ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2024.106.3.125
Annals of Surgical Treatment and Research

# Successful outcome with oral sirolimus treatment for complicated lymphatic malformations: a retrospective multicenter cohort study

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**Purpose:** Sirolimus has emerged as a safe and effective treatment for complicated lymphatic malformations (LMs). We aim to prove the effectiveness and safety of sirolimus as a therapeutic option for patients with complicated LMs.
**Methods:** Fifty-eight patients with complicated LMs treated with sirolimus for at least 6 months at multicenter between July 2018 and January 2023 were enrolled. All patients were administered oral sirolimus starting at 0.8 mg/m$^2$ every 12 hours, with target serum concentration levels of 8–15 ng/mL. Evaluation for clinical symptoms and LMs volume on MRI were reviewed to assess treatment response and toxicities. Evaluation of disease response was divided into 3 values: complete response, partial response (significant, moderate, and modest), and progressive disease.
**Results:** The median age at the initiation of sirolimus treatment was 6.0 years (range, 1 month–26.7 years). The median duration of treatment was 2.0 years (range, 6 months–4.4 years). The most common lesions were head and neck (25 of 58, 43.1%). Forty-six patients (79.3%) demonstrated a reduction in LMs volume on MRI or improvement of clinical symptoms including 2 complete responses. The young age group and the patients who underwent few prior therapies showed better responses. None of the patients had toxicities attributable to sirolimus with a Common Terminology Criteria for Adverse Events grade of ≥3.
**Conclusion:** Oral sirolimus treatment brought a successful outcome without severe adverse effects. It could be the first-line therapy, especially for the young age group of complicated LMs, and an additional option for refractory lesions that did not respond to conventional treatment.
**[Ann Surg Treat Res 2024;106(3):125-132]**

**Key Words:** mTOR inhibitors, Lymphangioma, Lymphatic malformation, Pediatrics, Sirolimus

## INTRODUCTION

Lymphatic malformations (LMs) are congenital low-flow vascular anomalies caused by abnormal development of the lymphatic vascular system. The incidence rate is approximately 1 in 4,000 [1]. Through the lymphatic channels, the body fluid

**Received** October 18, 2023, **Revised** December 18, 2023, **Accepted** January 2, 2024

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and solutes that leak from the blood capillaries to the tissue interstitium are reabsorbed, and this fluid, called lymph, is transported back to the venous circulation to control the tissue fluid balance. Lymphatic vessels also play a pivotal role in immunity as pathways by which immune cells are transported to lymph nodes, and lymphatic vessels of the intestinal villi absorb dietary lipids from the intestine. When lymphatic function is impaired, fluid accumulates in tissues between the cells, resulting in lymphedema. Furthermore, this can lead to impairment of humoral homeostasis and immune function and can cause malnutrition through the accumulation of chyle or the development of protein-losing enteropathy [2].

The International Society for the Study of Vascular Anomalies classified vascular anomalies in 2014, and LMs are divided into cystic LM, generalized lymphatic anomaly, Gorham-Stout disease, etc. Cystic LMs are the most common LM, manifesting in solitary lesions of various sizes, and are classified as macrocytic, microcytic, or mixed cystic LMs. Macrocystic LMs manifest as large cysts with a diameter of more than 2 cm, whereas microcystic and mixed cystic LMs are made up of smaller cysts and diffuse vessel-like lesions [3]. In addition to the cystic form, LMs may have other manifestations, including generalized lymphatic anomalies, LM in Gorham-Stout disease, channel-type LM, primary lymphedema, and others. LMs may cause various symptoms depending on the size and location of the lesion, which determine the disfigurement and functional damage of the surrounding structures or organs. LMs primarily penetrate soft tissues and can occur anywhere in the body, including in the extremities, trunk, abdomen, retroperitoneum, and thorax. In many cases, the boundaries of the lesion are unclear, and the invasive involvement with infiltration of adjacent tissues can lead to serious complications, including organ dysfunction, airway obstruction, impairment of oral feeding, and speech or communication difficulties [4].

Physicians have to decide whether to treat or not for symptomatic LMs and asymptomatic LMs causing concern for cosmesis. Various treatment options, such as radiofrequency ablation (RFA), laser therapy, sclerotherapy, and surgical resection, can provide local control and symptom relief in patients with LM. However, complicated LMs involve vital organs, major vessels, and nerves that cannot be surgically removed. Non-surgical treatments have been accepted as optional therapy for complicated LMs. However, most of them remained refractory lesions that do not respond well because sclerotherapy or laser, RFA have limited ability to alleviate symptoms and are not effective in deep areas of LM [5,6]. Furthermore, in complicated LMs, these treatments may lead to substantial morbidity: cosmetic deformity, organ injury, buildup of scar tissue which may be associated with LM recurrence and regrowth, complications from serial anesthesia, and sclerosing agent risks [6]. Through multidisciplinary approach, complicated LMs are regarded as intractable untreatable diseases.

Since 2010, satisfactory outcomes of mammalian target of rapamycin (mTOR) inhibitors administration have been sporadically reported for patients with complicated LM [7]. The mTOR is a serine/threonine kinase regulated by phosphoinositide 3-kinase (PI3K) and is the basis of various cellular processes, such as metabolism, growth, and proliferation. The PI3K/mTOR pathway increases the expression of vascular endothelial growth factor, which is an important regulator of angiogenesis and lymphangiogenesis. Inhibitors of mTOR may have antiangiogenic effects [8,9] and have been used as immunosuppressants after kidney transplantation. Many reports have shown excellent clinical improvements in complicated vascular anomalies [10-14]. We also evaluated the safety and therapeutic potential of sirolimus in patients with a small number of vascular anomalies [15]. Based on these data, we conducted the present study in multicenter to evaluate the efficacy and safety of sirolimus in complicated LM using a dedicated protocol.

## METHODS

### Ethics statement

This is a retrospective study conducted by collecting electronic medical records with deliberation and approval from the Institutional Review Board (IRB) of Dong-A University Hospital (No. DAUHIRB-21-193). The acquisition of informed consent was waived by the IRB. All clinical images were published with written informed consent obtained from the patient.

### Study design

It is a retrospective cohort study. It was described according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement (available at: https://www.strobe-statement.org/).

*Setting*

We collected the data on patients who were treated with sirolimus for complicated LM between July 2018 and January 2023. The treatment response was evaluated every 6 months. We collected the data at the latest follow-up or the data at the end of January 2023. Six medical centers in South Korea (Hanyang University Guri Hospital, Asan Medical Center Children's Hospital, Ulsan University Hospital, Chonnam National University Hospital, Keimyung University Dongsan Hospital, and Inje University Busan Paik Hospital) with pediatric surgeons participated in this study.

*Enrolled participants*

1) Indication of sirolimus

Sirolimus therapy was administered to: (1) patients with LM confirmed to be unresectable by imaging or histological studies because of proximity to a vital organ or diffuse range effect, (2) patients whose symptoms worsened under or failed conventional treatment, and (3) patients with complications of LM, such as frequent respiratory infections, coagulopathy, recurrent cellulitis (>3 episodes per year), or visceral involvement. Subjects with LM were excluded from the study if they had local lesions that could be resectable, used chronic steroids, or had other chronic medical diseases.

2) Enroll criteria

We enrolled only those who took sirolimus for more than 6 months to ensure the therapeutic effect.

*Sirolimus administration and monitoring*

The initial dose was 0.8 mg/m$^2$ per dose, administered every 12 hours, and subsequently adjusted to maintain a target 12-hour trough level of 8–15 ng/mL. For the first month after beginning treatment, laboratory tests were performed at weekly intervals for therapeutic drug monitoring (TDM). After the TDM stabilized, the test period was flexibly adjusted. The severity of complications was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0 [16].

## Data sources/measurement

Data on patient demographics and clinical characteristics of LM, such as lesion size, location, and type; previous treatment history; age at first administration of sirolimus; duration of sirolimus treatment; need for tracheostomy or gastrostomy; complications; and outcomes were collected from the medical records and documented until January 2023. A diagnosis of LM was made on a clinical basis and confirmed using MRI and/or CT, which were obtained for all patients.

