Review

Treatment of Lymphatic Malformations with the mTOR Inhibitor Sirolimus: A Systematic Review

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Abstract

Background: Extensive lymphatic malformations are low-flow vascular malformations that can cause devastating complications. Treatment of these malformations is challenging. This systematic review presents current use of sirolimus in patients with extensive lymphatic malformations.

Methods: MEDLINE and Google scholar search was conducted for studies on sirolimus treatment of lymphatic malformations up to July 2017. Search items included “lymphatic malformation,” “lymphangioma,” “cystic hygroma,” “vascular malformation,” “low-flow malformation,” “sirolimus,” “rapamycin,” and “mTOR inhibitor.”

Results: Twenty studies, including 71 patients receiving sirolimus, were included into this review. Forty-five patients had lymphatic malformations, eight patients venolymphatic malformations, and 19 patients capillary-lymphatic-venous malformations. Sirolimus led to a partial remission of disease in 60 patients, three patients had a progressive disease, and the outcome of eight patients was not reported. Dosing, target trough level, and duration of treatment differed between the studies. Common adverse effects were hyperlipidemia and neutropenia.

Conclusions: Available literature indicated that sirolimus therapy might be effective for lymphatic malformations. However, further randomized controlled studies are required to analyze the efficacy and long-term adverse events and to clarify the potential role for sirolimus in the management of lymphatic malformations.

Keywords: lymphatic malformation, sirolimus, rapamycin

Introduction

Vascular anomalies summarize a wide spectrum of diseases, which are classified by use of the system of the International Society for the Study of Vascular Anomalies (ISSVA), which divides vascular tumors from vascular malformations based on clinical, genetic, and pathologic characteristics. Lymphatic malformations are low-flow vascular anomalies of the lymphatic system that most frequently affect the head and neck and are typically present at birth. Only some become manifest at a later stage. Their precise pathogenesis is still unknown. The incidence of lymphatic malformations is estimated to 1.2–2.8 lymphatic malformations per 1000 births and 2.8 patients per 100,000 hospital admissions. Their growth is proportional to the patients’ body growth, but related to infection, trauma, and hormonal changes there could be further enlargement.

Histologically, lymphatic malformations consist of cysts which are lined by a single layer of endothelium and contain an amorphous collection of lymph. Depending upon the location and surrounding tissues the cysts can vary in size, and therefore, lymphatic malformations can be characterized into macrocystic (cyst diameter >1 cm), microcystic (cyst diameter <1 cm), or mixed.

The clinical presentation of patients with lymphatic malformations can be diverse ranging from focal swelling to large diffusely infiltrating masses with compromise of adjacent structures. Symptoms depend on localization and size of the malformation and can include airway obstruction, neurovascular dysfunction, and deformity. The correct diagnosis of lymphatic malformation is key to appropriate therapy. Radiologic studies, including computed tomography, magnetic resonance imaging, and ultrasound, were necessary to define the extent and type of malformation, as well as its relationship to vital structures.

Treatment of lymphatic malformation varies and, therefore, should be individualized for each patient. This personalized approach has to address functional restriction, esthetic...
impairment, and pain. In case of life-threatening functional impairment early intervention is mandatory. In macrocystic lymphatic malformations, surgery and sclerotherapy are effective. Surgery of microcystic lymphatic malformations remains challenging due to their infiltrative nature. Sclerotherapy of microcystic lymphatic malformations is often impossible. As especially large microcystic and mixed malformations are still a therapeutic challenge, pharmaceutical treatment is very desirable.

The mammalian target of rapamycin (mTOR) is an evolutionarily highly conserved serine/threonine protein kinase. mTOR activates protein synthesis, leading to numerous cellular processes, including cell proliferation and increased angiogenesis. Deregulation of the mTOR pathway has been implicated in several diseases such as cancer, diabetes, neurological diseases, and genetic disorders. mTOR is also suspected to play a key role in the pathogenesis of various vascular anomalies. The first compound inhibiting mTOR, sirolimus (rapamycin), was identified in the 1970s. It is a natural macrolide isolated from a bacteria strain of the Streptomyces genus (Streptomyces hygroscopicus) collected on Easter island (Rapa Nui). Although rapamycin was isolated as an antibiotic and antifungal agent, subsequent studies have revealed impressive cytostatic, antiproliferative, and immunosuppressive properties. Rapamycin was approved in 1999 by the US Food and Drug Administration (FDA) for use in the prevention of kidney allograft rejection.

