HK J Paediatr (new series) 2023;**28**:20-26

Original Article

Sirolimus for the Treatment of Benign Vascular Anomalies in Children: A Single Centre Experience

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Abstract

mTOR inhibitors have become a new and valid treatment choice for patients with refractory vascular anomalies. We aimed to present paediatric cases with benign vascular anomalies treated with sirolimus. The clinical data of 30 patients were reviewed retrospectively: 46.7% (n=14) had infantile haemangioma and 53.3% (n=16) had vascular malformation. Response to treatment was defined as improvement in radiologic imaging and/or reduction of lesion size and symptoms. The median age of the patients was 2.6 (1.2-17) years. The dosage of oral sirolimus was 0.8 mg/m^2/12 hours. The overall successful response rate was 66.7% (n=20) at a median duration of 5 months. Three patients with infantile haemangioma and four patients with venous, one patient with lymphatic, one patient with capillary, and one patient with arteriovenous malformation had no response. There was neither complete response nor worsening on therapy. Sirolimus was well tolerated with no patient required premature termination of treatment. We conclude that sirolimus may be a valid treatment choice for paediatric patients with refractory benign vascular anomalies. Further prospective studies on the optimal therapeutic regimen including dosage and duration should be performed.

Key words *Benign; Children; Sirolimus; Vascular anomaly*

Introduction

Vascular anomalies are disorders originating from the blood and/or lymphatic vessels. As a result of abnormal growth and development of vessels, a wide range of clinical presentations occur. Typically infants, children and young adults are affected and the condition may present as a simple "birthmark" or with a life-threatening manifestation. Because of phenotypic heterogenity and variations in signs and symptoms, the diagnoses of vascular anomalies are often challenging. Vascular anomalies are classified by the International Society for the Study of Vascular Anomalies (ISSVA) based on different pathobiologies to provide medical and surgical specialists a common terminology, and to ensure an accurate diagnosis, evaluation and management. Vascular tumours, vascular malformations and unclassified anomalies are the three categories in the ISSVA classification system.[1,2]

Vascular tumours are neoplastic disorders characterised by increased proliferation of endothelial and other vascular cells. Infantile haemangioma (IH) is a benign vascular tumour and is also the most common tumour of infancy. The underlying pathology of IH is the dysregulation of both vasculogenesis and angiogenesis. Hypoxia, both as a consequence of maternal events creating hypoxic stress as well as by the infant's own hypoxia-induced factors triggers an increased expression of proangiogenic factors. These factors then stimulate the differentation of

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Received December 13, 2019

mesenchymal stem cells into immature endothelial cells, which subsequently form tumourous masses and progress into the early rapid growth phase of IH after birth. In later childhood, the immature vasculature transforms into a fibrofatty residuum in the regression phase. Solid vascularised mass presents as strawberry-like patch at any part of the body is the most common initial clinical sign which typically appears after the first two weeks of life. After infancy, the gradual spontaneus regression of the IH allows observation without specific treatment to serve as one of the options in the clinical management. However, treatment is required for complicated IH and propranolol is the first-line pharmacological therapy in this situation.[3]

On the other hand, vascular malformations do not demonstrate neoplastic endothelial cell proliferation or involution. These congenital vascular lesions are always present at birth, grow commensurately with the child, and expand haemodynamically with the growth of the child. Localised or diffuse lesions may have variable appearances and complications. The vascular malformations are classified into four categories: simple malformations, combined malformations, vascular malformations of major named vessels, and vascular malformations associated with other anomalies. Simple vascular malformations are divided into slow-flow [venous (VM), lymphatic (LM), and capillary (CM) malformation] and fast-flow [arteriovenous malformation (AVM) and arteriovenous fistula] malformations (Table 1). The treatment approach for vascular malformation is determined by its location(s), proportion of abnormal vessels, involved body structures, flow rate of abnormal vessels, and presence of nonvascular anomalies.[4]

In the recent years, mTOR (mammalian Target of Rapamycin) inhibitors have been found to be useful in the treatment for vascular anomalies. mTOR is a serine/threonine kinase in the phosphoinositide-3-kinase (PI3K)/AKT pathway which is an important signaling pathway in regulating the cell cycle. Therefore, it is directly related to

