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Other Conditions

Effectiveness of sirolimus in the treatment of complex lymphatic malformations: Single center report of 56 cases

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ABSTRACT

Background: Lymphatic malformations are common congenital vascular lesions. Neither surgical resection nor other surgical treatments have been found to be effective for invasive cases. Recent research has suggested that sirolimus is effective in treating complex lymphatic malformations (LMs). We aimed to evaluate the effectiveness and safety of oral sirolimus for children living with LMs in our hospital.

Methods: Fifty-six cases of complex LMs treated with sirolimus were collected from Shanghai Children's Medical Centre between June 2016 and March 2019. All cases were confirmed either by pathology (44) or enhanced MRI (12). Following informed consent, sirolimus 0.8 mg/m^2 bid was administered orally to participants and maintained at a trough concentration of 10–15 ng/ml. Children's ages at diagnosis were neonate to 16 years (mean 44.3 months). All children were followed up for 5 to 30 months, with a mean of 16.8 months.

Results: During the follow-up period, blood, liver and kidney function as well as disseminated intravascular coagulation was regularly reviewed in all 56 children. Enhanced MRI was regularly performed to evaluate therapeutic effects. Total effective rate (complete response or partial response) of LMs was 89.3% (50/56). No serious adverse reactions were found.

Conclusion: This study suggests that sirolimus is effective and tolerable for decreasing lesions in children with complex LMs, leading to fewer and more tolerable side effects. There is no need to pursue an excision rate to reduce unnecessary operative complications since adjuvant sirolimus therapy modifies the complex LMs clinical appearance and alleviates their symptoms.

Type of study: Clinical research.

Level of evidence: Level IV.

Lymphatic malformations, previously called lymphangioma, are common congenital vascular lesions. According to the ISSVA classification for vascular anomalies, lymphatic malformations can be categorized into common (cystic) LM, Generalized Lymphatic Anomaly (GLA), Kaposiform Lymphangiomatosis (KLA), LM in Gorham–Stout Disease (GSD), Channel-Type LM, primary lymphedema (which covers various subtypes) and others [1]. LMs are the second most common type of congenital head and neck vascular lesion, with an incidence of approximately 1/2000 to 1/4000 live births [2]. LMs can occur in any anatomic region with a lymphatic network. Around 48% of lesions occur in the head and neck, followed by trunk and extremities (42%), abdomen and thorax (10%) [3].

The etiology of LMs is poorly understood. It is likely that LMs represent a clinical spectrum of lymphatic pathological processes [4]. The pathological changes of LMs can range from a minimally swelling lesion area to the large area of diffuse infiltrating abnormal lymphatic vessels or, more seriously, systemic infiltration such as bone and viscera. When examined histologically, LMs consist of irregular lymphatic spaces with thin walls of varying sizes and lymphatic endothelial cells (LECs). In addition to routine pathological diagnosis, enhanced MRI can provide more reliable objective images as well as identify lymphatics and blood vessels for LMs [5]. Authors have recently suggested that both the occurrence and development of LMs are caused by somatic activating mutations in PIK3CA. This abnormal mutation leads to an abnormal activation of the phosphatidylinositol-3′-kinase (PI3K)/AKT signaling pathway, which in turn leads to lymphatic hyperplasia [6–8].

Sirolimus, also known as rapamycin, is a serine/threonine kinase which regulates the signaling pathway PI3K/AKT/mTOR, which in turn plays a pivotal role in cell mortality, angiogenesis and cell growth [9,10]. The drug was approved as an immunosuppressant in 1999 owing to its

Abbreviations: LMs, Lymphatic malformations; GLA, generalized lymphatic anomaly; GSD, Gorham–Stout disease; KLA, kaposiform lymphangiomatosis; PI3K, phosphatidylinositol-3′-kinase; LECs, lymphatic endothelial cells.

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immunosuppressive properties. Its antiangiogenic and antiproliferative properties may be the mechanisms involved in the treatment of LMs. It is thought that sirolimus may reduce phosphoinositide-3-kinase phosphorylation and thus reduce the proliferation and sprouting of LM LECs [8]. Rodriguez-Laguna established Prox1-CreERT2 mice to verify that overexpression of the PI3K/AKT signaling pathway in LECs leads to lymphatic hyperplasia and dysfunction [6]. Results suggest that sirolimus may target the PI3K signaling pathway when treating LMs.

To date, there is no uniform handbook in the literature to guide the treatment of complex LMs and determine appropriate therapy. Complex LMs treatment is intended to control related symptoms, maintain functionality and preserve aesthetic integrity. Thus a multifocused and multidisciplinary approach is needed to improve the quality of patients' lives. There are many types of LMs treatments including surgery, laser therapy, sclerotherapy (with bleomycin, doxycycline or, picibanil) and pharmacotherapy (with treatments such as sildenafil) [11–13]. However, surgical treatment and sclerotherapy tend to be used for macrocystic LMs rather than microcystic LMs. Sirolimus was derived from the bacterium Streptomyces hygroscopicus and has been used in complex vascular anomalies [20]. Subsequently, its application has been used in an increasing number of complex vascular malformations [14,21–26]. Meanwhile, a growing number of authors have indicated that sirolimus can decrease the size of LMs and alleviate associated symptoms [15,16,18,19,27–32]. Therefore, we explored 56 cases of complex LMs treated with oral sirolimus to investigate the drug's efficacy and safety in our hospital.

1. Methods

1.1. Participants

All patients treated for complex LMs with sirolimus at Shanghai Children's Medical Center between June 2016 and March 2019 were included. Patients were categorized into three groups according to the duration of their treatment. Group 1 = 1–6 months, Group 2 = 7–12 months, Group 3 = 13–24 months.

1.2. Patient treatment and evaluation

All participants were treated with sirolimus oral liquid (Hangzhou Sino-US Huadong Pharmacy Co., Ltd., Hangzhou, China, 1 mg/ml), administered according to body surface area. Initial dosing was at 0.8 mg/m^2 body surface per dose, administered every 12 h, as in previous studies [14,20]. The use of the drug was fine-tuned for each individual, depending on the patient's response, and was maintained at a trough concentration of 10–15 ng/ml. All participants were given SMZ (Shandong Xinhua Pharmaceutical Co. Ltd., 400 mg Sulfamethoxazole & 80 mg Trimethoprim / piece) with 20–30 mg/kg, divided into two oral doses and given three days per week to prevent pneumocystis infection.

Objective indicators of efficacy included reduction of lesion size, soft texture, and pain relief. Clinical manifestations, treatment schemes, complications and prognosis follow-up were reviewed and analyzed. Blood, liver and kidney function as well as DIC was reexamined during monthly follow-ups, and enhanced MRI was performed every three months. The longest period of treatment with the medication was two years, while the shortest period medication was six months. After drug cessation, patients were followed up for six months. During follow-up, those treated with sirolimus did not undergo surgery. Participants who demonstrated a poor efficacy of sirolimus treatment underwent surgery to alleviate the condition. Lesions volume was assessed by Materialise Mimics using MRI data.

Effective response was defined in the following manner [14]:

- Complete Response (CR), defined as a complete disappearance of either the lesion (clinical and/or radiological), and the symptoms,
- Partial Response (PR), defined as a reduction of >20% in size of the lesion (clinical and/or radiological) and improvement in symptoms,
- Progressive Disease (PD), defined as an enlargement of >20% in size of the lesion (clinical and/or radiological) or as new lesions appearing.
- Stable Disease (SD), none of above.
- Effective group, defined as CR and PR following disease evaluation.
- Ineffective group, defined as SD and PD following disease evaluation.

Adverse events were assessed by the Common Terminology Criteria for Adverse Events (version 5.0).

1.3. Statistical analysis

Statistical analysis was performed using Graph Pad Prism, Version 6. Chi-square and *t*-tests were used to evaluate the effective of oral sirolimus, while $p < 0.05$ was considered significant. This study was approved by the Ethics Committee of Shanghai Children's Medical Centre

Table 1
Patient characteristics.

Demographics		
Gender, no. (%)		
Male	32	57.1
Female	24	42.9
Diagnosis mode, no. (%)		
Pathological	44	78.6
Enhanced MRI	12	21.4
Age at treatment (months)		
Mean age	44.3	
Median age	24.0	
Age range	2–192	
Age group, no. (%)		
0–2 years	33	58.9
2–10 years	16	28.6
10–16 years	7	12.5

Table 2
Different therapies and effects before oral sirolimus in complex LMs.

	Count	%
Past operation history		
Biopsy	9	16.1
Partial excision	22	39.3
Recurrence after Operation	4	18.2
No relapse after Operation	18	81.8
Sclerotherapy history		
Sclerotherapy	7	12.5
effective	2	28.6
ineffective	5	71.4
Other treatment		
Puncture and aspiration of lesions	4	7.1
Thoracentesis and drainage	1	1.8
Total	43	76.8

Table 3
Sirolimus therapy in complex LMs.

Average medication time, months	13.4	
Median of medication time, months	12.0	
Treatment for 1–6 months, no. (%)	15	
Effective	11	73.3
Ineffective	4	26.7
Treatment for 7–12 months, no. (%)	16	
Effective	15	93.8
Ineffective	1	6.2
Treatment for 13–24 months, no. (%)	25	
Effective	24	96
Ineffective	1	4
Overall Response, no. (%)	50	89.3
CR	2	3.6
PR	48	85.7
PD	6	10.7
SD	0	0

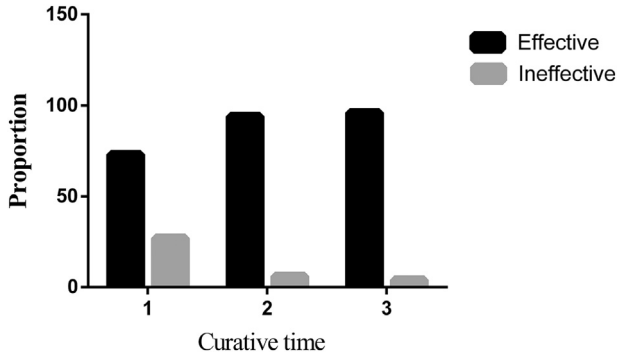

Fig. 1. Comparison of curative effect with different treatment times. Group 1 = 1–6 months, Group 2 = 7–12 months, Group 3 = 13–24 months. Effective group: CR + PR. Ineffective group: SD + PD. $p < 0.001$.

(SCMCIRB-K2017004), and written informed consent was obtained from all participants.

2. Results

2.1. Patient data

All participants were diagnosed either by pathology (44 cases) or enhanced MRI (12 cases). On this basis, 56 patients, 32 males and 24 females, were included and were treated with oral sirolimus for complex LMs between June 2016 and March 2019. The mean age at diagnosis was 44.3 months and the median was 24.0 months (2–192 months) (see Table 1). All participant characteristics are summarized in Supporting Information Table (S1).

2.2. Different therapies and effect before oral sirolimus

Before oral administration of sirolimus for the treatment of complex LMs, 43 patients had already undergone biopsy, surgical partial resection, sclerotherapy, thoracentesis or drainage (see Table 2). Surgical resection as a primary treatment has the ability to not only eliminate macrocystic lesions but can also remove large areas of microcystic lesions. However, owing to extensive involvement of LMs, surgery only partially resected the larger lesions to improve the patients' quality of life. Meanwhile, any remaining lesions were treated with sirolimus to evaluate its efficacy. Some patients with residual tissue after resection find that remaining lesions are resolved following sirolimus treatment. Four children with recurrence after resection still had a good response to sirolimus.

Seven patients with complex LMs were treated with sclerotherapy, of which two cases were effective and five were not. Three of the five participants who did not respond to sclerotherapy were sensitive to sirolimus. Thoracic and mediastinal lesions in one patient were treated with sirolimus after chylous effusions, and lesions were reduced 29.7%.

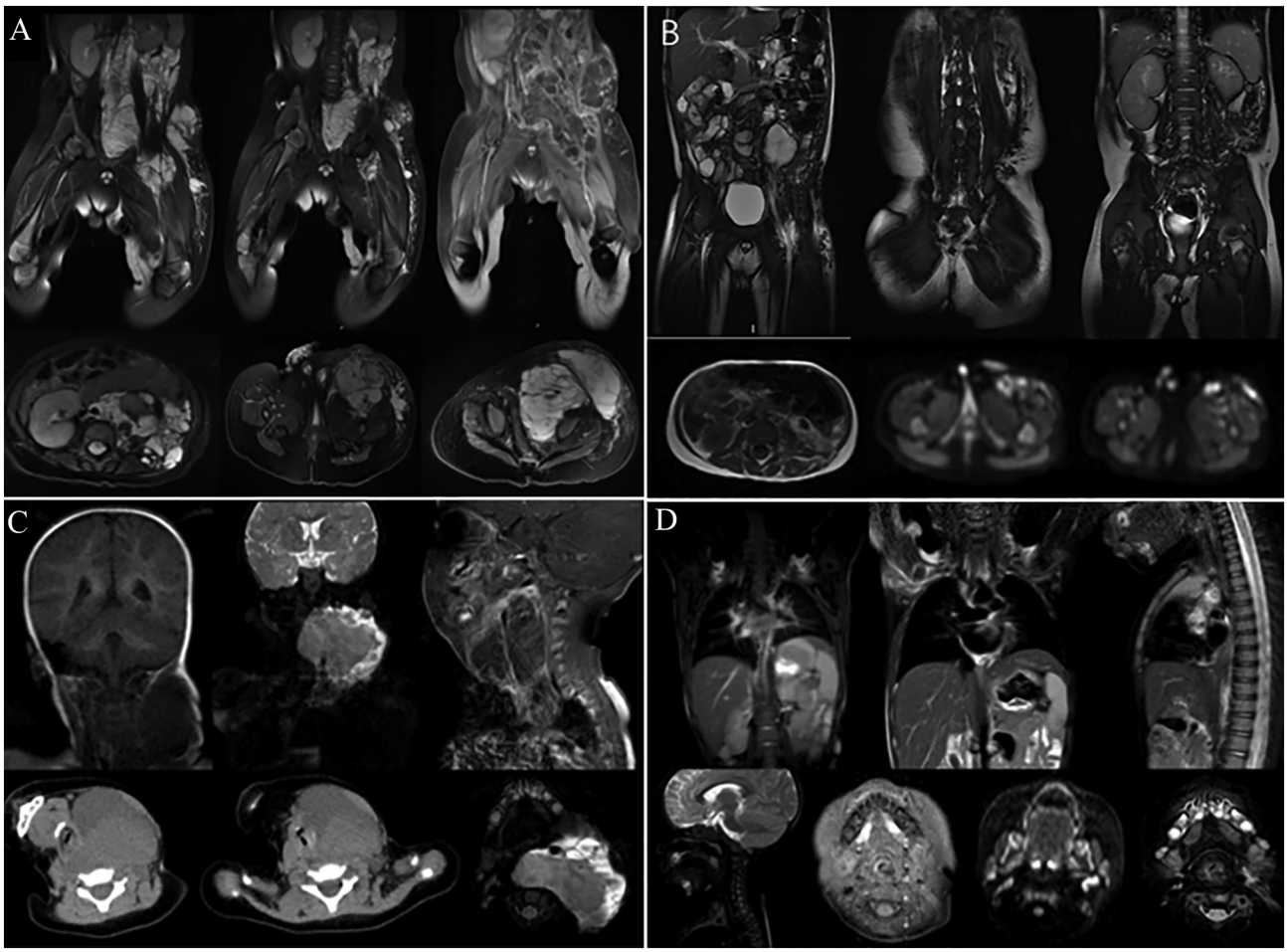

Fig. 2. Image of two patients. (A) A 4-year-old boy with GLA in the abdominal wall, back, left thigh and pelvic cavity (before treatment). (B) GLA subsided significantly with sirolimus treatment for 24 months after left groin and back partial excision (after treatment). (C0 Boy, 17 months old, with complex LMs in left neck, throat and left upper mediastinum (before treatment). (D) Lesions subsided significantly with sirolimus treatment for 24 months after partial excision (after treatment).

Table 4
Complications of sirolimus in the treatment of complex LMs.