In 2015, the FDA approved sirolimus as first drug to treat lymphangioleiomyomatosis, a rare, progressive lung disease that primarily affects women of childbearing age. A role for sirolimus to treat vascular malformations is supported by the fact that sirolimus causes a decrease in vascular endothelial growth factor (VEGF), which is a known key regulator in lymphangiogenesis and angiogenesis. The first report on the successful use of sirolimus as an antiangiogenic agent was published in 2010. However, data about the use of sirolimus in treatment of patients with vascular anomalies are still rare. This review presents the current knowledge on sirolimus therapy in lymphatic malformations.

Materials and Methods

This study was designed as a systematic review. Inclusion criteria were as follows: original reports (study, case series, case reports, and posters) describing systemic treatment of lymphatic malformations with sirolimus (rapamycin) in humans. A search was performed for all case reports, retrospective case series, original articles, and randomized clinical trials pertaining to the use of sirolimus in the treatment of lymphatic malformations, venolymphatic malformations, and capillary-lymphatico-venous malformations. The search was conducted using MEDLINE and Google Scholar, employing the terms “lymphatic malformation,” “lymphangiomia,” “cystic hygroma,” “vascular malformation,” “low-flow malformation,” “sirolimus,” “rapamycin,” and “mTOR inhibitor.” The search was concluded in July 2017 at the end of our study period.

In addition, the reference sections of suitable sources were searched for related articles. Language or study design restrictions were not used. Whenever titles and/or abstracts fit our search terms, abstracts were reviewed to exclude irrelevant studies. Review articles, duplicate publication, or reports with insufficient information (full text not accessible, full text did not contain any raw data) were excluded. The remaining articles were carefully checked to determine whether they contained data that were applicable to our study. In cases where articles reported the same data, only information from the most recent publication was included, unless data could only be obtained from older reports. Reports on generalized lymphatic anomaly, Gorham-Stout disease, lymphangiomatosis, lymphangiectasia, and chronic lymphedema, as well as reports on topical treatments, were excluded.

Through these methods, 20 articles were identified, containing a total of 71 cases in which sirolimus was used to treat lymphatic malformations, venolymphatic malformations, and capillary-lymphatico-venous malformations. After identifying these articles, all text and figures were carefully assessed for relevant data. The following information on study characteristics and clinical treatments was extracted from all included studies: publication metrics (name of first author and year of publication), subject information (age, gender, and localization of malformation), and treatment information (sirolimus dose, planned target trough level, treatment duration, treatment outcomes, additional therapies, and adverse events).

Results

Included studies and clinical characteristics of the patients

Twenty studies, including 71 patients treated with sirolimus for lymphatic malformations, venolymphatic malformations, and capillary-lymphatico-venous malformations, were included into this review. Most studies were retrospective case series or case reports, and there was only one phase II trial. In all, 16 publications about 45 patients with lymphatic malformations were identified (Table 1), five publications about eight patients with venolymphatic malformations (Table 2) and four publications about 18 patients with capillary-lymphatico-venous malformations (Table 3). All patients had extensive malformations, which were distributed about the whole body. The age of the patients ranged from newborn to 64 years; however, most of the patients were children. All patients have been treated before, and most of them have been heavily pretreated. Although some patients had shown a minimal response to prior therapies, these were insufficient (Tables 1–4).

Treatment with sirolimus

In most studies, sirolimus was administered orally at an initial dosage of 0.8 mg/m² per dose, twice daily at 12-hour intervals. The dose was then subsequently adjusted to reach the planned target blood level. In three studies a different dose was used; sirolimus was initially administered orally at a dosage of 0.1 mg/kg per 24 hours twice daily, 0.05 mg/kg twice daily, or 0.07 mg/kg twice daily. In six publications, the initial dose of sirolimus was not reported.

