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Sirolimus in the Treatment of Microcystic Lymphatic Malformations: A Systematic Review

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Abstract

Background: Genetic alterations in lymphatic development can lead to microcystic lymphatic malformations (micro LMs). LMs can have both microcystic and macrocytic components or be exclusively one or the other. LMs can result in serious, sometimes life-threatening, sequelae. Absent consensus guidelines, treatment has been largely empiric. Recent advances in our understanding of the pathogenesis of micro LMs have provided a foundation for novel therapeutic approaches. This review examines clinical data over the last 10 years on the role of sirolimus, an inhibitor of the PI3K/AKT/mTOR signaling pathway implicated in micro LM development, in the treatment of micro LM.

Methods and Results: Systematic review of published clinical studies from January 1, 2011, to July 15, 2021, using the PubMed, Google Scholar, and Cochrane Reviews databases, and utilizing delimiters to focus specifically on sirolimus in the treatment of micro LM. A total of 16 studies were identified (13 case studies or case reviews; 3 prospective) that included 52 subjects treated with topical ($n = 15$) or oral ($n = 37$) sirolimus for micro LM. Clinically meaningful, long-term improvement (up to 3 years) was noted in 92% (46/50), mostly previously treated subjects. Sirolimus yielded improvements in key manifestations such as lymphatic leakage, bleeding, vesicle bulk, pain, and skin discoloration. Some subjects experienced a rapid onset of effect (within 2 weeks). No unexpected adverse events were seen.

Conclusion: Sirolimus appears to be an effective and safe option in the management of cutaneous and complex micro LM. However, prospective, controlled trials are clearly needed to accurately elucidate the benefits and risks of sirolimus in the management of micro LM. ClinicalTrials.gov Identifier: NCT05050149.

Keywords: microcystic lymphatic malformation, lymphatic malformation, sirolimus

Introduction

LYMPHATIC MALFORMATIONS (LMs) are nonmalignant, congenital, abnormal lymphatic vessels that result in enlarged fluid-filled lymphatic spaces.[1] Clinical manifestations vary considerably, ranging from local enlargements to widespread diffuse lesions.[2] Depending on their location, these malformations can lead to disfigurement, organ dysfunction, recurrent infection, and potentially life-threatening airway obstruction.[3]

The International Society for the Study of Vascular Anomalies divides LMs into 3 types based on cyst size and distribution:

- Macrocystic LMs: Typically large, smooth, translucent, multi-lobular lesions present at birth.
- Microcystic LMs (micro LMs): Manifest as small, often disseminated dermal lesions that permeate the subcutaneous tissue and muscles resulting in diffuse infiltration and can appear as localized masses.

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- Mixed LMs: A form that includes aspects of both the macrocystic and microcystic types.[1,4–7]

Regardless of form, the majority of LMs result from postzygotic mutations typically in *PIK3CA* that lead to an overgrowth of lymphatic vessels. Although they are histologically similar, macrocystic LMs and micro LMs are phenotypically different and often have different treatment paradigms and outcomes.[8]

Unlike macrocystic LMs, micro LM vessels connect to the epidermis in the form of vesicles, papules, and plaques, which can leak at the surface (lymphorrhea). Hyperkeratosis often results during the healing process and can bleed spontaneously, particularly when overlying a capillary malformation or due to minor trauma. Since micro LMs appear to be caused by activating mutations in genes that control growth, these lesions enlarge, and with recurrent leaking and healing tend to become more papular and keratotic over time.

Treatment success for micro LMs remains low.[1–3] Though several treatment modalities exist, current interventional therapies are less than ideal, and none are Food and Drug Administration (FDA) approved for this disorder.[3] For example, surgical resection remains challenging, if not impossible, due to the infiltrative, diffuse nature of micro LMs. In addition, due to underline somatic mutation associated with micro LM, it is difficult to achieve accurate and clear surgical margins, resulting in high recurrence rates post resection. Moreover, the benefits of surgical interventions were not sustained. Recurrence rates for micro LM after surgical resection have been reported to range from 17% with complete resection and 40% with incomplete resection, thus increasing the risk for iatrogenic morbidity with repeat surgeries.

Sclerotherapy, the first-line treatment for macrocystic LMs, may not be effective or practical in patients with micro LMs due to a lack of accessible therapeutic targets, although positive results have been reported for several sclerotherapy agents, mainly bleomycin, especially in cases of large diffuse micro LMs.[1,9] Efficacy of other surgical interventions including radiotherapy and laser therapy remains to be determined.[7] The drawbacks associated with surgical approaches for micro LMs have spurred the search for treatment alternatives that target the underlying pathological mechanisms of this disorder.

Although the pathogenesis of LMs remains to be clearly elucidated, important insights gained over the last decade have implicated abnormal activation of the PI3K/AKT/mTOR signaling pathway.[3] Enhanced mTOR signaling has been shown to enhance the expression of the vascular endothelial growth factor, a key promoter of angiogenesis and lymphangiogenesis, and leads, in turn, to uncontrolled and disorganized vascular development. The mTOR inhibitor sirolimus (rapamycin) offers a biologically plausible mechanism as a targeted therapy in the management of LMs, especially difficult-to-treat micro LMs.[10,11] By directly targeting the PI3K/AKT/mTOR pathway within LMs, sirolimus has been shown to downregulate lymphangiogenesis and attenuate clinical complications including lymphorrhea, bleeding, infection, and pain.

This systematic review of the literature examined clinical data on the role of topical and systemic sirolimus in the treatment of children and adults with micro LMs.

Methods

Search strategy

The focus of the search was to identify and evaluate recently published clinical studies specifically on the role of sirolimus in the treatment of micro LMs. The search was completed per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12]

Search criteria

All searches included a ''Disease'' and a ''Drug'' term and used the connector word ''AND'' to return ''hits'' (Table 1).

For instance, the search format was as follows: ''microcystic lymphatic malformation'' AND (sirolimus OR rapamycin OR mTOR inhibitor). The title and/or abstract of the

Table 1. Search Delimiters

Period	*January 1, 2011 to July 20, 2021*	
Terms	Diseases • Cavernous lymphangioma • Complex lymphatic malformations • Cystic hygroma • Lymphangiomatosis • Lymphangioma circumscription • Lymphatic malformation • Microcystic lymphatic malformation • Superficial lymphangioma • Vascular anomalies	Drugs • Sirolimus • Rapamycin • mTOR inhibitor
Sources (databases)	• PubMed (title and abstract) • Google scholar (title) • Cochrane reviews	
Study types	• Clinical trials (all) • Review articles • Case reports or series	
Languages	• English	

search studies were required to indicate that the publication contained clinical data directly related to sirolimus in the treatment of patients with micro LMs.

Data extraction

From each relevant study, the following details were extracted and a table containing those details was created.

- Publication details
- Study type
- Number of subjects as well as demographics
- Number of subjects with micro LMs
- Prior treatments
- Details of sirolimus treatment including dosing and duration
- Outcome measures
- Results, including the impact of sirolimus on micro LM symptomatology
- Sirolimus-related adverse events

Statistical analyses

Because of the heterogeneity in outcome measures and subject selection criteria among the studies identified, no formal statistical analyses were conducted. Only descriptive statistical analyses were completed when necessary for clarity.

Institutional review board approval

For this retrospective study, an Institutional Review Board approval was not required.

Results

The search strategy yielded a total of 251 publications (Table 2).

After removing duplicates, the remaining publications were reviewed to ensure they contained clinical data related specifically to the use of topical or oral sirolimus in the treatment of patients with micro LMs. The review yielded a total of 16 relevant studies that included 52 subjects with micro LMs (Table 3).[7,13–27] Studies identified were mostly case studies (10) or retrospective hospital case reviews (3). The 3 prospective clinical trials identified included 13 subjects with micro LMs.[13–15]

Table 2. Overall Number of Publications Identified

Diseases	*"Hits"*[a]
Cavernous lymphangioma	0
Complex lymphatic malformations	4
Cystic hygroma	15
Lymphangiomatosis	30
Lymphangioma circumscription	0
Lymphatic malformation (s)	69
Microcystic lymphatic malformation	10
Superficial lymphangioma	0
Vascular anomalies	123
Total	251

[a]Using drug terms (sirolimus OR rapamycin OR mTOR inhibitor.

Demographics

Ages at treatment initiation ranged from a few days of life[27] to 34 years.[25] For studies reporting the gender of subjects with micro LM, the proportion of women was somewhat higher than men (16 women, 10 men).

Treatment

Specific sirolimus treatment information is presented in Table 3. Sirolimus was administered orally in 10 ($n = 37$) and topically in 6 ($n = 15$) studies, usually in a twice-daily regimen. The initial oral dose was typically 0.8 mg/m^2 twice daily. In all 10 studies with oral dosing, doses were adjusted to maintain systemic sirolimus trough levels (range: 4–15 ng/mL). Topical dosing concentrations ranged from 0.1% once daily to 1% twice daily. Most subjects (62%; 32/52) received at least 1 prior treatment for this disorder before starting sirolimus treatment.

Sirolimus efficacy

Outcome measures. Because most studies included in this analysis were uncontrolled, observational, and retrospective in design, prospective outcome measures were not used in most. However, 2 prospective studies[13,14] used outcome measures categorized as complete, partial, and no response (stable or progressive disease). In these studies, those parameters were typically defined as follows:

- Complete response: Complete disappearance of the lesion (clinically and radiologically) and normalization of quality of life (QoL)
- Partial response: A reduction of ≥20% in size of the vascular lesion (clinical and/or radiological) or improvement of symptoms or QoL
- Stable response: No evidence of response or disease progression
- Progressive disease: An increase in lesion size, symptoms, or decreased QoL assessment

Overall response to treatment. Of the 50 mostly previously treated micro LM subjects with evaluable efficacy findings, 92% (46) demonstrated a clinically meaningful response to sirolimus treatment. Sirolimus efficacy was noted across a wide age range, from neonates[13,15,27] to adults over 30 years.[25] Most subjects experienced a notable reduction or elimination of the micro LM mass/lesion and improvements in key symptoms such as leakage, infection, and pain in response to sirolimus treatment. Overall, sirolimus administered topically (6 studies) and orally (10 studies) both yielded improvements in cutaneous outcomes such as lesion size.

Topical application. For all 15 subjects treated with topical sirolimus (Table 3), treatment provided clinically meaningful relief for a variety of micro LM signs and symptoms including reductions in exudate, vesicle volume, pain, bleeding, and superinfection. Most of the subjects—60% (9/15)—had undergone previous treatment for micro LM with less than optimal results. Treatment duration varied considerably from 3 to 24 months,[7,16] but improvement was noted as early as 3 weeks for 1 subject.[19]

TABLE 3. TOPICAL SIROLIMUS TREATMENT FOR CUTANEOUS LYMPHATIC MALFORMATION

Study	*Study type*	*MLN S#*	*Sex/age years*	*Previous Tx*	*Main symptoms*	*Anatomical site*	*Sirolimus dose*	*Outcomes*	*Tx (mos)*	*AEs*
Topical sirolimus										
Çalışkan[7]	Case study	1	F/8	No	• Papule clusters	• Trunk	0.75 mg/mL lotion BID to QD	• Lesions cleared • S requested discontinuation of therapy once lesions cleared	3	• Contact reaction at app site • Reaction resulted in change from BID to QD dosing on day 15
García-Montero[16]	Case series	1	F/6	No	• Exudate	• Right arm	1% ointment/BID	• Reduced exudate • Color attenuation • Reduced surface area • Reduced vesicle volume	12	NA
		2	M/5	• Sclerotherapy • Pulsed dye laser	• Exudate • Superinfection	• Right buttock	1% ointment/QD	• Reduced exudate • Reduced superinfection • Color attenuation • Reduced surface area • Reduced vesicle size	24	NA
		3	F/13	• Cryotherapy	• Exudate • Superinfection • Inflammation • Pain	• Right buttock	1% ointment/BID	• Reduction in all major symptoms • Color attenuation • Reduced vesicle size	24	NA
		4	F/10	• CO_2 laser	• Inflammation • Pain	• Right inframammary	1% ointment/BID	• Reduction in inflammation and pain • Reduced vesicle volume	15	NA
		5	F/16	No	• Exudate	• Right scapular	0.8% ointment/QD	• Reduction in exudate • Color attenuation • Reduced vesicle size and volume	24	NA
		6	F/14	No	NA	• Posterior cervical region	0.4% ointment/QD	• Color attenuation	18	NA
		7	F/13	• Sclerotherapy • Electrosurgery	• Exudate	• Right inframammary	O.4% ointment/BID	• Reduced exudate • Reduced vesicle volume	6	NA
		8	F/11	No	NA	• Left shoulder	0.4% ointment/QD	• Color attenuation • Reduced surface area	24	NA
García-Montero[17]	Case study	1	F/13	No	• Exudative papular and vesicular lesions • Superinfection • Pain	• Right buttock	1% ointment/OD	• Flattening of the lesions • No new episodes of bleeding or malodorous exudate • Reduction in pain and discomfort • Reduction in size, number of vesicles, and exudation	4	• Transient swelling and discomfort at app site
		2	M/5	• Laser multiplex treatment • Intralesional bleomycin injections	• Exudate • Vesicular lesions	• Buttock above surgical scar	0.8% ointment BID to OD	• Reduction in vesicle size and exudate	6	• None
Ivars[18]	Case report	1	M/20s	• Intralesional bleomycin sclerotherapy	• Lymphorrhea • Periodic lymphangitis	• Scrotum	0.8% ointment OD	• Lesion size reduced dramatically • Lymphorrhea disappeared • Symptoms did not recur	3	• None

(*continued*)

TABLE 3. (CONTINUED)

Study	*Study type*	*MLN S#*	*Sex/age years*	*Previous Tx*	*Main symptoms*	*Anatomical site*	*Sirolimus dose*	*Outcomes*	*Tx (mos)*	*AEs*
Le Sage[19]	Case series	1	F/9	• Laser	• Exudate • Pain	• Right hip	0.1% solution BID	• Decrease in lesion leakage • Moderate decrease in size • Reduction in discomfort	22	• Local irritation at app site
		2	F/8	• Laser	• Pain • Exudate	• Right hemithorax cluster of vesicles	0.1% solution QD	• Reduction in vesicle number • Reduction in exudate • Improvement noted within 3 weeks	18	• Local irritation
Leducq[20]	Case report	1	M/17	• Sclerotherapy • CO_2 laser therapy • Retinoid therapy	• Pain • Exudate	• Gluteal area	0.1%–0.25% concentration QD	• Decrease in the number of vesicles (estimated at 30%) • Decrease in thickness of oozing, and bleeding	>6	• Slight application site tingling
Oral sirolimus										
Adams[13]	Clinical trial (Phase II)	5[b]	NA/21days to 20 years	• Yes (unspecified)	• Symptomatic MLM	• Verified vascular anomaly (unspecified)	• Dose: max dose-BID trough @ 10–15 ng/mL • BTDA: 10–15 ng/mL	• 2=PR (improvement in key outcome measures) • 2=PD (worsening in outcome measures) • 1=No data available	12 courses (28 days each)	• Blood/bone • GI • AEs not specified by type of LM
Ghariani Fetoui[21]	Case study	1	F/2	• 20 mg/kg prednisone for 1 week	• Vesicular lesions	• Tongue	• Dose: 0.4–0.8 mg/m^2 BID • BTDA: 10–12 ng/mL	• 80% decrease in mass size • Complete resolution of associated vesicles	5	• Pulmonary infection
Hammer[14]	Clinical trial	1	M/3	• Surgery • Antibiotherapy	• Tongue enlargement • Infection	• Cervicofacial (tongue)	• Dose: 0.8 mg/m^2 BID • BTDA: 10–15 ng/mL	• PR • Reduction in malformation • Cessation of infection • Functional improvement (speech and chewing)	≥28	NA
Hammill[22]	Case review	1	M/6	• Interferon • Celecoxib, • Decortication • Pleurodesis • Chest tube	• Chylous pleural effusions	• Lung	• Dose: 0.8 mg/m^2 BID • BTDA: 10–15 ng/mL	• Drainage decline; removal of chest tube • Response within 14 days	28	• None
		2	F/14	• Chest tube • Interferon • Celecoxib	• Chylous pleural effusions	• Lung	Same as above	• Drainage decline; removal of chest tube • