2-1-2021

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Paediatrics & Child Health, 2021, e25–e32
doi: 10.1093/pch/pxz090
Original Article
Advance Access publication 20 August 2019

OXFORD

Original Article

The use of rapamycin to treat vascular tumours and malformations: A single-centre experience

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Abstract

Objectives: To assess the safety and efficacy of rapamycin in treating children with vascular tumours and malformations.

Study design: We performed a retrospective review at a large tertiary care paediatric centre to assess the efficacy and safety of using rapamycin to treat vascular tumours and malformations. Response to therapy was defined by patient-reported symptom improvement, radiological reduction in size of lesions, and/or improvement of laboratory parameters.

Results: Forty-two patients (7 with vascular tumours and 35 with vascular malformations) have been treated with rapamycin. Despite 33 of 42 patients being diagnosed in the first year of life, the median age of initiating rapamycin was 11 years. Of the 38 children treated for a minimum of 4 months, 29 (76%) exhibited a clinical response. Twenty-one patients had follow-up imaging studies and of these, 16 (76%) had radiographic decrease in lesion size. Median time to demonstration of response was 49 days. All five children with vascular tumours and all three children with vascular malformations under the age of 4 years showed a clinical response. Response rate was lower for children ≥ 4 years of age (0/2, 0% for vascular tumours; 21/28, 75% for vascular malformations). No patient experienced an infection directly related to rapamycin or discontinued rapamycin due to toxicity.

Conclusions: Rapamycin is safe and efficacious in most children with select vascular tumours and malformations. Young children appear to respond better, suggesting that early initiation of rapamycin should be considered.

Keywords: *Rapamycin; Sirolimus; Vascular malformation; Vascular tumour*

Vascular anomalies (VAs) are a heterogeneous group of disorders that are characterized according to the classification system of the International Society for the Study of Vascular Anomalies (ISSVA) (1). These are broadly divided into vascular tumours, which are proliferative lesions, and vascular malformations, which are thought of as being nonproliferative anomalies of vascular channel morphogenesis and may be associated with overgrowth.

VAs may cause significant morbidity: growth of lesions can result in external compression of vital structures and organ

Received: January 26, 2019; Accepted: April 1, 2019

dysfunction, and may be associated with significant acute and chronic pain, coagulopathy, bleeding, or thrombosis (2,3). In addition, depending on their location, patients may experience psychological trauma from disfiguring lesions (4). Conventional therapies for vascular malformations have focused on relieving symptoms by a combination of methods, including interventional approaches such as sclerotherapy and laser ablation, as well as surgical debulking. However, the infiltrative pattern of many lesions prevents their complete excision. Similarly, while sclerotherapy is suitable for improving pain in many patients with vascular malformations, it is not always possible, is noncurative, and requires multiple treatments. In contrast, vascular tumours have been managed medically with corticosteroids, interferon, antiangiogenic therapies such as bevacizumab, and chemotherapeutic agents such as vincristine (5). However, these medical therapies are not without significant toxicities.

In 2011, the first report on the use of rapamycin in the treatment of five children with vascular tumours and one child with a vascular malformation led to the realization that perhaps a medication with significantly less toxicity could now be used for children with vascular tumours (6). Most importantly, it was suggested that perhaps vascular malformations could also be treated medically, thereby offering such patients a new, previously unavailable form of therapy. Over the next several years, an increasing number of case reports emerged demonstrating the effectiveness of rapamycin in a variety of vascular tumours and malformations (7). Finally, in 2016, Adams et al. reported the first prospective (phase 2) study which demonstrated that rapamycin was safe and efficacious in patients with complex VAs (8).

Rapamycin is an inhibitor of the mammalian target of rapamycin complex (mTOR). mTOR is a serine and threonine kinase that functions as a key regulator of cellular growth and metabolism by integrating both intracellular and extracellular signals. The mTOR pathway consists of several signalling proteins (e.g., PI3K, AKT), and its activation has been associated with angiogenesis and lymphangiogenesis (9,10). Various mutations that impact the mTOR pathway have been identified in a number of VAs: TIE2 mutations in 50% of common venous malformations, AKT mutations in Proteus syndrome, and P13K mutations in both isolated and syndromic lymphatic malformations such as CLOVES syndrome (11,12,13).

The Hospital for Sick Children in Toronto is the largest tertiary care paediatric centre in Canada. It follows over 600 children with complex vascular tumours and malformations. Over the last 6 to 7 years, an increasing number of such children have been treated with rapamycin. Herein, we present our considerable and rapidly growing experience in treating such children using rapamycin.

METHODS

A single-centre retrospective cohort study was performed on children with VAs who were treated with rapamycin between February 2012 and December 2018. All patients treated at The Hospital for Sick Children, Toronto were included. Patients were diagnosed as having VAs based on clinical and imaging findings, with 17 having confirmed pathologic examination. The primary outcome measure was response to therapy (described below). Institutional review board approval was obtained prior to conducting this study.

Rapamycin was initiated at 0.8 mg/m^2 per dose administered twice daily or 2.5 mg/m^2 administered once daily in children above the age of 5 years, with subsequent dose adjustments made to target a trough level between 5 and 15 ng/mL. Laboratory parameters including, but not limited to, a complete blood count, differential, liver and renal function, lipid profile, fibrinogen, and d-dimer were monitored. Response to therapy was defined as patient-reported improvement of symptoms (e.g., pain), clinical or radiological reduction in the size of the lesion, and/or improvement of laboratory parameters (e.g., d-dimer, platelets, hemoglobin [in cases where patients were bleeding secondary to their vascular malformation], or albumin [in cases where patients exhibited protein losing enteropathy]). Follow-up imaging studies were obtained after a minimum of 6 months on therapy, or as clinically indicated. Patients were treated for a minimum of 4 months before assessing clinical response. Patients who had a response were treated with therapeutic dose rapamycin for a minimum of 12 months prior to tapering. Demographic and clinical data are summarized descriptively.

RESULTS

Patient characteristics

Forty-two patients with VAs were treated with rapamycin. Thirty-eight of these 42 patients were treated for a minimum of 4 months; these 38 patients were included in the final analysis. Most patients were diagnosed at birth with their VA: median age of diagnosis was birth (range: 0 to 11 years). However, median age at initiation of rapamycin therapy was 10 years of age (range: 0 to 17.5 years). Median follow-up was 22 months (range: 4 to 80 months).

Of the 38 patients included in the analysis, 7 had vascular tumours (5 with kaposiform hemangioendothelioma, 1 with a diffuse transmural infantile hemangioma in the GI tract, and 1 with a biopsy-proven infantile hemangioma of the face that grew in adolescence) and 31 had vascular malformations (Tables 1 and 2). Among the 31 patients with vascular malformations, there were 2 patients with Klippel-Trenaunay syndrome, 1 with Blue Rubber Bleb Nevus (BRBNS) syndrome, and 1 with a fibroadipose vascular malformation (FAVA). Apart from cosmetic concerns all patients were symptomatic; pain was the most common symptom in patients with vascular malformations. Other indications for initiating therapy with rapamycin included recurrent cellulitis (two patients), stridor or airway compromise (seven patients), protein-losing enteropathy (two patients), gastrointestinal bleeding (two patients),

Table 1. Diagnoses and disease response in patients treated for a minimum of 4 months

Diagnosis	N	Clinical response (N)	Median time to response (d)	Remain on rapamycin (N)
Vascular Tumours				
Kaposiform Hemagioendothelioma	5	4 (80%)	46	2
Other	2	1 (50%)	56	1
Vascular Malformations				
Lymphatic (includes one pt with intestinal lymphangiectasia)	15	11 (73%)	49	12
Mixed (five LVM, three CLVM)	8	7 (87%)	42	8
Venous (includes one pt with BRBN)	6	5 (83%)	63	5
Capillary (Phakomatosis pigmento vascularis)	1	0 (0%)	n/a	0
Fibro-adipose vascular anomaly	1	1 (100%)	98	1
Total	**38**	**29 (76%)**	**49**	**29**

BRBN Blue rubber bleb nevus syndrome; CLVM Capillary-lymphatic-venous malformation; LVM Lymphatic-venous malformation.

pleural/pericardial effusions (two patients), and orbital mass with risk to vision (two patients).

Prior therapy

Most patients had received other therapies prior to initiating rapamycin. All patients with vascular tumours had received either steroids, vincristine, beta-blockers, or a combination thereof. Two patients, one with a large venous malformation, and another with a combined slow-flow malformation (venous and lymphatic) had received low molecular weight heparin for localized intravascular coagulopathy (LIC). Thirteen patients had undergone surgical procedures: 11 had undergone debulking surgeries, one had insertion of a titanium rod for recurrent fractures because of a vascular malformation (LVM) involving his femur, and another underwent obliteration of his right middle ear because of a persistent cerebrospinal fluid (CSF) leak causing recurrent meningitis. Sixteen patients underwent sclerotherapy either prior to or concurrently with rapamycin therapy.

Response

Twenty-nine out of 38 children (76%) showed a clinical response based on a decrease in mass size or pain (25 patients; as judged by the patient/family) or a decrease/cessation of gastrointestinal blood loss (2 patients), protein losing enteropathy (1 patient), and/or pleural/pericardial effusions (1 patient). Median time to demonstration of a response was 49 days (range: 12 to 134 days). Clinical response rates were similar across diagnoses (Table 1 and Figure 1). Of note, all eight children (five vascular tumours and three vascular malformations) under 4 years of age showed a clinical response. None of the patients had frankly progressive disease.

Of the 21 children with follow-up imaging (20 MRIs, 1 ultrasound), 16 (76%) showed a decrease in lesion size.

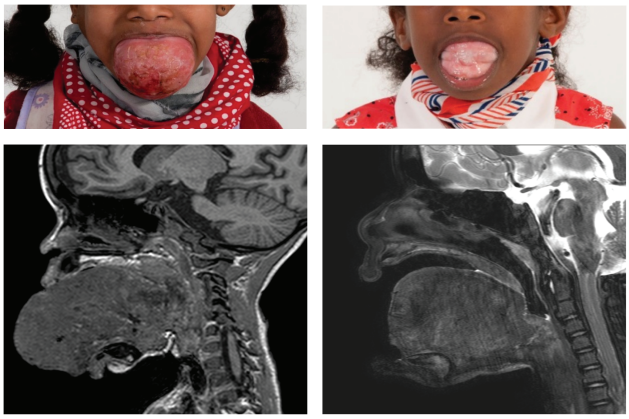

Figure 1. Photograph and MRI of lymphatic malformation of the tongue before and after 3 years on rapamycin. Permission to publish these photographs was provided by the patient's parents. This is patient #17 in Table 2.

Twenty-four children had abnormalities in baseline blood work; of these, 17 (71%) showed improvement, including normalization of d-dimers (10), improvements in hemoglobin (11), platelet count (1), gamma globulin levels (1), albumin (1), or fibrinogen (1).

Median duration of treatment was 12 months (range: 4 to 45 months) with median follow-up of 22 months (range: 4 to 80 months). Of the 29 patients who responded to rapamycin 5 were weaned off rapamycin after a good response; 3 of these had a recurrence of clinical symptoms and were re-started on rapamycin. Upon restarting rapamycin, all three patients again showed a clinical response with improvement of pain and decrease in lesion size. One of these three patients (with kaposiform hemangioendothelioma [KHE]) discontinued

Table 2. Patient characteristics and response to rapamycin. Patients are grouped by diagnoses and then by ascending age

Pt	Diagnosis	Location	Age at initiation	Prior therapy	Response to Rapamycin
Vascular tumours					
Kaposiform Hemagioendothelioma					
1	KHE	Neck and thorax	1 m	Corticosteroids	Modest reduction in bulk, resolution of pleural and pericardial effusions, normalization of platelet count
2	KHE	Face and neck	3 m	Propranolol	Modest reduction in bulk
3	KHE	Lower extremity	1 y 8 m	Propranolol	Moderate reduction in bulk, normalization of d-dimer
4	KHE	Lower extremity	2 y 9 m	Corticosteroids and vincristine	Modest reduction in bulk, decreased pain, improvement of d-dimer
5	KHE	Lower extremity	15 y 1 m	Corticosteroids	No response
Other tumours					
6	Diffuse hemangiomas	Face, neck, abdomen	3 y 3 m	Red cell transfusions; Corticosteroids and vincristine	Resolution of GI bleeding, normalization of Hb and ferritin
7	Infantile hemangioma	Neck, airway	10 y	Corticosteroids, vincristine, nadolol, laser	No response
Vascular malformations					
Lymphatic Malformations					
8	LM – microcystic	Face and neck	1 m	Nil	Significant reduction of bulk, resolution of stridor
9	LM – mixed cystic	Upper extremity, neck	2 m	Sclerotherapy	Significant reduction of bulk
10	LM – mixed cystic	Face, neck, airway	4 y 1 m	Tracheostomy, sclerotherapy	No response
11	LM – microcystic	GI tract, abdomen, pelvis	4 y 2 m	Nil	No response
12	LM – mixed cystic	Face, neck, airway	4 y 6 m	Partial resection, tracheostomy, sclerotherapy	Significant reduction of bulk, improvement of d-dimer
13	LM – mixed cystic	Face and neck	6 y	Tracheostomy, sclerotherapy	Modest reduction in bulk, marked improvement in ability to cap tracheostomy
14	LM – mixed cystic	Upper extremity, neck and thorax	7 y 7 m	Multiple resections, sclerotherapy	No response
15	LM – mixed cystic	Face and neck	8 y 9 m	Partial resection	Modest reduction of bulk
16	LM – mixed cystic	Retroperitoneum	13 y 1 m	Two partial resections	Significant reduction of bulk, improvement of pain and d-dimer
17	LM – microcystic	GI tract, retroperitoneum	14 y	Nil (repeated infusions of albumin)	Resolution of protein-losing enteropathy and edema
18	LM – microcystic	Pelvis and lower extremity	14 y 9 m	Propranolol, partial resection, sclerotherapy	Marked improvement of pain and ambulation
19	LM – microcystic	Lower extremity	14 y 11 m	Nil	Significant reduction of bulk
20	LM – microcystic	Orbit	16 y 9 m	Nil	Modest reduction in bulk

Table 2. Continued

Pt	Diagnosis	Location	Age at initiation	Prior therapy	Response to Rapamycin
21	LM – microcystic	Upper extremity	17 y 6 m	Sclerotherapy, skin debridement	Modest reduction of bulk, significant improvement of pain and reduced bleeding
22	LM – possible GLA	Head, neck, thorax, abdomen	4 y 2 m	Surgical correction of CSF leak	No response
Combined Malformations					
23	LVM	Thorax	1 year	Sclerotherapy	Modest reduction in bulk
24	LVM	Orbit	4 y 3 m	Partial resection, sclerotherapy	Marked reduction in bulk and proptosis
25	LVM	Face and neck	5 y 7 m	Nil	Significant reduction of bulk, improvement of d-dimer
26	LVM	Upper extremity	10 y 9 m	Partial resection	Significant reduction of bulk, resolution of recurrent cellulitis
27	LVM (primarily venous)	Lower extremity	14 y 10 m	Reduction of fractures, osteotomy, LMWH	Marked improvement of pain, resolution of LIC
28	CLVM + overgrowth = KTS	Upper extremity with overgrowth, hepatic, intraspinal	8 y 9 m	Topical beta blocker	Modest improvement of bulk, improvement of d-dimer
29	CLVM + overgrowth = KTS	Lower extremity with overgrowth, pelvis	11 y 10 m	Multiple resections, venous embolization	Moderate reduction in bulk of cutaneous lesions, marked improvement of pain, normalization of d-dimer
30	CLM + overgrowth	Thorax, retroperitoneum, pelvis	14 y 10 m	Sclerotherapy	No response
Venous Malformations					
31	VM	Face and neck	12 y 1 month	Nil	Modest reduction of bulk, improvement of d-dimer
32	VM	Face and neck	13 y	Tracheostomy, Sclerotherapy	No response
33	VM	Lower extremity	16 y 6 m	Sclerotherapy	Marked improvement of pain and ambulation, improvement of d-dimer
34	VM	Tongue, oropharynx	17 y 1 m	Corticosteroids	Marked improvement of pain and resolution of opioid use
35	VM	Upper extremity and thorax	17 y 9 m	LMWH, Sclerotherapy	Marked improvement of pain and range of motion, modest reduction in bulk
36	VM - BRBNS	GI tract and skin	15 y 8 m	Red cell transfusions, surgical resection	Moderate reduction in bulk of cutaneous lesions, normalization of Hb
Capillary malformations					
37	PPV	Lower extremities and GI tract	16 y	Red cell transfusions	No response
Other malformations					
38	FAVA	Lower extremity	15 y 6 m	Sclerotherapy	Marked improvement of pain and ambulation, moderate reduction of bulk