The target blood level of sirolimus was similar (≤15 ng/mL), but slightly differed between the studies. The target blood level was 10–15 ng/mL in seven studies, 5–15 ng/mL in four studies, and 10–13 ng/mL in one study. In seven studies, the authors did not
<table>
<thead>
<tr>
<th>Author</th>
<th>Level of evidence</th>
<th>No. of patients</th>
<th>Localization</th>
<th>Age</th>
<th>Sex</th>
<th>Starting dose</th>
<th>Target blood level (ng/mL)</th>
<th>Additional therapy</th>
<th>Result</th>
<th>Therapy duration</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al. 12</td>
<td>IV</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>No</td>
<td>PR: 2 PD: 2 NE: 1</td>
<td>12 months Whole group (60 patients): blood/bone marrow 27%, metabolic/laboratory 3%, gastrointestinal 3%, infection 2%, lymphatic 2%, pulmonary/upper respiratory 2%. Dose reduction: 2 (laryngospasm, hypertriglyceridemia) withdrawal: 2 (nausea, lymphedema)</td>
<td></td>
</tr>
<tr>
<td>Akbayrak et al. 13</td>
<td>IV</td>
<td>1</td>
<td>Thorax, upper left extremity</td>
<td>11 y</td>
<td>m</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>NR</td>
<td>Physiotherapy No</td>
<td>PR</td>
<td>NR</td>
<td>12 months No</td>
</tr>
<tr>
<td>Akyüz et al. 14</td>
<td>IV</td>
<td>1</td>
<td>Tongue</td>
<td>10 y</td>
<td>m</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>NR</td>
<td>No</td>
<td>PR (70%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Alemi et al. 15</td>
<td>IV</td>
<td>2</td>
<td>Larynx, neck, mediastinum, face, neck, chest wall, larynx, mediastinum, oropharynx</td>
<td>4 mo 1 mo</td>
<td>m</td>
<td>NR</td>
<td>NR</td>
<td>Laser surgery No</td>
<td>PR</td>
<td>PR</td>
<td>2 years, 8 months discontinued 5 months (ongoing) 11 months (ongoing) weeks (ongoing) 6 weeks (ongoing) 8 weeks (ongoing)</td>
</tr>
<tr>
<td>Altawil et al. 16</td>
<td>IV</td>
<td>3</td>
<td>Upper trunk and bilateral axillary neck parotid/neck</td>
<td>2 y 20 mo 12 y</td>
<td>m</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–13</td>
<td>No</td>
<td>PR</td>
<td>8 months Neutropenia in all cases</td>
<td></td>
</tr>
<tr>
<td>Azouz et al. 17</td>
<td>IV</td>
<td>1</td>
<td>Neck, cheek, tongue</td>
<td>1 mo</td>
<td>m</td>
<td>0.07 mg/kg given twice daily</td>
<td>NR</td>
<td>No</td>
<td>PR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Boon et al. 18</td>
<td>IV</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10–15</td>
<td>No</td>
<td>PR: 17 PD: 1 (whole group)</td>
<td>NR Minor side effects</td>
<td></td>
</tr>
<tr>
<td>Ersoy et al. 19</td>
<td>IV</td>
<td>1</td>
<td>Axilla</td>
<td>Newborn</td>
<td>f</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>PR</td>
<td>8 months (ongoing)</td>
<td>NR</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Author</th>
<th>Level of evidence</th>
<th>No. of patients</th>
<th>Localization 1</th>
<th>Age</th>
<th>Sex</th>
<th>Starting dose</th>
<th>Target blood level (ng/mL)</th>
<th>Additional therapy</th>
<th>Result</th>
<th>Therapy duration</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escoda et al.</td>
<td>IV</td>
<td>1</td>
<td>Neck</td>
<td>Newborn</td>
<td>m</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>4–8</td>
<td>No PR</td>
<td>2 months, (ongoing)</td>
<td>Hypertriglyceridemia, hypercholesterolemia, nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>Hammill et al.</td>
<td>IV</td>
<td>4</td>
<td>Mediastinum, paraspinal, bone lesions, cutaneous (chest/back/shoulder) mediastinum, spleen, bone lesions pericardial effusion, bone lesions thorax, bone lesions T11-L4, liver, retroperitoneal, and subcutaneous</td>
<td>7 mo</td>
<td>y</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>No PR</td>
<td>NR</td>
<td>Mucositis, hypercholesterolemia, headache, elevation of AST and ALT neutropenia discontinuation of sirolimus due to side effects: 1</td>
<td></td>
</tr>
<tr>
<td>Lackner et al.</td>
<td>IV</td>
<td>1</td>
<td>Orbit</td>
<td>9 y</td>
<td>m</td>
<td>0.05 mg/kg twice daily perorally</td>
<td>5–15</td>
<td>No PR</td>
<td>6 months</td>
<td>Mild reversible leukopenia</td>
<td></td>
</tr>
<tr>
<td>Margolin et al.</td>
<td>IV</td>
<td>1</td>
<td>Neck, tongue, mediastinum, floor of mouth</td>
<td>17 mo</td>
<td>f</td>
<td>NR</td>
<td>10–15</td>
<td>No PR</td>
<td>12 months (ongoing)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Roessler and Niemeyer</td>
<td>IV</td>
<td>2</td>
<td>Flank, subcutis, skin, iliopsoas muscle, and scrotum axilla, arm, and thoracic wall</td>
<td>16 y</td>
<td>y</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>No PR</td>
<td>3 years, 6 months paused, reinitiated, 3 years (ongoing)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Triana et al.</td>
<td>IV</td>
<td>11</td>
<td>4 cervicofacial 2 facial 1 pelvis 2 thorax 1 upper limb 1 cervical</td>
<td>Median age 12.8 (0.16–47) in all 41 patients</td>
<td>m</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>5–15</td>
<td>No PR: 10 PD: 1</td>
<td>median of 8.5 (1–51) months in all 41 patients</td>
<td>Whole group (41 patients): hyperlipidemia, increased liver enzyme level: 1, lymphopenia and opportunistic infection: 1</td>
<td></td>
</tr>
<tr>
<td>Tschauner et al.</td>
<td>IV</td>
<td>4</td>
<td>Head neck</td>
<td>6 mo-4 y</td>
<td>f</td>
<td>NR</td>
<td>NR</td>
<td>No PR (49%–75%)</td>
<td>NR</td>
<td>9 months</td>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td>Yesil et al.</td>
<td>IV</td>
<td>1</td>
<td>Tongue</td>
<td>1 y</td>
<td>f</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>No PR (90%)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

