Safety and efficacy of sirolimus in patients with refractory vascular anomalies

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Background
Vascular anomalies are a heterogeneous group of anomalies. The majority follow a benign course. However, some, for example, kaposiform hemangioendotheliomas, may be life threatening. Many lines of treatment have been described; however, no single agent is always successful. It has been suggested that Mammalian Target of Rapamycin (mTOR) inhibitors such as sirolimus could be beneficial.

Patients and methods
Twelve patients with different vascular malformations refractory to different modes of treatment presented to our vascular malformations clinic, including three patients with Klippel-Trenuany Syndrome, three with kaposiform haemangioendothelioma, two with hereditary hemorrhagic telangiectasia, two with Parkes Weber syndrome, and two with lymphatic malformations. The patients were clinically examined, and them and their caregivers were asked to fill the pediatric quality-of-life inventory version 4.0 (pedsQL Generic Core Scale). Then they were put on oral sirolimus 0.8 mg/m^2 adjusted to achieve serum level 10–15 ng/ml. Participants were followed up prospectively and asked to fill the quality-of-life assessment form once more after 12 months.

Results
Mean age of participants was 7.9 years with female predominance (8/12). Mean duration of treatment was 14.6 months. All the 12 patients significantly improved on sirolimus regarding quality-of-life score and symptoms.

Conclusion
Sirolimus is a valid and safe option in the treatment of refractory vascular malformations.

Keywords:
sirolimus, vascular anomalies, vascular malformations

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Introduction

Vascular anomalies are a heterogeneous group of anomalies arising from blood and/or lymph vessels. The most recent classification agreed upon by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996 divides these lesions into true vascular tumors and vascular malformations [1]. Most of these lesions follow a benign course, such as infantile hemangiomas, which typically resolve without any active treatment. However, other vascular tumors such as kaposiform hemangioendotheliomas (KHE) may be life threatening [2]. Treatment of vascular anomalies needs multidisciplinary team including experienced hematologist, radiologist, and surgeon. Many lines of treatment have been described; however, no single agent is successful in all cases. Some cases are still refractory to all conventional modalities. Treatment modalities include anti-inflammatory drugs, corticosteroids, interferon and other antiangiogenic drugs, sclerotherapy, embolization with or without surgery, and pulsed dye laser [3].

PTEN is an important tumor suppressor protein in the Mammalian Target of Rapamycin (mTOR) signaling pathway, whose mutations have been identified in both fast-flow vascular malformations and slow-flow lesions with associated overgrowth. Therefore, it has been suggested that mTOR inhibitors such as sirolimus could be beneficial in the treatment of such lesions [4]. Sirolimus is the only mTOR inhibitor approved by Food and Drug Administration for immunosuppression in pediatric renal transplant

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recipients. Sirolimus directly inhibits mTOR via preventing downstream protein synthesis and subsequent cell proliferation and angiogenesis [5].

Patients and methods

After approval of IRB of Surgery Department, Faculty of Medicine, Ain-Shams University, 12 patients with different types of vascular malformations that were refractory to different modes of treatment were included (Table 1). They were presented to the vascular malformations clinic, Pediatric Surgery Department, Ain-Shams University. Three patients had Klippel-Trenuany Syndrome (KTS), three KHE, two hereditary hemorrhagic telangiectasia, two Parkes Weber syndrome, and two lymphatic malformations.

All patients were examined clinically, and available radiological reports were reviewed. Their caregivers were asked to fill the pediatric quality-of-life inventory version 4.0 (pedsQL Generic Core Scale). They were put on oral sirolimus 0.8 mg/m^2. The dose was adjusted to achieve serum level of 10–15 ng/ml. Serum sirolimus level was measured every 3 months. Participants were followed up prospectively and asked to fill the quality-of-life assessment form once more after 12 months of treatment.