Table 1 Classification of vascular malformations*

Simple		
Capillary malformations (CM)	Cutaneous and/or mucosal CM	
	Telangiectasias including hereditary haemorrhagic telangiectasia (HHT)	
	Cutis marmorata telangiectatica congenita	
	Nevus simplex/salmon patch	
	Others	
Venous malformations (VM)	Common VM	
	Familial VM cutaneomucosal	
	Blue rubber bleb nevus syndrome	
	Glomuvenous malformation	
	Cerebral cavernous malformation	
	Others	
Lymphatic malformations (LM)	Common LM (macrocystic, microcystic, mixed)	
	Generalised lymphatic anomaly	
	Gorham–Stout disease	
	Channel type LM	
	Primary lymphoedema	
	Others	
Arteriovenous malformations (AVM) or arteriovenous fistula	Sporadic	
	In HHT	
	In CM–AVM	
	Others	
Combined	CM + VM (CVM)	CM + LM + VM (CLVM)
	CM + LM (CLM)	CM + LM + AVM (CLAVM)
	CM + AVM (CAVM)	CM + VM + AVM (CVAVM)
	LM + VM (LVM)	CM + LM + VM + AVM (CLVAVM)
Vascular malformations of major named vessels		
Vascular malformations associated with other anomalies		

* Adapted from 2014 ISSVA Classification

cellular anabolism and catabolism, motility, angiogenesis, and growth.[5] The mTOR inhibitor, sirolimus was initially used successfully to treat PTEN mutation positive disorders and hamartoma syndromes involving the PI3K/AKT pathway.[1] Hammill et al then reported an infant with refractory vascular anomaly (Kaposiform haemangioendothelioma with severe Kasabach-Merritt Phenomenon) who was successfully treated with sirolimus. Complete resolution of coagulopathy with significant improvement in clinical status with tolerable side effects was experienced within two months of sirolimus treatment.[6] Subsequently, in a phase II prospective clinical trial on treating complicated vascular anomalies with sirolimus, it was found that sirolimus was both safe and efficacious when used on children and young adults.[7]

In this study, we aimed to assess the efficacy, safety and tolerance of sirolimus in children with IH and vascular malformations in Turkish population.

Methods

In this retrospective study, data were obtained from patients who were treated with sirolimus at the Paediatric Oncology Department between September 2015 and September 2019. All patients, under this period, with IH or vascular malformation who initiated treatment with sirolimus and continued treatment for at least 3 months were enrolled in this study. The list of the patients was retrieved through reviewing electronic prescription record system. Approval was obtained from local ethics committee (MEU 2019/399).

The inclusion criteria were a diagnosis of IH or vascular malformation after physical examination, radiologic imaging, and histological examination as required. The diagnoses were made on the basis of history and clinical presentation of the vascular lesion supported by ultrasound and/or magnetic resonance imaging.[8] The demographics of patients, the clinical features of the vascular lesions, and the details of treatments were retrieved by reviewing the medical records.

During the study period, the first choice medication was propranolol (2 mg/kg/day) for IH and surgery was not needed as a first-line treatment for any patients. If there was no involution during post-proliferative stage or a continued growth during proliferative stage, patients would receive adjuvant oral prednisone (2 mg/kg/day). If there was no response to the combined propranolol and prednisone treatment, the vascular lesion would be biopsied for histological examination. Immunolabelling of glucose transporter-1 would be performed to confirm the diagnosis of IH. As health insurance did not cover the cost for multiple sessions of laser therapy, patients with IH resistant to combined oral propranolol and corticosteroid would receive sirolimus treatment.

Patients with vascular malformations would receive sirolimus treatment when there was a complex diffuse lesion (diffuse CMs involving large body surface area; VMs and LMs unresponsive to sclerotherapy) or a malformation that was not amenable to surgery (non-embolised AVMs).

The initial dose of sirolimus was 0.8 mg/m^2 every 12 hours. Improvement in symptoms was defined as an improvement in lesion colour, size, volume, dystrophic skin changes, ulceration, pain, bleeding, or extremity functional limitation.[9] The response to treatment was serially assessed by the same physician and radiologist during the outpatient visits. Lesion size was measured with a ruler by the physician or measured using radiological scans by the radiologist. The physician recorded the lesion size, symptoms, complications, and the feedback from patients and families monthly. Complete response was defined as a disappearance of all clinical and/or radiological evidence of lesion. A partial response was defined as an improvement of symptoms and reduction of lesion size but with the persistence of the anomaly. Progressive anomaly was defined as an increase of symptoms and lesion size. No response was defined when the lesion did not belong to any of the above categories.