BRBN Blue rubber bleb nevus syndrome; CLVM Capillary-lymphatic-venous malformation; FAVA Fibro-adipose vascular anomaly; Hb Hemoglobin; KHE Kaposiform hemangioendothelioma; KTS Klippel-Trenauny syndrome; LIC Localized intravascular coagulation; LM Lymphatic malformation; LVM Lymphatic-venous malformation; VM Venous malformation; PPV Phakomatosis pigmento vascularis.

and then re-started therapy a total of three times, with an excellent response seen each time. Two patients remain off rapamycin while 27 remain on rapamycin.

Safety

Overall, rapamycin was very well tolerated, and toxicities were consistent with previously reported side-effects. Twenty-nine (76%) had mild hypertriglyceridemia, and no patients required statin therapy. In 20 patients (52%), mouth sores were reported without need for therapy discontinuation. Infectious complications included the following: culture-negative sepsis while travelling in South Asia (1), recurrence of pre-existing *Clostridium difficile* colitis (1), serum sickness secondary to antibiotic use to treat an acute otitis media and subsequent pneumonia (1), recurrent meningitis secondary to a CSF leak from a temporal bone defect (1). In each case, the patient was treated for the infection and remained on rapamycin with no interruption except in one case (case of sepsis) where rapamycin was interrupted for 2 months.

DISCUSSION

To the best of our knowledge, this retrospective cohort review constitutes the largest Canadian experience in treating children with VAs using rapamycin. We demonstrate that rapamycin is an efficacious and well-tolerated therapy for children with VAs, including patients who have not responded to treatment with other modalities. This was noted as improvements in pain, reduction in lesion bulk, and improvement of associated complications such as LIC, as evidence by the d-dimer, as well as reduced bleeding and protein losses from gastrointestinal VA. These findings are compatible with other reported case series (6,8,14–16). Of note, rapamycin was effective in both vascular tumours and malformations, and in a variety of anatomic locations. The success of rapamycin in treating different lesion types may stem from the critical role of mTOR in integrating multiple signalling pathways, including PI3K and TIE2, which are important for cellular proliferation (11,17).

In some patients, the effect of rapamycin was dramatic and life changing. Examples of this include two patients who had recurrent gastrointestinal bleeding (patients #6 and #36 in Table 2). Both patients were receiving monthly red cell transfusions and had undergone unsuccessful intestinal resections to reduce their GI bleeding. Shortly after commencing rapamycin, these patients became transfusion independent. Similarly, one patient (patient #17 in Table 2) with a diffuse GI lymphatic malformation had a severe protein losing enteropathy and debilitating edema for over 10 years leading to numerous hospitalizations and albumin infusions. At the time of initiating rapamycin, her serum albumin was 9 g/L (normal: 32 to 52 g/L) and her serum IgG was 2.4 g/L (normal: 6.6 to 15.3 g/L). Within 6 months of starting rapamycin both values had normalized, and have remained so after 3 years. These cases suggest that the use of rapamycin may enable avoidance of hospitalizations and invasive procedures associated with significant morbidity.