y, year; mo, months; m, male; f, female; NR, not reported; NE, not evaluable; PR, partial response; PD, progressive disease.
<table>
<thead>
<tr>
<th>Author</th>
<th>Level of evidence</th>
<th>No. of patients</th>
<th>Localization</th>
<th>Age</th>
<th>Sex</th>
<th>Starting dose</th>
<th>Target blood level (ng/mL)</th>
<th>Additional therapy</th>
<th>Result</th>
<th>Therapy duration</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al. 12</td>
<td>IV</td>
<td>3</td>
<td>NR</td>
<td>0–29 y</td>
<td>NR</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>No</td>
<td>PR</td>
<td>12 months</td>
<td>Whole group (60 patients): blood/bone marrow 27%, metabolic/laboratory 3%, gastrointestinal 3%, infection 2%, lymphatic 2%, pulmonary/upper respiratory 2%. Dose reduction: 2 (laryngospasm, hypertriglyceridemia) withdrawal: 2 (nausea, lymphedema)</td>
</tr>
<tr>
<td>Kim et al. 27</td>
<td>IV</td>
<td>1</td>
<td>Periorbital, lateral forehead, temporal, preauricular</td>
<td>1 mo</td>
<td>f</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>Prednisolone 2 mg/kg</td>
<td>PR</td>
<td>7 months, 2 months paused, 3 months (ongoing)</td>
<td>Mild hypertriglyceridemia and hypercholesterolemia</td>
</tr>
<tr>
<td>Lackner et al. 21</td>
<td>IV</td>
<td>2</td>
<td>Orbit, pharynx, palatine cervical cervical</td>
<td>1. 7 y m 2. newborn m</td>
<td>f</td>
<td>0.05 mg/kg twice daily</td>
<td>5–15</td>
<td>No</td>
<td>PR</td>
<td>53 months (ongoing)</td>
<td>Mild reversible leukopenia</td>
</tr>
<tr>
<td>Lindberg et al. 28</td>
<td>IV</td>
<td>1</td>
<td>Vaginal, rectal</td>
<td>2 y m</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>PR</td>
<td>19 months</td>
<td>No</td>
</tr>
<tr>
<td>Yesil et al. 29</td>
<td>IV</td>
<td>1</td>
<td>Left axillary region, arm</td>
<td>5 y f</td>
<td>NR</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>5–15</td>
<td>No</td>
<td>PR</td>
<td>12 months, ongoing</td>
<td>Whole group (6 patients): oral mucositis; 1 hypercholesterolemia or hypertriglyceridemia: 4</td>
</tr>
</tbody>
</table>

y, year; mo, months; m, male; f, female; NR, not reported; NE, not evaluable; CR, complete response.
Table 3. Studies Concerning Treatment of Capillary-lymphatico-Venous Malformations with Sirolimus

<table>
<thead>
<tr>
<th>Author</th>
<th>Level of evidence</th>
<th>No. of patients</th>
<th>Localization</th>
<th>Age</th>
<th>sex</th>
<th>Starting dose</th>
<th>Target blood level (ng/mL)</th>
<th>Additional therapy</th>
<th>Result</th>
<th>Therapy duration</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al.</td>
<td>IV</td>
<td>13</td>
<td>NR</td>
<td>0–29 y (whole group of 60 patients)</td>
<td>NR</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>No</td>
<td>PR: 12</td>
<td>12 months</td>
<td>One patient died of presumed sepsis one year after completion of therapy whole group (60 patients): blood/bone marrow 27%, metabolic/laboratory 3%, gastrointestinal 3%, infection 2%, lymphatic 2%, pulmonary/upper respiratory 2%. Dose reduction: 2 (laryngospasm, hypertriglyceridemia) withdrawal: 2 (nausea, lymphedema)</td>
</tr>
<tr>
<td>Hammill et al.</td>
<td>IV</td>
<td>1</td>
<td>Lung, liver, left lower extremity, pelvis/ buttocks, retroperitoneum</td>
<td>6 y m</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>10–15</td>
<td>No</td>
<td>PR</td>
<td>NR</td>
<td>Whole group (6 patients): mucositis, hypercholesterolemia, headache, elevation of AST and ALT, neutropenia Self-limiting hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Vlahovic et al.</td>
<td>IV</td>
<td>1</td>
<td>Gluteal region, lower extremity</td>
<td>10 y m</td>
<td>0.1 mg/kg per day twice daily</td>
<td>5–15</td>
<td>physiotherapy</td>
<td>PR</td>
<td>18 months, (ongoing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yesil et al.</td>
<td>IV</td>
<td>4</td>
<td>Lower extremity</td>
<td>3 y m</td>
<td>0.8 mg/m² per dose twice daily</td>
<td>5–15</td>
<td>No</td>
<td>PR</td>
<td>12 months, 14 months (ongoing) 15 months (ongoing) 18 months</td>
<td>Superficial thrombophlebitis: 1 whole group (6 patients): oral mucositis: 1 hypercholesterolemia or hypertriglyceridemia: 4</td>
<td></td>
</tr>
</tbody>
</table>

y, year; mo, months; m, male; f, female; NR, not reported; NE, not evaluable.
ever, because of the response, the dose was kept at 0.8 mg/m².

In all studies the planned target trough level for sirolimus was not reported. Boon et al. analyzed a group of 18 patients with vascular malformations treated with sirolimus; six of these patients had lymphatic malformations. They reported that 17/18 (94%) of patients experienced almost complete relief of pain and symptoms and that magnetic resonance imaging showed a decrease in most of the patients’ malformations. However, detailed information on the patients with lymphatic malformations was missing.

**Adverse effects of sirolimus treatment**

Fourteen studies commented on adverse events associated with and probably being a result of sirolimus therapy. In three studies patients (n = 5) experienced no side effects. In the other 11 studies different adverse effects were reported. In the study of Adams et al. who analyzed a cohort of 57 patients with different vascular anomalies, the most common adverse events attributed to sirolimus were toxic effects on blood/bone marrow in 27% of the patients, whereas other toxicities were seldom observed (metabolic/laboratory 3%, gastrointestinal 3%). This was also true for sirolimus-associated infection at 2%, lymphatic at 2%, and pulmonary/upper respiratory at 2%. In the other studies the most common adverse effects were hyperlipidemia and neutropenia.

Dose reductions or discontinuation of medication due to side effects were reported only in two studies. Adams et al. stated about dose reductions being required in two of 57 patients, and further two patients were taken off study medicine secondary to toxicity. Hammill et al. also reported about one patient who discontinued sirolimus due to side effects. Furthermore, in the study of Adams et al. one patient with a capillary-lymphatico-venous malformation died of presumed sepsis one year after completion of therapy possibly related to the prior treatment.