The therapeutic response to sirolimus was evaluated using radiologic imaging (CT and MRI), digital photography, and quality of life determined through parental interviews. A baseline evaluation was conducted before initiating sirolimus therapy, and the response to treatment was evaluated at 6- or 12-month intervals. Volumetric assessments were performed using CT or magnetic resonance volumetry with manual segmentation. Although this method is time-consuming, it provides accurate 3-dimensional volume measurements [17,18]. The volume reduction rate was calculated between pre- and post-administration lesion volumes. The patient responses were categorized into 3 categories: complete response (CR), partial response (PR), and progressive disease (PD) utilizing digital photographs and radiographic images. Notably, the PR category was further subdivided into 3 levels: significant, moderate, and modest, enabling a comprehensive and detailed analysis of the study outcomes (Table 1).

The statistical analyses included the Mann-Whitney U-test, chi-square test, and linear by linear association. All analyses were performed with IBM SPSS Statistics ver. 21.0 (IBM Corp.). Significance was defined at $P \leq 0.05$.

# RESULTS

Fifty-eight patients were treated with sirolimus for LM

**Table 2.** Demographic findings (n = 58)

| Variable | Data |
|---|---|
| Sex, male:female | 27:31 |
| Birth body weight (kg) | 3.3 (2.6–4.1) |
| Childbirth method | |
| Unknown | 16 (27.6) |
| NSVD | 19 (32.8) |
| Caesarean-section | 23 (39.7) |
| Diagnosis time | 0 (0 mo–14.5 yr) |
| Prenatal | 25 (43.1) |
| At birth | 11 (19.0) |
| During growth | 22 (37.9) |

Values are presented as number only, median (range), or number (%).
NSVD, normal spontaneous vaginal delivery.

**Table 1.** Evaluation of disease response

| Disease response | Definition |
|---|---|
| Complete response | >95% Complete disappearance in radiologic imaging and clinically no gross lesion |
| Partial response | |
| Significant | Volume reduction >50% in radiologic imaging or remnant lesion in radiologic imaging but no gross lesion identified |
| Moderate | Volume reduction >20% to ≤50% in radiologic imaging or self-reported improvement of gross lesion |
| Modest | Volume reduction ≤20% in radiologic imaging or stable disease status |
| Progressive disease | Enlargement in size of the lesion in radiologic imaging or self-reported worsening of gross lesion or new lesions appearing |

between July 2018 and January 2023. Twenty-seven boys and 31 girls were enrolled, with a median birth weight of 3.3 kg (range, 2.6–4.1 kg) (Table 2). Most of the patients were diagnosed with LM prenatally through ultrasonography (25 of 58, 43.1%). Among the remaining patients, 11 were diagnosed at birth, and 22 were diagnosed during childhood.

As shown in Table 3, patients with refractory head and neck LM accounted for the majority with 25 cases (43.1%). Multiple sites with 3 or more lesions accounted for 7 patients (12.1%). Five patients underwent tracheostomy due to respiratory difficulties following airway compression, and 2 patients underwent gastrostomy due to difficulties in feeding through the esophagus. Two of the 5 patients who underwent tracheostomy could be weaned off mechanical ventilation with 1 year of sirolimus treatment with an improvement of lung atelectasis following size reduction of the mediastinal LM as shown in Fig. 1.

**Table 3.** Clinical characteristics of lymphatic malformations (n = 58)

| Characteristic | Data |
|---|---|
| Main location | |
| Head and neck | 25 (43.1) |
| Chest and mediatinum | 3 (5.2) |
| Abdomen | 2 (3.4) |
| Extremities | 17 (29.3) |
| Buttock | 3 (5.2) |
| Bladder | 1 (1.7) |
| Multiple sites | 7 (12.1) |
| Type | |
| Macrocystic | 10 (17.2) |
| Microcystic | 16 (27.6) |
| Mixed | 10 (17.2) |
| Lymphatic-venous | 22 (37.9) |
| Treatment history | |
| None | 8 (13.8) |
| Excision | 10 (17.2) |
| Sclerotherapy | 32 (55.2) |
| Beta-blocker | 8 (13.8) |
| Multimodal | 23 (39.7) |
| Same treatment more than 4 times | 19 (32.8) |

Values are presented as number (%).

Among the patients with LMs, the lymphatic-venous type, characterized by a combination of vascular and lymphatic lesions, exhibited the highest prevalence (n = 22, 37.9%). Ten macrocystic LMs, 16 microcystic LMs, and 10 mixed macrocystic-microcystic types were observed. Nineteen patients (32.8%) had a treatment history of the same modality 4 or more times, including sclerotherapy and excision.

The median age at the initiation of sirolimus treatment was 6.0 years (range, 1 month–26.7 years) (Table 4). The median duration of sirolimus use was 2.0 years (range, 6 months–4.4 years), and most patients were administered sirolimus until the end of the study period. Four patients have discontinued sirolimus treatment. Among them, 2 patients ceased the treatment due to complete resolution, while 1 patient discontinued it due to disease progression, prompting consideration of alternative therapeutic approaches. And the other one discontinued treatment due to a preexisting mood disorder deterioration. Thirteen patients (22.4%) temporarily halted sirolimus during treatment (the median sum of the time off sirolimus, 31 days; range, 3–130 days). Ten patients (17.2%) temporarily discontinued the drug due to the occurrence of adverse reactions. Recurrent viral infection of the upper respiratory tract was the cause in 3 patients (5.2%). Four of the 9 patients with gastrointestinal discomfort had time off sirolimus (6.9%). Other causes of temporary drug cessation included headache and hypercholesterolemia, accounting for 1 (1.7%) and 2 (3.5%), respectively.

A significant to moderate reduction in mass volume in the

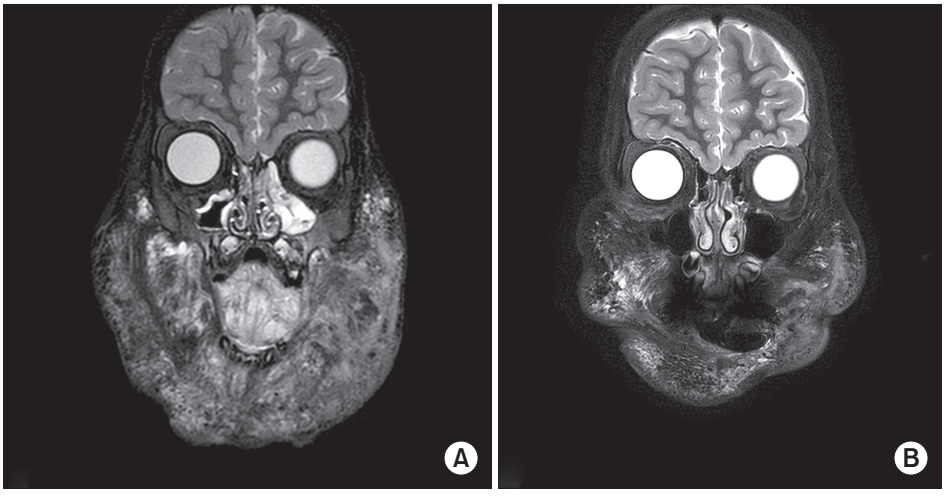


**Fig. 1.** Coronal T2-weighted MRI of a patient. (A) At the beginning of therapy. (B) At 1 year of sirolimus therapy.

radiologic evaluation was observed in 40 patients, ranging from 20.2% to 94.8%. Eight of the 15 patients who had a volume reduction of less than 20% on MRI showed clinical improvement such as external portion size reduction, relief of pain, and reduced bleeding episode (Fig. 2), and removal of tracheostomy and gastrostomy. As shown in Table 4, 51 patients (87.9%) showed results ranging from complete to partial, according to the evaluation of the disease response.