Unsurprisingly, given the responses seen, most patients reported here remain on rapamycin. After a period of disease stability, several patients have weaned off therapy and, in five cases, discontinued therapy. In three cases, due to regrowth of the lesion (KHE) or recurrence of bleeding (diffuse hemangioma of the GI tract and blue rubber bleb nevus syndrome), they have restarted rapamycin and had a good response again. Our experience suggests that most patients may need to remain on rapamycin for long periods of time, although they may remain on very low doses.

There were no major toxicities directly attributable to rapamycin. The rate of mouth sores seen in our study (52%) was notably higher than the reported 17% by Adams et al. (8). It is possible that our use of once daily dosing led to higher peak serum rapamycin levels and/or higher local concentrations in patients taking liquid rapamycin. Nevertheless, dose reduction was only required in three patients. In addition, we began to prescribe a lidocaine-based mouth wash or a triamcinolone-lidocaine oral gel (Oracort, Taro Pharmaceuticals, NY) which helped mitigate pain associated with mouth sores.

The rate of hypercholesterolemia/hypertriglyceridemia was very high (74%) and is explained by the fact that most samples were drawn without asking children to be strictly fasting. Importantly, elevations were mild, and there were no patients who required statin therapy. While the short-term elevation of cholesterol/triglycerides may be of little clinical consequence in children, the potential need for prolonged therapy and the use of rapamycin in adults with concurrent cardiovascular risk factors warrants consideration.

Four infectious complications were noted, none of which could be directly attributed to rapamycin. Of note, one child experienced recurrent meningitis but was found to have a CSF leak secondary to a petrous bony defect. Recently, two cases of *pneumocystis jiroveci* pneumonia (PJP) presenting in neonates on rapamycin but heavily pretreated with steroids were reported, highlighting the need for PJP prophylaxis in very young children (18).

We noticed an association between the patient's age at initiating rapamycin and their likelihood to respond. Of the patients with vascular tumours, all five patients under the age of 4 years (four KHE, one diffuse hemangiomas) responded to rapamycin, while the two older patients did not (Figure 2A). Similarly, for vascular malformations, all three patients under the age of 4 years (100%) responded to rapamycin as compared to 75% (21 of 28) of patients above the age of 4 years (Figure 2B). It is possible that our use of twice daily dosing in younger patients led to steadier drug levels, and thus an improved response as compared to older patients. However, all patients had doses adjusted to have trough levels between 5 and 15 ng/mL. There may be many