Results

Mean age of the patients was 7.9 years, with female predominance (8/12). Mean duration of treatment was 14.6 months. All patients gained better quality-of-life on sirolimus (Table 2), whereas seven (58.3%) patients had their symptoms improved. Patient 1 had from extensive arteriovenous malformation at the right side of the neck extending to superior mediastinum, posterior aspect of the right side of the neck, right shoulder girdle, and slightly to the right side of posterior chest wall. The patient had heart failure, and his right upper limb blood pressure was 50/20 and the heart was enlarged with preferential dilatation of the right atrium. Although he was on captopril, lasix, and sildenafil, he was complaining of pain and fatigue with limb in dependent position that was relieved only with limb elevation. He is now still on anti-failure medications but is pain free. Patient 3 had marvelous decrease in size of swelling as seen in Fig. 1. Patients 4 and 7, with KTS, were previously experiencing pain interfering with their daily activities and causing their absence from school most of the time. After sirolimus, they rarely miss their classes and are more able to contribute actively in simple school activities with their peers. Attacks of bleeding per rectum experienced by patient 2 became less frequent and decreased in its severity. Patients 5 and 6 required

Table 1 Patient's characteristics

	Age	Sex	Diagnosis	Previous treatment	Duration of treatment (months)	Remarks
Patient 1	10	Male	PWS	Injection sclerotherapy	18	Heart failure with right limb in dependent position
Patient 2	17	Female	KTS with bleeding per rectum	Surgery and garmets	23	
Patient 3	4.5	Female	Right thigh KHE	Surgery, steroids, and vincristine	9	Pain, school absence
Patient 4	8	Female	KTS	Surgery and garmets	10	
Patient 5	5	Male	HHT with severe epistaxis	Tamoxifen, Tranexamic acid, and sclerotherapy	15	Blood transfusion
Patient 6	4	Male	HHT with severe epistaxis	Tranexamic acid and sclerotherapy	22	Blood transfusion
Patient 7	7	Female	KTS	Garmets	11	Pain, school absence
Patient 8	5	Female	Right arm KHE	Steroids, interferon, and vincristine	10	
Patient 9	12	Male	PWS	Injection sclerotherapy	20	
Patient 10	4.5	Female	Orbital LMF	Surgery and bleomycin injection	18	
Patient 11	15	Female	Left thigh KHE	Surgery, steroids, and vincristine	10	
Patient 12	3	Female	Cervical LMF	Surgery and bleomycin injection	9	

HHT, hereditary hemorrhagic telangiectasia; KHE, kaposiform hemangioendotheliomas; KTS, Klippel-Trenuany Syndrome; LMF, lymphatic malformation; PWS, Parkes Weber syndrome.

Table 2 Quality-of-life assessment before and after sirolimus

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8		Patient 9		Patient 10		Patient 11		Patient 12	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Physical function	50	100	0	25	50	50	50	75	0	25	25	50	0	25	0	50	50	50	50	50	25	50	25	50
Role functioning	75	100	25	25	75	100	25	50	25	50	50	75	25	25	25	75	25	50	50	50	25	50	50	50
Bodily pain	0	25	25	50	75	100	50	75	25	25	25	50	25	75	0	50	50	50	25	75	25	75	50	75
General health	50	75	50	75	25	25	50	75	50	75	50	75	25	75	50	75	25	50	50	75	25	75	50	75
Vitality	50	50	50	50	50	50	25	50	25	50	50	75	50	75	50	75	25	50	50	75	25	50	50	75
Social functioning	25	50	25	50	50	50	25	50	25	50	50	50	50	50	50	75	50	75	25	75	50	75	25	75
Role emotional	50	50	25	50	25	50	25	50	50	75	25	75	50	50	50	75	75	75	25	75	50	75	25	75
Mental health	50	50	75	75	50	50	75	75	50	75	50	50	75	75	50	75	75	75	50	75	75	75	50	75

no blood transfusion for 18 months and 3 years, respectively. Adverse effects seen in our patients were previously reported with the use of sirolimus in children [5]. Elevated liver enzymes were seen in two patients, one had hypercholesterolemia, and three experienced chest infection associated with neutropenia. Adverse effects were easily controlled by dose adjustment.