**Table 4.** Sirolimus response

| Variable | Data |
|---|---|
| Age at initiation | 6.0 yr (1 mo–26.7 yr) |
| Sirolimus duration | 2.0 yr (6 mo–4.4 yr) |
| Follow-up | 2.0 yr (6 mo–4.4 yr) |
| Time off sirolimus | 13 (22.4) |
| Sum of the time off sirolimus | 31 d (3–130 d) |
| LM volume reduction by MRI (%) | |
| >50 | 19 (32.8) |
| >20, ≤50 | 21 (36.2) |
| ≤20 | 18 (31.0) |
| Clinical symptoms | |
| Improved | 38 (65.6) |
| No change | 20 (34.5) |
| Overall results | |
| Complete response | 2 (3.5) |
| Partial response | 49 (84.5) |
| Significant | 17 (29.3) |
| Moderate | 27 (46.6) |
| Modest | 5 (8.6) |
| Progressive disease | 7 (12.1) |
| Adverse reaction | 20 (34.5) |
| Skin[a] | 3 (5.2) |
| Recurrent respiratory infection | 3 (5.2) |
| Gastrointestinal discomfort | 9 (15.6) |
| Central nervous system[b] | 1 (1.7) |
| Laboratory finiding[c] | 4 (6.9) |

Values are presented as median (range) or number (%).
LM, lymphatic malformation.
[a]Acne and pruritus. [b]Headache. [c]Hypercholesterolemia.

To compare treatment outcomes, patients were categorized based on their response to the drug (Table 5). Those who demonstrated a significant response, including CR and significant/moderate response (a subgroup of PR), were classified into group A. On the other hand, patients who showed PD despite undergoing treatment and modest response (a subgroup of PR) were categorized into group B, showing an ineffective response to the drug. This classification allowed for a comprehensive evaluation of the drug's efficacy in the study population. It is evident that group A exhibited a younger age at the time of treatment initiation and a lower number of previous treatments, although statistically insignificant. In group A, a slightly higher incidence of sirolimus-related adverse reactions in patients was observed. However, the median duration of drug discontinuation due to these adverse reactions was 10 days in group A and 26.5 days in group B.

The graph presented in Fig. 3 illustrates the regional effects of sirolimus treatment. It was observed that patients with lesions in the head and neck exhibited relatively better results compared to those with lesions in other locations.

None of the patients developed systemic or opportunistic bacterial infection during the study period. No CTCAE grade ≥3 toxicity was observed during the study or on follow-up. Patients have been monitored on an outpatient basis for persistent long-term side effects; however, none have occurred thus far.

**Table 5.** Comparison of factors affecting curative effect

| Variable | Group A (n = 46) | Group B (n = 12) | P-value |
|---|---|---|---|
| Age at initiation (yr), median | 5.5 | 9.3 | 0.701 |
| Duration (yr), median | 1.9 | 2.3 | 0.652 |
| No. of other treatments | 2 | 4 | 0.146 |
| Adverse reaction, n (%) | 17 (37.0) | 3 (25.0) | 0.520 |

Group A, complete response + significant/moderate of partial response; group B, modest of partial response + progressive disease.

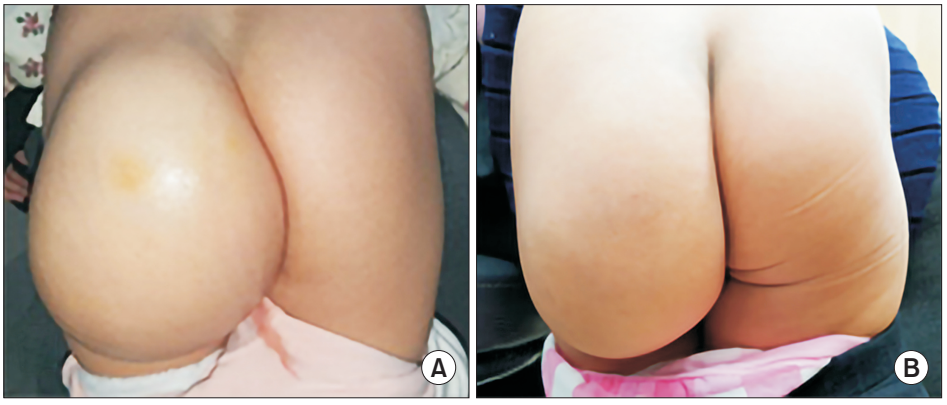


**Fig. 2.** Clinical photograph of a patient showing a buttock lymphatic malformation before the initiation of sirolimus (A) and interval decrease of in the size of the lesion (B).