Results

Thirty patients with benign vascular anomalies who were treated with sirolimus were reviewed. There were 14 male and 16 female. The diagnosis was IH in 14 (46.7%) patients and vascular malformation in 16 (53.3%) patients. The median age of patients was 2.5 (1.2-17.0) years.

Amongst the vascular malformations, eight patients had venous, three patients had arteriovenous, three patients had macrocystic lymphatic, and two patients had capillary (cutis marmorata telangiectatica congenita) malformations. The results were shown in Table 2.

All patients and/or parents had aesthetic concerns. Disfigurement, pain, and deformity were common symptoms. Mass effect in LMs and ulceration in IHs also caused significant symptoms. The most common

indication for sirolimus treatment was propranolol-resistant oral cavity lesions in the group of IHs, lesions unresponsive to sclerotherapy in the group of LMs and VMs, extensive lesions in the group of CMs, and lesions failed to respond to embolisation in the group of AVMs. With laser treatment and surgical excision either unavailable or inappropriate for the lesions, these patients were started on sirolimus.

All patients were prescribed oral sirolimus twice a day, at an initial dosage of 0.8 mg/m^2/12 hours, and in a dosage range of 1.2-1.6 mg/m^2/day. Serum drug level monitoring was performed monthly to ensure a serum level between 5-15 ng/ml (based on the effective range in immunsuppression for kidney transplants).[10] The median value of sirolimus level was 8.6 (5.9-14.2) ng/ml. The patients did not receive any other treatment during sirolimus therapy. Radiological imaging was performed in eight patients with orbital or cervical, cervicofacial or cervico-thoracic vascular anomalies at 3-6 monthly intervals.

Overall, 20 patients (66.7%) had partial response at a median time of 5 (3-12) months of sirolimus treatment. All these 20 patients had improvement in symptoms on naked-eye examination (Figure1) and seven of them had improvement in radiologic imaging. Three patients with IH and four patients with venous, one patient with lymphatic, one patient with capillary, and one patient with arteriovenous malformation had no response. There was neither complete response nor progressive anomaly. Sirolimus was well tolerated with two patients developed mildly elevated liver enzymes and one patient developed mild lymphopenia. Lymphocyte count and liver enzyme

Table 2 Demographic and clinical characteristics by the study group

Characteristic	Vascular anomaly (n=30)
Age, year	2.5 (1.2-17.0)
Infantile haemangioma	4.2 (1.7-17.0)
Vascular malformation	2.5 (1.2-10.2)
Gender, female	16 (53.3)
Type and location	
Infantile haemangioma	14 (46.7)
- Oral cavity	5
- Face, head	4
- Trunk	2
- Lower limb	1
- External genital	1
- Orbita	1
Vascular malformation	16 (53.3)
- Common VM, facial	4
- Common VM, cervical	2
- Common VM, cervicofacial	2
- Cutis marmorata telangiectatica congenita, whole body	2
- Sporadic AVM, upper limb	2
- Sporadic AVM, facial	1
- Macrocystic LM, cervico-thoracic	2
- Macrocystic LM, lower limb	1
Age to start sirolimus treatment, year	2.1 (0.5-16.0)
Infantile haemangioma	3.6 (1.2-16.0)
Vascular malformation	2.0 (0.5-9.5)
Duration of sirolimus treatment, month	5.0 (3.0-12.0)
Infantile haemangioma	5.0 (4.0-12.0)
Vascular malformation	5.5 (3.0-12.0)
Partial response	20 (66.7)
Infantile haemangioma	11 (78.6)
Vascular malformation	9 (56.3)
No response	10 (33.3)
Infantile haemangioma	3 (21.4)
Vascular malformation	7 (43.7)

Abbreviations: VM, venous malformation; AVM, arteriovenous malformation; LM, lymphatic malformatin

Data are shown as median (min-max), number (%) as appropriate

levels recovered at the fourth-fifth months of treatment with sirolimus continued without dosage adjustment.

In the group with a diagnosis of IH, the median age was 4.2 (1.7-17.0) years and the median duration of prior propranolol use was 9 (6-33) months. The characteristics of patients with propranolol-resistant and histologically confirmed IH were summarised in Table 3.

Discussion

Vascular tumours and vascular malformations are both vascular anomalies which may occur at birth or in infancy. A correct diagnosis is essential as misdiagnosis leading to inappropriate therapy can result in disfigurement, pain, deformity, functional and vital complications. Even if the definitive diagnosis is available timely, the management of vascular anomalies could be complex. While first-line therapies may not provide adequate disease control, new therapeutic agents such as sirolimus may be needed although supportive evidence from prospective clinical trials have been limited.[8,11,12] Sirolimus, also known as rapamycin, is a macrolide compound exhibiting potent antitumour and immunosuppressive activity. Via inhibiting mTOR pathway, sirolimus presents anti-angiogenic and anti-lymphangiogenic effects.[13] It has

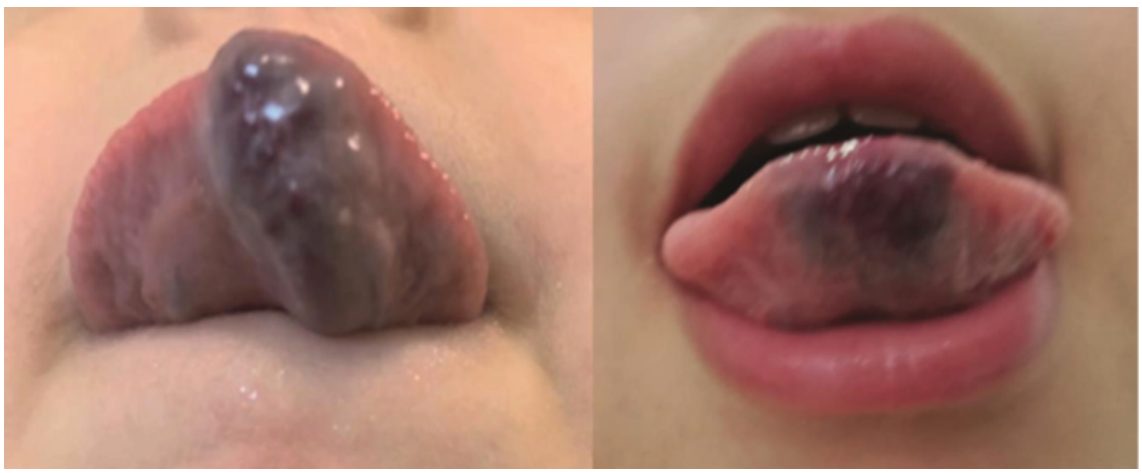

Figure 1 Effect of sirolimus on an infantile haemangioma of the oral cavity. Left: pretreatment lesion. Right: after 10 months of treatment, reduction in lesion size and functional recovery were observed. The plan is to continue with sirolimus for the treatment.

Table 3 Characteristics of the patients with propranolol-resistant infantile haemangioma

Gender	Location	Propranolol use, month	Sirolimus introduction	Sirolimus use, month	Response to sirolimus
Female	Oral cavity	6	6 years of age	4	Partial
Male	Oral cavity	33	6.5 years of age	4	Partial
Male	Oral cavity	13	15 months of age	7	Partial
Male	Oral cavity	9	5.5 years of age	11	Partial
Male	Oral cavity	29	16 years of age	12	Partial
Male	Face, head	6	13.7 years of age	5	Partial
Male	Face, head	13	15 monthsof age	5	Partial
Male	Face, head	9	17 months of age	7	Partial
Female	Face, head	6	7 years of age	8	Partial
Male	Trunk	9	15 months of age	5	No
Female	Trunk	15	18 months of age	6	No
Male	Orbita	12	15 months of age	5	Partial
Female	External genital	6	16 months of age	5	Partial
Female	Lower limb	6	9.2 years of age	5	No

been approved for indications including treatment for lymphangioleiomyomatosis, prevention of rejection in organ transplants, and prevention of coronary in-stent restenosis. In this article, we reviewed 30 paediatirc cases with benign vascular anomalies treated with sirolimus.

