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The Role of Sirolimus in the Treatment of Lymphatic Malformations

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ABSTRACT

Background: Lymphatic malformations (LMs) are complex vascular anomalies that pose significant therapeutic challenges due to their infiltrative nature and potential for serious complications. Sirolimus, a macrolide with antiproliferative and immunosuppressive properties, has emerged as a promising pharmacologic treatment.

Objective: To assess the effect of sirolimus in patients with lymphatic malformations in terms of the improvement of symptoms and QOL and the reduction of the size of the lesion.

Patients and methods: This prospective interventional study evaluated the efficacy and safety of sirolimus in 16 pediatric patients (aged 0.5–15.8 years) with microcystic, mixed, or lymphaticovenous malformations. Patients received oral sirolimus at a dose of 0.05–0.07 mg/kg twice daily, with serum levels maintained between 4–12 ng/mL. Clinical response was assessed through symptom improvement, quality of life (QOL) evaluation, and radiological follow-up with MRI at 3, 6, and 9 months.

Results: The majority of patients demonstrated significant clinical improvement, with 66.7% showing improvement in disfigurement and pain, 100% improvement in fluid leakage, ulceration, and bleeding, and notable reductions in lesion size on MRI. QOL improved significantly in 50% of patients and partially in 37.5%. Adverse events were generally mild and manageable, including pneumonia (12.5%), glossitis (6.25%), hypercholesterolemia (18.75%), neutropenia (12.5%), and elevated liver enzymes (12.5%).

Conclusion: These findings support the use of sirolimus as a safe and effective treatment option for pediatric patients with difficult-to-treat lymphatic malformations.

Keywords: Sirolimus, Vascular anomalies, Vascular malformations, Lymphatic malformations.

INTRODUCTION

Errors in embryologic vasculogenesis that affect capillaries, veins, arteries, lymphatics, or a combination of these can lead to vascular malformations (VMs) [(1,2)]. Categorized as macrocytic, microcytic, or mixed cystic LMs, cystic LMs are the most prevalent kind of LM and present as solitary lesions of different diameters. Microcystic and mixed cystic LMs are composed of smaller cysts and diffuse vessel-like lesions, while macrocystic LMs appear as massive cysts bigger than 2 cm in diameter [(3)].

LMs can induce a variety of symptoms based on the size and location of the lesion, determining the disfigurement and functional harm to the surrounding tissues or organs. They typically enter soft tissues and can spread throughout the body, including the extremities, trunk, abdomen, retroperitoneum, and thorax[(4)].

The lesion's margins are frequently ambiguous, and the invasive involvement with infiltration of surrounding tissues can result in major consequences such as airway obstruction, organ malfunction, speech or communication difficulties, and impairment of oral feeding [(5)].

Because microcystic LMs are infiltrative, surgery is still difficult, and sclerotherapy is frequently not an option. Pharmaceutical therapies like sirolimus have been adopted as a line of treatment with excellent effectiveness in recent years since big microcystic and mixed abnormalities remain a therapeutic problem [(6)].

A natural macrolide called sirolimus was discovered in a strain of Streptomyces genus and Streptomyces hygroscopicus bacterium. Its first use was as an antifungal and antibacterial. Further research has demonstrated remarkable immunosuppressive, cytostatic, and antiproliferative qualities. With no discernible impact on healthy lymphatics, sirolimus not only inhibits the development of aberrant lymphatics but also causes lesions to partially recede [(7)].

The aim of this study was to assess the effect of sirolimus in patients with lymphatic malformations in terms of the improvement of symptoms and QOL and the reduction of the size of the lesion. In addition, the safety and side effects profile of sirolimus treatment in patients with lymphatic malformations were also assessed.

PATIENTS AND METHODS

This prospective interventional study was conducted at the Department of Pediatric Surgery, Sohag University Hospitals in the period from January 2023 to March 2025.

The study included pediatric patients under 16 years of age with pure microcystic, mixed micro- and macrocystic lymphatic malformation and lymphaticovenous malformations. The diagnosis was made on a clinical basis and further confirmed and characterized using MRI.

