AST (Grade III) ^b	Resolution of chylous pleural effusion, removal of chest tube, stabilization of bony lesions
5	2 months	8 days: removal of 1st chest tube; 9 days: removal of 2nd chest tube	Mucositis (Grade III) ^b	Resolution of effusions, removal of chest tubes, stabilization of bony lesions
6	12 months ^a	15 days: extubated; 5 weeks: removal of 1st chest tube; 6 weeks: removal of 2nd chest tube; 9 weeks: removal of 3rd chest tube; 1 year: improvement in bony lesions	Hypercholesterolemia (Grade I), increased ^b AST (Grade II) and ALT (Grade III), neutropenia (Grade III, possibly attributable)	Extubation, resolution of respiratory failure, resolution of pleural effusions, near-complete resolution of abdominal lesions, removal of chest tubes, normalization of coagulation studies (PT, PTT, fibrinogen) improvement in bony lesions, improvement in gross motor skills

JP, Jackson-Pratt; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; PTT, partial thromboplastin time.

^aTherapy is ongoing. ^bResolved at lower dose.

improvement in their signs and symptoms. While one of six patients stopped the drug due to side effects (mucositis requiring fentanyl PCA, improving with decreasing drug level), all side effects clearly related to the sirolimus (mucositis, hypercholesterolemia, and elevated liver enzymes) were reversible with dose reduction or cessation of the drug.

One difficulty in interpreting these data is that many of these patients were initially on a number of potentially therapeutic agents. However, several observations support our conclusion that sirolimus was responsible for the observed disease responses. First, these patients had already received multiple prior therapies, some of which were ongoing at the time of sirolimus initiation, without resolution of their symptoms; thus, it unlikely that the observed response after sirolimus was coincidental. Second, other therapies, including vincristine and steroids, were able to be discontinued. Given the substantial risks and side effects of long-term use of these therapies, this outcome alone should prove highly beneficial to these patients.

As a retrospective study, this case series had no enrollment criteria so it is possible that selection bias was present in determining which patients should be treated with sirolimus; however, in practice, each of these patients began sirolimus only after failing all other reasonable treatments while continuing to experience organ dysfunction and/or life-threatening complications. The small size of this case series, with multiple diagnoses included, makes it impossible to identify specific predictors of response in this setting. In order to overcome these limitations, a prospective

clinical trial of the mTOR inhibitor sirolimus is indicated for patients such as these with complicated vascular anomalies.

The patients presented here all had vascular anomalies with significant lymphatic components. Even KHE, with its classic spindle cell morphology, is thought to have a significant lymphatic component, since these lesions stain with lymphatic endothelial markers D2-40 (podoplanin) and Prox-1 [30,31]. The strong effect of sirolimus on these lymphatic-based lesions correlates well with our current understanding of the lymphangiogenesis pathway, in which ligand-binding induced signaling through VEGFR-3 on the surface of lymphatic endothelium results in activation of the PI3K/Akt/mTOR pathway [32,33]. The mTOR inhibitor sirolimus has been shown to inhibit lymphangiogenesis reproducibly in three independent model systems, including wound healing [34], embryonic development [35], and tumor formation and metastasis [36].

It is interesting to note that sirolimus appeared to work well both on vascular tumors such as KHE and on lymphatic malformations, despite its antiangiogenic and antiproliferative mechanisms. This observation challenges the classic view of malformations, which have traditionally been thought of as stable and non-proliferative. Additional biological markers need to be identified and analyzed in order to begin to address these questions.

In order to gain further insight into these disorders while providing safe clinical care, these patients should be treated and carefully monitored through prospective clinical trials. A Phase II

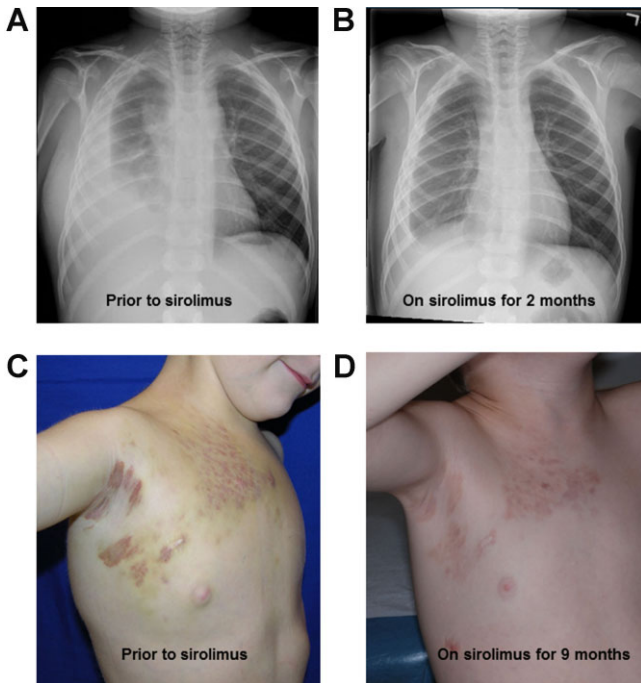


Fig. 4. Response to sirolimus in patient 2. Started on sirolimus at the age of 6 years for a persistent pleural effusion, this patient had resolution of his effusion (A,B) with no further need for chest tubes, shrinkage of his lesion, and some lightening of his superficial lymphatic lesion (C,D). Chest X-rays show the status of the patient's effusions in (A) prior to starting sirolimus, and in (B) 2 months later. Photos show the appearance of his lymphatic lesion, with visible skin involvement, prior to sirolimus in (C) and several months later in (D).

clinical trial is currently underway to evaluate the effectiveness of this mTOR inhibitor in the treatment of children and young adults with complicated vascular anomalies (ClinicalTrials.gov NCT00975819). This study includes diagnostic and therapeutic response criteria, as well as biologic marker analysis. The hope is that this study will help to identify a population of high-risk vascular anomaly patients in whom sirolimus is effective and safe. The ultimate goal is to stimulate development of future prospective trials for the treatment of these complicated patients with their rare but devastating disorders.

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