The majority of proliferating vascular tumours are haemangiomas and 70% of all haemangiomas are IHs.[8] Haemangiomas located in the orbital, oral, nasal cavity or subglottic region and haemangiomas with ulceration, disfigurement, high-output cardiac failure, mass effect or life-threatening bleeding are indications for specific treatment. Propranolol is the first-line pharmacological therapy for complicated IHs with its beta-blocking effect and cell proliferation regulating potential.[3] In case propranolol is contraindicated or haemangioma is unresponsive to propranolol, further treatments may be required. However, studies on patients with propranolol-resistant IHs are limited. As it has been reported that propranolol efficacy was deemed minimal after 2 years of age, the age of initiating propranolol treatment may be a factor affecting treatment efficacy. In addition, treatment resistance to propranolol may occur at any time during the proliferation stage of IH and at all ages during early childhood.[14,15] It is known that sirolimus inhibits proliferation and increases vascular maturation of GLUT1-positive endothelial cells from IH.[16] Successful use of sirolimus in an infant with PHACE syndrome and segmental IH who was heavily pretreated with corticostreoid, propranolol, and vincristine was reported in 2013. Sirolimus improved the mass effect and ulceration of refractory IH and was well tolerated in the reported infant.[17] In another case report, a 3-year-old girl with refractory diffuse IHs and multiorgan involvement had significant clinical improvement in her pulmonary hypertension and radiological improvement in liver lesions with sirolimus treatment.[18] In the present study, the response rate of IH to sirolimus was 78.5%. Three patients with IH (2 truncal, 1 lower limb) were unresponsive to sirolimus. Further studies are necessary to demonstrate whether and how the mTOR inhibitor rapamycin is an effective treatment for childhood IHs.

Several recent studies have reported that sirolimus is effective not only in the treatment of macrocystic and microcystic LMs, but also benefical for combined malformations with lymphatic component. It has been shown that sirolimus could inhibit lymphatic vessel regeneration and invasion and reduce lymphatic leakage and blebs. These histological changes would result in improvement in disease severity and reduction in infection associated complications.[5,19] Clinical stabilisation and improvement in associated manifestations have been reported in patients with diffuse LMs who were treated with sirolimus.[7,9] Youssef et al studied safety and efficacy of sirolimus in patients with refractory vascular anomalies with a mean age of 7.9 years.[20] In his study, all patients including two LMs improved significantly in their symptoms and quality-of-life scores.[20] In the study by Triana et al, 10 out of 11 patients with LMs responded to sirolimus.[9] More significantly, two patients born with large lymphatic malformations with airway involvement experienced symptomatic improvements with sirolimus.[21] In our present study, although one patient with more aggressive lower limb LM did not respond well to sirolimus, two patients with LMs involving critical areas improved with the use of sirolimus.

The evidence of sirolimus efficacy in the treatment of VMs is limited and mixed. In a study involving both VM models in mice and human subjects, it has been demonstrated that rapamycin could bring clinical improvement.[22] Cases with blue rubber bleb nevus syndrome (a multifocal venous lymphatic malformation) and VMs refractory to standard therapies have also been reported to experience reduction in symptoms.[23,24] In the present study, the partial response rate of VMs to sirolimus was 50% while half of the patients did not demonstrate improvement in pain, lesion size, and phlebitis.

While first line treatment for CMs is multiple sessions of pulsed dye laser, sirolimus was found to be a safe and effective adjunctive treatment to laser.[25] In this study, two patients with cutis marmorata telangiectatica congenita with no associated anomalies received sirolimus as the sole treatment, one of them responded to therapy with improved skin atrophy and ulceration while the other did not have significant improvement.

It has been reported that sirolimus treatment may be benefical to hereditary haemorrhagic telangiectasia, a disease characterised by mucocutaneous telangiectasias and visceral AVMs.[26] A retrospective study by Triana et al reported all four patients with AVMs (3 extracranial, 1 intracranial) did not respond to sirolimus.[9] We treated three patients with extracranial AVMs, and two of them with upper limb AVM experienced reduction in lesion volume and activity limitation while one patient with facial AVM did not improve. To investigate the variation of sirolimus efficacy on various types of AVMs, further studies would be required.

Conclusion

In conclusion, sirolimus may be a valid treatment choice for paediatric patients with refractory benign vascular anomalies. Further prospective studies on the optimal therapeutic regimen including dosage and duration should be performed. In addition, there is an ongoing need to evaluate the efficacy of sirolimus on individual type of vascular anomalies.

Conflict of Interest

The authors have no conflicts of interest or funding to disclose.

Acknowledgements

We dedicate this manuscript to our co-author Professor Elvan Çağlar ÇITAK who passed away prior to the publication of the research paper. We would like to thank Yavuz Selim AYHAN, MD for his help in collecting data.

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