Discussion

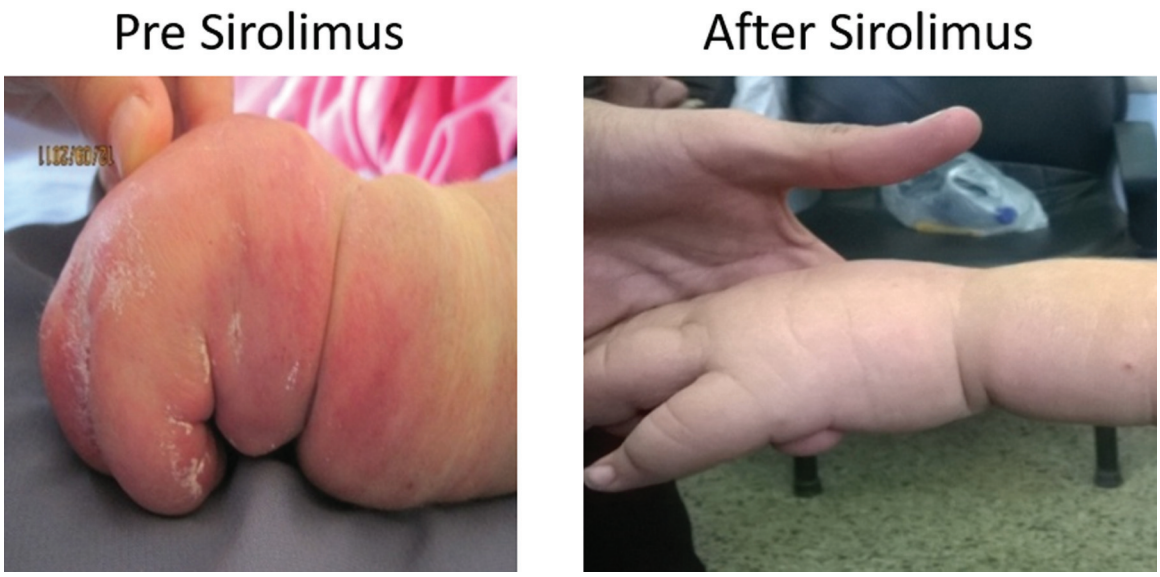
A new classification of vascular anomalies based on cellular proliferative activity and invasive potential was introduced in 1996 [1]. Because of the quiet similarity between vascular tumors and malformations regarding their clinical features and imaging, an accurate diagnosis to distinguish between both is essential to choose an appropriate approach.

Sirolimus use started to evolve in 2010 especially in treating conditions like KHE, but only sporadic cases were reported in the literature [6]. Hammill *et al*. in 2011 [4] reported the use of sirolimus on five patients with complicated lymphatic malformation and one case with KHE. In the period between 2011 and 2016, few case reports were reported on the use of sirolimus on children with vascular anomalies such as lymphatic malformation and KHE [7–9]. The first clinical trial that proved safety and efficacy of sirolimus in vascular anomalies was reported by Adams *et al*. [10] and was conducted on 61 patients.

We have applied sirolimus on patients with such lesions who have failed other modalities presented to the vascular anomalies clinic, Ain-Shams University. Our results suggest that sirolimus is a safe and a valid treatment option for children and young adults with complicated vascular malformations resistant to other modalities. There was marked improvement of the 12 patients who were included in this study regarding the quality-of-life score. The most significant results were on patients with KHE and KTS. Some patients experienced adverse effects related to the use of sirolimus, which were similar to what was reported in the literature [5] and cured by adjusting the dose.

One difficulty in interpreting these data is that those patients were initially treated by other drugs which can act as confounders. However, what supports that sirolimus was responsible for patients' improvement is that symptoms were present at the time of initiation of sirolimus and only improved later on after sirolimus use. All other drugs like vincristine and steroid were discontinued once sirolimus serum level has reached the desired value. The main proof that sirolimus is an

Figure 1



Patient 3 before and after treatment showing marvelous improvement.

effective modality of treatment in patients with resistant vascular anomalies is that all patients who were included in the study were previously treated by different drugs and showed marked improvement only after using sirolimus, which leaves no doubt of the efficacy of sirolimus. Our results were similar to that reported by others in the literature. Adams *et al*. [10] published their work on 61 patients in 2016 proving the safety efficacy of sirolimus in treating vascular anomalies. Triana *et al*. [11] in 2016 also had a retrospective study conducted on 41 patients considering sirolimus as a novel therapeutic option for treating vascular anomalies. The reason why our study included less number of participants is that we only included cases refractory to conventional means. This study has a limitation owing to its small sample size; therefore, we need a larger sample size to implement a randomized clinical trial.

Conclusion

Sirolimus seems to be a valid and safe option for patients with refractory vascular malformations. However, further clinical trials including larger number of patients are required.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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