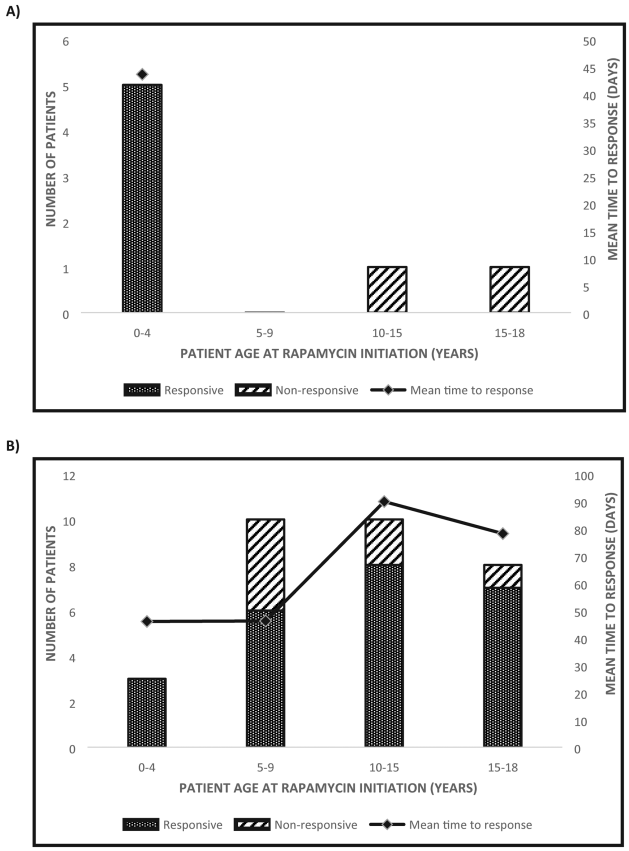

Figure 2. Response to rapamycin by age for vascular tumours (A) and vascular malformations (B).

possible factors that contribute to a decreased response in older children, including physiologic maturation of the lymphatic system over time. Older children are more likely to have tried other therapies and may have scarring of the VA, either from sclerotherapy, surgery, or prior infections of the VA as can occur in cystic lymphatic malformations (LMs); such scarring is probably not likely to respond to medical therapy. An association between age and response to rapamycin has been suggested but is yet to be proven in a prospective study (8,19).

The two largest published cohorts of patients treated with rapamycin have shown that patients with KHE and LMs, particularly those with a microcystic lymphatic component, appear the most likely to respond (8,20). As a result, 28 of 38 patients referred to us had either KHE or a vascular malformation with a lymphatic component (Table 1). Our experience mirrors that of the aforementioned studies, with 22 of 28 (79%) of these patients responding to rapamycin. We add to this literature our observation that young children with VA appear to respond better to rapamycin. This success has resulted in an increasing number of referrals for patients with VA seeking medical therapies; 11 of this cohort were referred in 2018 with an additional 5 patients (not captured here) being referred at the time of data collection.

Limitations of the study include its retrospective nature, and the fact that many patients received pre or concurrent sclerotherapy, making it challenging to accurately access the effect of rapamycin alone. Finally, pain is a notable feature of the morbidity suffered by patients but is challenging to assess in a retrospective study. Improvements in pain noted in Table 2 reflect objective decrease in analgesic use. Currently, a quality of life survey is being implemented in the clinic to improve global assessment of response to rapamycin.

The success of rapamycin in treating patients with selected vascular tumours and malformations does not detract from other modalities used to treat VAs. Indeed, several patients in our cohort received sclerotherapy with good effect. Similarly, there are case reports of complete surgical excision in otherwise inoperable VAs being facilitated by first using rapamycin to shrink the lesion (4). As such, rapamycin may be perceived in some cases as an adjunct to interventional or surgical therapy, while in others it may be the primary therapeutic modality.

In summary, our results suggest that rapamycin is safe and efficacious to treat children and adolescents with selected vascular anomalies. We note an association between younger age and response to rapamycin. This highlights the importance for community practitioners to recognize VAs and make early referrals. Several questions regarding the use of mTOR inhibition in VAs remain, including clearly defining which lesions respond best, duration of therapy, long-term complications, and the role of other rapalogs such as everolimus. Further cooperative prospective trials and are needed to answer these questions.

Funding: There are no funders to report for this submission.
Potential Conflicts of Interest: ILC reports being a consultant for Pfizer outside the submitted work. MC reports grants and personal fees from Bayer, Bioverativ/Sanofi, CSL-Behring, Novo-Nordisk, Octapharma, Pfizer and Shire, as well as personal fees from Biotest, Grifols, LFB and Roche outside the submitted work. ST's fellowship at the Hospital for Sick Children (Toronto, Canada) was supported by the Shire Endowment Fund for Training in Pediatric Hemostasis. There are no other disclosures. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
Statement of Ethics: The study was approved by the Hospital for Sick Children Research Ethics Board.
Author Contributions: ST collected the data, analyzed the data and drafted the initial manuscript. MC conceptualized the study and design, analyzed the data and revised the manuscript. All authors reviewed and revised the manuscript and gave approval of the manuscript as submitted.

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