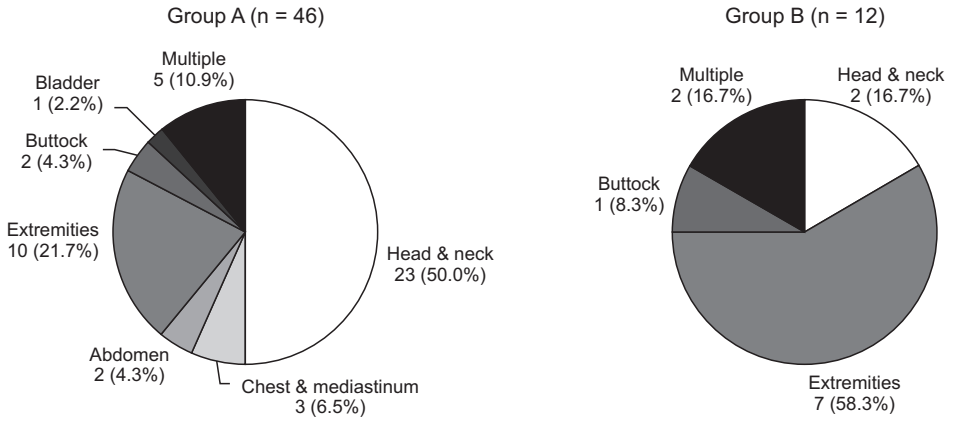


**Fig. 3.** Treatment results by group according to lesion location. Group A, complete response + significant/moderate of partial response; group B, modest of partial response + progressive disease.

## DISCUSSION

To date, many studies have shown that treatment of vascular anomalies with sirolimus is safe and well-tolerated under a well-planned protocol. These studies included heterogeneous patients with several types of vascular anomalies, including LMs, involving multiple sites [8,11,13,19]. They suggest that sirolimus could be a new therapeutic option for refractory lesions in current multimodal treatments or complicated cases. Based on our previous experience, we established a safe protocol through a study of a heterogeneous patient group [15] and conducted a multicenter study including only patients with complicated LMs.

LMs have a diverse natural history depending on their size, location, and complexity. Thus, it is difficult to assess treatment outcomes because patients often do not achieve complete remission even with repeated multimodal treatments. Therefore, treatment could be supportive, rather than curative [20-23]. Considering these points, we evaluated the patients' or parents' satisfaction with the improvement in clinical symptoms and quality of life, as well as the imaging results, to evaluate treatment response. In the imaging tests of patients participating in this study, the volume reduction varied from no change to 94.8%. Most patients underwent conventional treatments, such as surgery or sclerotherapy, prior to sirolimus administration. In particular, 32 patients (55.2%) received sclerotherapy the most, and 13 of them received sclerotherapy 4 or more times. Although sclerosing agents, such as OK-432, doxycycline, and bleomycin act via different mechanisms, they eventually deposit collagen and fibrin, resulting in the formation of dense adhesions and fibrosis [24,25]. Multiple treatments aggravated the conversion from cyst to scar in our patients, and this may have affected our treatment results. In our study, most patients with impressive disease outcomes as a significant result (CR and significant/moderate [subgroups of PR]) received only 1 other treatment before sirolimus treatment, and patients who experienced less effect (modest, a subgroup of PR) and no effect (PD) of received 3 or more treatments and adhered to conventional treatment up to 9 times. It is plausible that untreated LM responds better to medical treatment, sirolimus, than scarred tissues. It is consistent with the previous literature [19].

Even though it did not show a significant decrease in LM volume on imaging studies, the subjective satisfaction of patients or parents was quite considerable. Especially in case of complications with bleeding, the episode of bleeding and the amount of bleeding were dramatically decreased (Fig. 2). It might be associated with an antiangiogenic property of sirolimus.

Another factor influencing the outcome of sirolimus treatment is the age at initiation [26]. LMs often change from thin-walled macrocysts to fibrotic, thick-walled, or microcystic LMs with repeated infection or bleeding. Furthermore, as hormones that change with age also affect the natural history of LM, medical management becomes less effective over time. The physiological changes in the lymphatic system may explain why younger patients showed a favorable response [11,19,26]. Consistent with this explanation, Table 5 shows that the patients with significant results were younger than those in the other groups at the start of sirolimus administration, although statistically insignificant. However, this might lead to confusion because the older age group did not have an opportunity for sirolimus administration at their young age when we had not had the experience of sirolimus.

Surgery is usually preferred as the initial treatment [4,27], but it can be limited because of concerns about damage to vital organs, nerves, or large blood vessels. Our results are consistent with previous studies that showed the lesions close to the mucosal area or vital organs respond more effectively to sirolimus treatment because existing treatments are less likely to be aggressive [11,28]. In group A, which was effective for sirolimus treatment, patients with complicated LM in the head and neck accounted for the highest proportion. These promising results suggest that sirolimus can be the first

treatment option for head and neck LMs which mainly involve critical structures such as the airway, cranial nerves, brachial plexus, and mediastinum, etc.

The majority of patients with multiple lesions had significant effects with sirolimus (5 of 7, 71.4%). Sclerotherapy and surgical resection have limitations in patients with multiple lesions. These treatments may have side effects from repeated general anesthesia and reduced quality of life due to frequent hospital admissions. These findings provide evidence that sirolimus with systemic effects may be a more effective treatment method than local treatment such as excision or sclerotherapy in patients with multiple lesions.

No CTCAE grades 3 or 4 serious adverse reactions were observed in participating patients. Group A, which was effective for sirolimus treatment, experienced a higher rate of adverse reactions compared to group B (37.0% and 25.0%, respectively). The study results suggested that temporary drug discontinuation due to minor side effects does not significantly reduce the efficacy of sirolimus.

Though we observed many LMs and treatment complicated LMs for the last 5 years, we have several limitations in this study. At first, the enrolled patients were selected by individual pediatric surgeons depending on their own decisions. It could make a heterogenous group in that point of previous treatment outcome following different modalities, anatomical sites, and age groups. Second, to many researchers, the cessation of drugs or the tapering protocol of drugs was not clear. It might lead to different treatment periods with cumulative doses during the study period. Third, we did not get surgical biopsy specimens in most patients, we could not analyze histologic findings according to treatment response. In the literature, Pandey suggested one of the predictive factors of sirolimus treatment as the microvessel density within the LMs. Using D2-40 immunohistochemical staining, they found that the more the proliferation of vessels, the better the response to sirolimus [29]. It means lymphangiogenesis could be a valuable predictive biomarker for the therapeutic response to sirolimus in children with LMs. We anticipate our further study protocol, including surgical biopsy, to obtain the microvessel density and somatic mutation.

Notwithstanding, our study holds significant value as it provides reliable results based on a substantial cohort of patients and incorporates a relatively extended treatment duration and follow-up period compared to preceding sirolimus studies. Furthermore, we intend to continue our research efforts aimed at exploring clinical prognostic factors, histologic variables, and genetic markers that hold the potential to predict drug response. By conducting these supplementary investigations, we aim to develop a comprehensive sirolimus treatment protocol for favorable outcomes observed when initiating sirolimus therapy early, without the need for concurrent interventions. These efforts will contribute to an enhanced understanding of sirolimus's therapeutic effects and pave the way for more effective and tailored treatment strategies in the future.

Our study showed that sirolimus is an effective and well-tolerated therapeutic option in pediatric patients with complicated LMs who do not respond to conventional treatment. In patients treated with complicated LMs, the therapeutic effect was greater when sirolimus was started at a young age or exposure to other treatments was less. The timely administration of sirolimus, guided by careful patient selection, exhibits the potential to effectively manage the condition, thereby presenting a compelling case for its consideration as a first-line therapy in complicated LMs. Moreover, the establishment of a comprehensive treatment protocol in the future would further reinforce the rationale for sirolimus as a primary therapeutic option for managing this condition.

## ACKNOWLEDGEMENTS

### Fund/Grant Support

This work was supported by 2023 Inje University Busan Paik Hospital Research Grant.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Investigation: All authors
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