Patients with pure macrocystic lymphatic malformations and those with other varieties of slow flow malformations (pure venous or capillary malformations) or fast flow malformations (arterial or arteriovenous malformations) were excluded from the study. Notably, patients with syndromic forms of VMs

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were excluded from the study. We also excluded patients with lymphatic malformation that are organ- or life-threatening and that required immediate treatment. Patients who had contraindications to MRI or sirolimus (those with known allergy to the drugs, those with congenital or acquired immunodeficiency, those with chronic infectious disease, cancer patients on chemotherapy, those with liver insufficiency, cytopenia, or hypercholesterolemia) were also excluded from the study. A pregnancy test was performed routinely for female participants more than 12 years of age.

Data collected included patient demographics (sex and age at the start of treatment), symptoms (cosmetic disfigurement, chronic pain, recurrent cellulitis, ulceration, bleeding, functional impairment), lesion's location, type (pure microcystic or mixed) and size (clinical and radiological) and prior treatments offered (medical, surgical or injection therapies). The duration of sirolimus treatment and any adverse events during treatment were recorded.

Baseline laboratory investigations included CBC, liver and kidney function tests, serum electrolytes, lipid profile, and coagulation profile. These were repeated weekly in the 1st month of treatment, biweekly in the 2nd month, and monthly thereafter.

Oral sirolimus was given in a dose of 0.05-0.07 mg/kg twice daily, and the serum level was monitored and kept between 4-12 ng/mL. The available pharmaceutical form was 1 gm tablets (Rapamune®, Pfizer). The tablet can be scored and divided into two 0.5 mg halves. For patients who were unable to swallow the solid dose, it was crushed and dissolved in water or mixed into a small amount of soft food.

Doses were rounded to the nearest 0.5 mg or 1 mg (half tablet or full tablet) to facilitate dosing. If the daily dose was 0.5mg or less, it was given once.

During the trial period, sirolimus-interacting medications and treatments that may alter the malformation's progression were prohibited.

All patients were admitted for 24-hours at the start of treatment for early detection of any reactions to the drug. After discharge they were given a phone number to call if any concern regarding the drug arises. Follow up visits were scheduled weekly in the first month, biweekly in the second month, and monthly thereafter. Visits were scheduled to ensure compliance on the dose, report any side-effects and monitor the response to treatment.

Treatment was suspended in cases of severe toxicity, patient and/or parents who refused to continue, and patients who did not experience any benefit after 3 months of therapy.

Response to sirolimus treatment was evaluated by clinical assessment (history and physical examination), by using digital photography and by QOL assessment through parental interviews. Radiological follow up was done by MRI at 3, 6, and 9 months.

Ethical approval:

Sohag Faculty of Medicine's Ethical Committee gave its approval to the study protocol. The parents of the patients provided written informed consent. Throughout its implementation, the study complied with the Helsinki Declaration.

Statistical analysis

The recorded data were examined using SPSS version 23.0. The mean ± SD and ranges were used to show quantitative data for parametric (normal) variables, whereas the median with range were used for non-parametric (non-normally distributed) variables. Qualitative parameters were presented as frequency and percentage.

RESULTS

A total of 16 pediatric patients with microcystic, mixed lymphatic, and lymphaticovenous malformations were included in the study. The median age at the start of sirolimus treatment was 6.2 years, ranging from 0.5 to 15.8 years. Among the participants, 10 (62.5%) were males and 6 (37.5%) were females. Tables 1 and 2 and figures 1-4 show the detailed results

The types of lesions observed were mixed macrocystic and microcystic in 7 patients (43.75%), pure microcystic in 6 patients (37.5%), and lymphaticovenous in 3 patients (18.75%). The average size of the lesions was 9.2 ± 3.6 cm². Lesions were most commonly located in the head and neck region (50%). At the time of presentation, the most common symptom was disfigurement, reported in 15 patients (93.75%) and pain was reported in 12 patients (75%). Prior to sirolimus treatment, 10 patients (62.5%) had not received any prior treatment (Table 1).

Table (1): Data at the Start of Sirolimus Treatment*

	Values	Percentage
Demographics		
Age in years; Median (Range)	6.2 (0.5 to 15.8) years.	—
Male; n (%)	10/16	62.5%
Female; n (%)	6/16	37.5%
Type of the lesion (n = 16)		
Mixed macrocystic and microcystic	7/16	43.75%
Pure microcystic	6/16	37.5%
Lymphaticovenous	3/16	18.75%
Size in cm^2; Mean ± SD (Range)	9.2 ± 3.6 (3.1-1.1)	—
Locations (n = 16)		
Head and neck	8/16	50%
Extremities	6/16	37.5%
Trunk (Chest/Abdomen or both)	4/16	25%
Symptoms (n = 16)		
Disfigurement (Mass, color, texture)	15/16	93.75%
Pain	12/16	75%
Recurrent Cellulitis	4/16	25%
Functional Impairment (movement)	3/16	18.75%
Fluid Leakage	3/16	18.75%
Ulceration	3/16	18.75%
Bleeding	2/16	12.5%
Treatment History (n = 16)		
None	10/16	62.5%
Sclerotherapy	4/16	25%
Betablocker	4/16	25%
Surgical excision	0/16	0%

*Patients could have multiple entries for some categories

Sirolimus was administered orally at a dose of 0.05–0.07 mg/kg twice daily, with serum levels maintained between 4–12 ng/mL. The mean duration of treatment was 9 months.

Clinical response to sirolimus was generally positive. Among the 15 patients who presented with disfigurement, 10 (66.7%) showed improvement. Pain improved in 8 out of 12 patients (66.7%). Recurrent cellulitis improved in 2 out of 4 patients (50%). Functional impairment improved in 2 out of 3 patients (66.7%). All patients with fluid leakage (3/3) and ulceration (3/3) showed improvement, as did both patients with bleeding (2/2).

QOL assessments indicated that 8 patients (50%) experienced significant improvement their QOL. Radiologically, 8 patients (50%) had a reduction of 25%–50%.

Adverse events were generally mild and manageable. Two patients (12.5%) developed pneumonia, and 1 patient (6.25%) experienced glossitis. Laboratory changes included hypercholesterolemia in 3 patients (18.75%), neutropenia in 2 patients (12.5%), and elevated liver enzymes in 2 patients (12.5%) (Table 3).

Table (2): Clinical, Radiological, and Laboratory Response to Sirolimus Treatment*

Outcomes	Values	Percentage
Duration of Treatment; Mean ± SD (Range)	9 ± 2.75 (5.5-27) months	—
Daily Dose ; Median (Range)	2 (0.5–3) mg/day	—
Sirolimus Serum Level; Mean ± SD (Range)	10.3 ± 3.9 (4.2-14.6) ng/mL	—
Clinical Response		
Disfigurement (Mass, color, texture)	10/15	66.7%
Pain	8/12	66.7%
Recurrent Cellulitis	2/4	50%
Functional Impairment	2/3	66.7%
Fluid Leakage	3/3	100%
Ulceration	3/3	100%
Bleeding	2/2	100%
Quality of Life (QOL) (n = 16)		
No Improvement in QOL	2/16	12.5%
Some Improvement in QOL	6/16	37.5%
Significant Improvement in QOL	8/16	50%
Radiological Response		
Size Reduction of 0%–25%	`	25%
Size Reduction of 25%–50%	8/16	50%
Size Reduction of >50%	4/16	25%
Adverse events		
Pneumonia	2/16	12.5%
Glossitis	1/16	6.25%
Laboratory Changes		
Hypercholesterolemia	3/16	18.75%
Neutropenia	2/16	12.5%
Elevated Liver Enzymes	2/16	12.5%

*Patients could have multiple entries for some categories

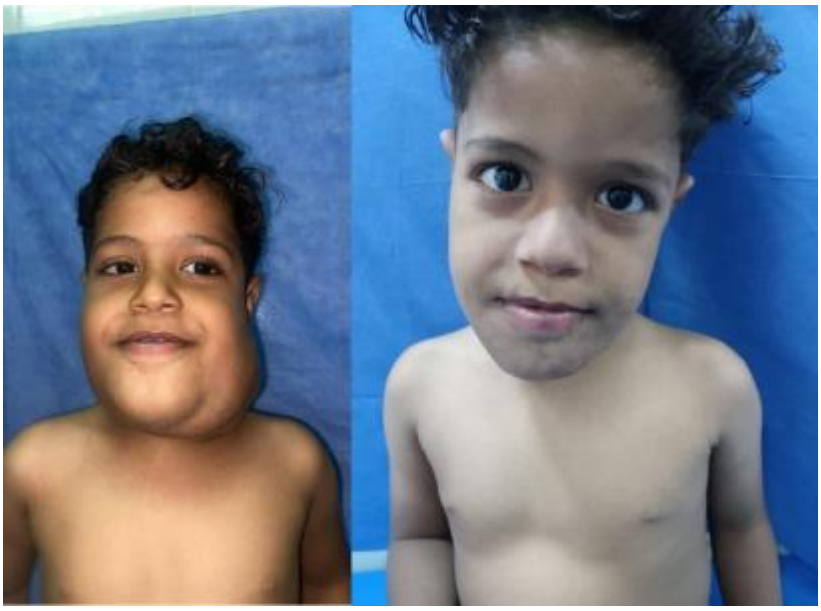

Fig. (1): A patient with huge lymphatic malformation of the head and neck, before and 8 months after the start of sirolimus.

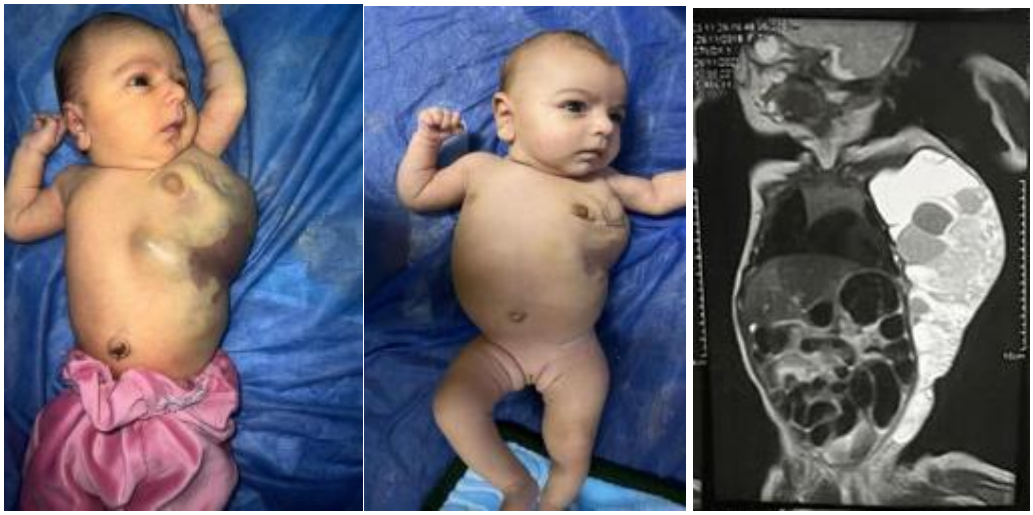

Fig. (2): A patient with huge lymphatic malformation of the chest, before and 6 months after the start of sirolimus.

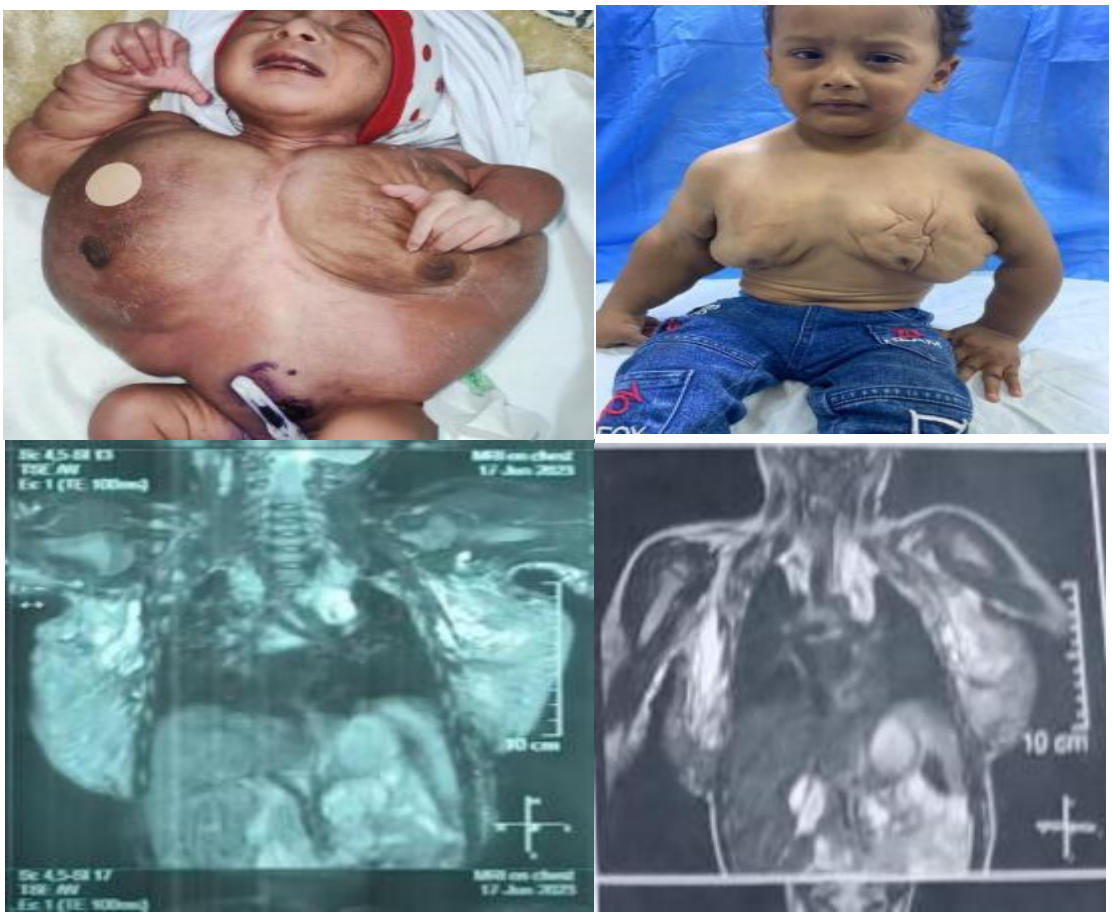

Fig. (3): A patient with huge lymphatic malformation of the chest and upper limbs, before and 9 months after the start of sirolimus.

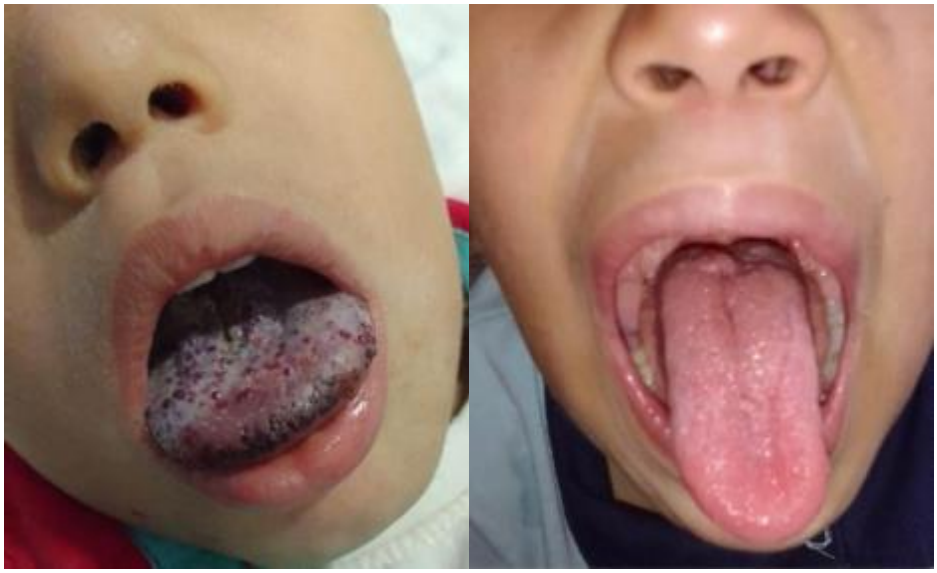

Fig. (4): Sirolimus induced glossitis.

DISCUSSION

Patients with LM may benefit from a variety of therapeutic options, including surgical resection, laser therapy, sclerotherapy, and radiofrequency ablation (RFA), which can give local control and alleviate symptoms. Non-surgical therapies have been recognized as an optional treatment for complex LMs, nevertheless, when they include important veins, nerves, and essential organs that cannot be medically removed. The majority of them, however, continued to be refractory lesions that do not react effectively because RFA, laser, and sclerotherapy are ineffective in deep LM regions and have a limited capacity to reduce symptoms [8].

Cho *et al.* [4] found that most patients had undergone conventional treatments, e.g., sclerotherapy, betablockers or surgery prior to sirolimus administration. In our study, 4 patients (25%) tried sclerotherapy and another 4 patients (25%) received betablocker. None of our patient had prior surgical treatment.

The age of starting sirolimus depends upon the

age of patient presentation and maximum symptoms. **Adams *et al.*** [9] found that the effectiveness of sirolimus treatment may be impacted by the patient's age at initiation. Younger individuals appeared to respond more significantly than older patients, even though they all had the same diagnostic and phenotype. This discovery might be explained by the lymphatic system's physiological changes over time, which reduce the effectiveness of medical treatment [9]. **Abdelbaky *et al.*** [10] reported a median age to start sirolimus of 3 years (5 months to 13 years). In our study found that the median age at sirolimus beginning was 6.2 (0.5 to 15.8) years.

Treatment for sirolimus can be somewhat controlled since serum levels can be measured. Nevertheless, there is currently no established serum level for a safe and effective treatment. It is yet unknown what the ideal dosages and matching plasma levels are for each patient in order to produce a response. However, the most common goal values were 5-15 ng/mL.

In this study, oral sirolimus was given in a dose of 0.05-0.07mg/kg twice daily, and the serum level was monitored and kept between 4-12 ng/mL. Other authors started sirolimus at a dose of 0.8 mg/m^2, with the level to be maintained between 4 and 12 ng/ml[10]. The majority of writers kept sirolimus at the recommended dosage. In order to determine the lowest effective dosage for each patient to maintain asymptomatic status, some writers advise lowering the dosage once the response to sirolimus has plateaued for a few months. Additionally, several individuals experienced stable illness after stopping the medication [11].

The results of our study demonstrated that the clinical response to sirolimus was generally positive. Disfigurement improved in 66.7%, pain and functional impairment improved in similar proportions of patients. Also, 50% of patients with recurrent cellulitis reported improvement of their symptoms. Moreover, all patients with fluid leakage, ulceration and bleeding showed improvement. The overall QOL significantly improved in half of the patients (50%) and improved to some extent in 37.5%, and only 2 patients (12.5%) reported no improvement. The impact of sirolimus on the size of the lesion was demonstrated in the radiological reduction of the size in all patients.

Our results are supported by those reported by others in the literature. **Adams *et al.*** [9] published their work on 61 patients in 2016 proving the safety efficacy of sirolimus in treating vascular anomalies. **Triana *et al.*** [12] in 2017 also had a retrospective study conducted on 41 patients considering sirolimus as a novel therapeutic option for treating vascular anomalies.

Also, **Uno *et al.*** [13] employed another mammalian target of rapamycin (mTOR) inhibitor, everolimus, in a patient with Kaposiform Hemangioendothelioma (KHE) and Kasabach-Merritt phenomenon (KMP) with excellent results and few adverse effects after ineffective therapy with propranolol, prednisolone, and cytostatics.

In 2011, **Hammill *et al.*** [14] conducted a retrospective analysis of four baby patients with diffuse microcystic LMs. All patients experienced considerable clinical improvement with manageable side effects.

In a recent review by **Wiegand *et al.*** [15]***,*** in earlier trials, sirolimus therapy was associated with some response in 95.2% (60/63) of patients. They comprised patients with venolymphatic malformations, capillary-lymphatico-venous malformations, and LMs.

Triana *et al.* [12] found that at a median duration of 10 (1–16) weeks, the overall effective response rate was 80.4% (33/41) of patients, exhibiting decreased symptoms and improved radiologic imaging. None of the patients responded completely.

Additionally, **Baluk *et al.*** [16] showed that sirolimus causes the partial regression of lesions and inhibits the formation of aberrant lymphatics without having any discernible impact on normal lymphatics. Reduced levels of Prox1 and vascular endothelial growth factor receptor-3 accompany this regression, although lymphatic endothelial cell caspase-dependent death is absent. Sirolimus reduced the size of lymphatic lesions in their investigation. Reduced lymph fluid flow and impairment of aberrant lymphatic flow could result from this. But the lymphatic wall remained dilated.

In this study no serious complications from sirolimus treatment were observed and no patients needed hospital admissions, pneumonia developed in 2 patients (12.5%) and one patient experienced reversible glossitis. Laboratory changes included hypercholesterolemia that occurred in 18.75% of the patients, in addition to neutropenia and elevated liver enzymes that occurred in 12.5% of the patients.

Pang *et al.* [17] found that the two most frequent adverse effects were mouth ulcers and dyslipidemia, both of which just needed to be monitored and reassured.

Moreover, **Hammill *et al.*** [14] found that the adverse effects seen in these individuals aligned with the side effects of sirolimus in children that have been previously documented. Grade II–III mucositis, Grade I hypercholesterolemia, Grade II–III AST and ALT increase, and Grade III neutropenia were among the consequences noted.

Also, **Triana *et al.*** [12] found that Sirolimus had negligible adverse effects and was well tolerated, even in newborns. One patient required statin treatment because of hyperlipidemia and elevated liver enzyme levels. Without having to stop medication, another patient experienced lymphopenia and an opportunistic infection. Similarly, **Hammer *et al.*** [18] found that the most common grade 1–2 adverse effects were headache, skin rash, mucositis, weariness, and diarrhea, while sirolimus was well tolerated. All of them were easily controlled with either temporary arrest or symptomatic therapy. Three individuals who had grade 2 headaches or exhaustion temporarily discontinued taking sirolimus.

In this study we found that the cholesterol levels

significantly increased after treatment compared to before treatment (P <0.05). **Wlodarczyk *et al.* [19]** demonstrated that serum total cholesterol levels increased by 7.4% and 15%, respectively, when sirolimus was administered at doses of 0.5 mg/d and 2.0 mg/d. Also, **Tenderich *et al.* [20]** found a spike in median total cholesterol levels of up to 25% and a rise in median serum triglyceride levels of up to 65% within a year after taking a daily dosage of 3.0 mg. Although sirolimus has been thought to have no effect on cholesterol synthesis, it may decrease the clearance of VLDL and LDL.

CONCLUSION

This study demonstrates that sirolimus is a safe and effective therapeutic option for pediatric patients with microcystic, mixed, and lymphaticovenous malformations. Treatment with sirolimus led to significant clinical improvement in symptoms such as disfigurement, pain, ulceration, and bleeding, along with radiological reduction in lesion size and enhanced QOL. Adverse effects were generally mild and manageable, with no severe complications observed. These findings align with previous studies supporting the use of sirolimus in managing complex LMs. Given its efficacy and tolerability, sirolimus should be considered a first-line therapy for patients with challenging, non-resectable LMs. Future studies with larger cohorts and longer follow-up periods are warranted to further establish optimal dosing, long-term safety, and durability of response.

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