Complication, no. (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Oral mucositis	6	10	1	0	17
Upper respiratory tract infection	0	6	0	0	6
Pneumonia	0	0	2	0	2
Rash	3	0	0	0	3
Be off one's feed	1	0	0	0	1
Constipation	1	0	0	0	1
Dry skin	1	0	0	0	1
Dizziness	1	0	0	0	1
Cystic hemorrhage	1	3	0	0	4
Hepatic dysfunction	1	0	0	0	1
Total	15	19	3	0	37

2.3. Clinical evaluation of sirolimus in the treatment of complex LMs

Treatment was deemed to be effective for 50 participants (CR + PR, 50/56, 89.3%). Among them, two recurred following drug withdrawal (recurrence rate 2/25, 8%). Six participants with complex LMs did not respond to sirolimus treatment (PD + SD, 6/56, 10.7%). Participants were divided into three groups according to the time of oral sirolimus administration (see Table 3). Meanwhile, it is suggested that the impact of sirolimus was strengthened after prolonged administration (Fig. 1).

Some 48 children were sensitive to sirolimus in the early stage, at approximately three months, while two children demonstrated a slight reduction in lesions after one year of treatment. For one participant with GLA which involved the sternum, the lesion gradually shrank (PR, 72.4%) after a year of sirolimus administration. In eight cases which involved the buttocks and scrotum, lesions were significantly reduced or even disappeared under the effect of sirolimus. One case showed an almost complete disappearance of lesions at all sites following oral administration of sirolimus (Fig. 2A and B). One case was also significantly decreased following sirolimus treatment (Fig. 2C and D). As a medical treatment, it is clear that sirolimus is effective in controlling complex LMs, although most cases cannot be completely cured.

There can be no doubt about the effectiveness of sirolimus. Most adverse events are grade 1 and grade 2. Two participants were admitted to the pediatric intensive care unit (PICU) with pneumonia following oral administration of sirolimus. Serum biochemical parameters, mainly a decline in the proportion of CD4/CD8, reveal the inhibition of immunity by sirolimus. Therefore, we further examined the immunologic function of six patients and found no significant correlation between severe oral ulcers and hypoimmunity (Supporting Information Table S2). There was one case of hepatic dysfunction, in which ALT was 65 U/L and AST was 50 U/L. Reexamination returned to typical levels one month after stopping sirolimus.

Overall, the side effects of sirolimus are acceptable. Following the above adverse events, patients' conditions significantly improved after temporary drug withdrawal and symptomatic treatment. Acute side effects typically abate or disappear as sirolimus is reduced. Thus far, sirolimus and its adverse events were not found to have an effect on growth or development (see Table 4).

3. Discussion

Given that clinical data on the use of sirolimus in complex LMs are still rare, we present our findings around 56 cases treated with oral sirolimus. Following oral sirolimus treatment, a favorable response (CR + PR, 50/56, 89.3%) was demonstrated by an improvement in clinical signs and quality of children's lives in our study. Approximately 58.9% (33/56) of these lesions are initially identified by the age of two [8]. This aligns with the fact that the vast majority of reported lymphatic malformations are diagnosed before the age of two [17]. Sirolimus was tolerated and effective and adverse events were manageable after symptomatic treatment.

Our study explored 56 cases with complex LMs to confirm the effectiveness of sirolimus, contributing to better adjuvant treatment of children living with complex LMs in the future. Those children who have LMs which involve the thoracic cavity, abdominal cavity or viscera have a poor quality of life, while the therapeutic effect of sirolimus is limited. This is consistent with previous references. Sirolimus trough concentrations were mostly around 10–15 ng/ml in 56 cases, although four cases were more than 20 ng/ml, which are also consistent with other references [14, 20]. Additionally, we found that sirolimus can be completely cured in children with scrotal and buttock involvement compared to patients with involvement of other areas. Hamill reported that mean response time was 25 days, while we found that the drug tended to take more than a month to start being effective [20].

Our study was limited by inconsistent treatment approaches owing to ethical concerns.

Meanwhile, many follow-up questions remain for therapeutically effective cases. For example, the effective therapeutic dose of complex LMs must be safe and effective as the optimum concentration needs to be reached. Therefore, when should the drug be decreased after the initial treatment? And how long should the treatment course be maintained? Beyond that, it remains difficult to treat complex LMs in patients who have drug resistance.

4. Conclusion

Our results show that sirolimus appears to be effective and tolerable for decreasing lesions in children living with complex LMs. Early administration of sirolimus can help patients control LMs while still eliminating lesions after recurrence.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2019.12.021.

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Conflict of interest statement

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was given approval by the Ethics Committee of Shanghai Children's Medical Centre (SCMCIRB-K2017004), and written informed consent was obtained from all participants.

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