**Discussion**

The use of sirolimus in pharmaceutical therapy of lymphatic malformations is not well established, but based on published data about few and mostly limited numbers, and grade of adverse events appears to be safely applicable. Despite only seldom observed complete response of lymphatic malformations to sirolimus, most studies highlighted that the majority of patients experienced a partial response and had benefit from its pain-relieving action. Therefore, sirolimus may be a useful option for the treatment of extensive lymphatic malformations that always is challenging.

Specific recommendations regarding treatment for the whole patient group and the sequence of treatments cannot be made due to variations in the size and location of malformations. The goal of treatment is to maintain functionality, control associated symptoms, and preserve esthetic integrity. The treatment should be individualized and the treatment decision should be based on the characteristics of the lymphatic malformation, as well as the age of the patient and the wishes of the patients and parents.

In extensive lymphatic malformations, it is often impossible to perform a complete surgical resection but preserve the function. Especially the infiltrative nature of microcystic lymphatic malformations renders complete surgical excision technically demanding, and sirolimus may find, in particular, a place in treatment of these lesions. Sclerotherapy is a therapeutic

<table>
<thead>
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<th>Table 4. Patient and Treatment Characteristics</th>
<th>LM</th>
<th>CLVM</th>
<th>VLM</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>17</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>1</td>
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</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Not reported</td>
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<tr>
<td>Age at treatment initiation</td>
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<td>2</td>
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<tr>
<td>&lt;6 months</td>
<td>5</td>
<td>—</td>
<td>1</td>
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<tr>
<td>6 months–2 years</td>
<td>5</td>
<td>1</td>
<td>—</td>
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<td>3–6 years</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7–12 years</td>
<td>4</td>
<td>—</td>
<td>—</td>
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<tr>
<td>12–18 years</td>
<td>26</td>
<td>16</td>
<td>4</td>
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<td>Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to treatment</td>
<td>35</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Partial response</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Complete response</td>
<td>3</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Not reported</td>
<td></td>
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</tbody>
</table>

LM, lymphatic malformations; CLVM, capillary-lymphatico-venous malformations; VLM, venolymphatic malformations.
SIROLIMUS IN LYMPHATIC MALFORMATIONS

SIROLIMUS IN LYMPHATIC MALFORMATIONS

option particularly in macrocystic lymphatic malformations.7
Watch-and-wait is a reasonable option, especially if there are no
or little symptoms or functional deficits. However, the potential
risk of acute enlargement of the lymphatic malformation sec-
tory to infections or spontaneous or traumatic hemorrhage is
always to be kept in mind. Pharmacologic treatment with dif-
ferent medications like sildenafil and pranopanol has been ex-
amined to treat extensive lymphatic malformations without
striking success.31–35 Therefore, the potential utilization of sir-
olimus should be investigated.

The first report on the use of sirolimus in patients with
lymphatic malformations was published in 2011.8 The
complete mechanism of action is not clear. VEGF is known
to play a role in lymphangiogenesis by upregulating mTOR
signaling followed by proliferation. Recent studies have
shown that sirolimus inhibits lymphangiogenesis by de-
creasing synthesis and promoting degradation of VEGF re-
ceptor 3.36 Since 2011, several case reports and case series
have been published regarding this topic. In our systematic
review 20 publications, including 71 patients with lymphatic
malformations treated with sirolimus, could be identi-
fied.8,12–30 Some of these publications included patients with
other vascular anomalies like venous or arteriovenous mal-
formations or other lymphatic diseases.8,12,18,21,24,29 The
evaluation of these diseases was not the goal of this review,
and these patients were therefore not included in this analysis.

In all, the data reported in the included studies were het-
erogeneous and were not reported in a standardized manner.
Furthermore, incomplete reporting limited our ability to com-
pare the results of the analyzed studies. For example, the
outcome after therapy was not reported for all patients, but in those
cases with a reported result, 95% showed a response to siro-
limus of a different extent. Only in three cases a progressive
disease was reported. However, since most of the studies
present qualitative and not quantitative response data and there
was much heterogeneity in terms of definition of response and
measurement of response, the results were difficult to compare.

The dosage of sirolimus and the duration of treatment also
differed since no evidence-based guidelines exist for proper
dosing of sirolimus in patients with lymphatic malformations
or duration of treatment. In most studies, an initial dosage of
0.8 mg/m² sirolimus per dose administered twice daily at 12-
hour intervals was used.8,12–14,16,20,23,24,26,29 The
target blood level was 5–15 ng/mL or 10–15 ng/mL in most of the
studies; however, some studies reported difficulties in maintain-
ing the desired sirolimus level. Margolin et al.22 reported about a 17-month-old infant who had a
significant reduction in size of the lymphatic malformation,
but rarely met the sirolimus target trough level range of 10–
15 ng/mL and more often had a level of <10 ng/mL or even
<2 ng/mL. Kim et al.27 reported a marked clinical response in
a neonate with a blood level of 3.5 ng/mL; therefore, the
investigators kept this dose stable. These examples show that
even a lower dose of sirolimus might offer the same thera-
peutic benefit while minimizing adverse effects. This might
be true, as there doesn’t seem to be an association between
serum levels and grade of response.

Sirolimus is FDA approved for use in pediatric kidney
transplantation in patients aged 13 years and older. Therefore,
it is not known what dose of sirolimus is safe and effective in
newborns and small children. In many studies, the dosage of
sirolimus and target blood level were not mentioned. Until
now, the optimal dose of sirolimus, target blood level, and
duration of treatment in patients with lymphatic malformations
remain unclear. Additional studies are needed.

The safety of long-term use of sirolimus in organ transplant
recipients has been demonstrated. However, patients and care-
givers must be keenly aware of potential side effects of sirolimus.
Main and most common adverse effects of sirolimus treatment
are anemia, thrombocytopenia, leukopenia, and increases in
triglyceride and cholesterol levels.37 Due to the intrinsic im-
munosuppressive potential of sirolimus, which is the reason for
its use in transplant medicine, there is a high risk for infections.38
Other adverse effects associated with sirolimus include hemo-
dynamic (e.g., hypertension), dermatologic (e.g., rash, mucositis),
renal (e.g., proteinuria), and hormonal problems.39

This analysis demonstrated different adverse events in
patients with lymphatic malformations receiving sirolimus
although not all studies commented on adverse events asso-
ciated with sirolimus therapy. Adverse effects reported were
in most cases benign and manageable. However, they may
affect quality of life and demand dose modification or drug
withdrawal. There were only few reported cases without any
side effects experienced when using the drug. Dose adjust-
ments or treatment discontinuations due to drug toxicity were
also reported in two studies.8,12 Side effects did not correlate
with the blood level of sirolimus. Altawil et al.16 reported a
case with fever and neutropenia, while the sirolimus level
was 2.4 ng/mL. Therefore, patients should be well educated
on potential adverse effects, and the decision for the use of
sirolimus should be based on individual patient characteris-
tics and risk factors. Due to potential side effects, sirolimus
should not be considered as treatment for small lymphatic
malformations that respond to standard treatment.

This systematic review is not without limitations. Like all
systematic reviews, there may be publication bias with re-
spect to centers publishing good outcomes. The articles in-
cluded in this study were case series or case reports from
individual institutions and are prone to the bias involved with
retrospective studies. Thus, the results are difficult to inter-
pret. There is a small sample size which is due to the rarity of
this condition. In addition, as these data were obtained from
separate articles, there are wide variations in the clinical
management and treatment durations. Numerous gaps exist
in terms of the data being reported.

As further possible limitations of the present study, we can
cite the low methodological quality of the included studies, the
lack of randomized controlled trials, the heterogeneity re-
garding drug dosage, definition of response, measurement of
response, and measurement of toxicity. The significant het-
rogenicity between the studies will limit the applicability of
the findings. This is hardly surprising considering the differ-
ences in study populations and case selection between centers.

Conclusions

Although limited, this review suggests that sirolimus
might be an effective treatment for patients with extensive
lymphatic malformations and expands the range of ther-
peutic options. Randomized controlled trials are lacking, but
would be needed to fully assess the therapeutic efficacy of
sirolimus, especially as we know that some lymphatic mal-
formations show a partial remission without any treatment.
Questions remain regarding the correct timing for treatment
initiation and discontinuation of sirolimus, dosing, the serum level to be achieved, and possible long-term side effects and their management.

This article is a systematic literature review and does not require review by an ethics committee for human subjects.

Author Disclosure Statement

No competing financial interests exist.

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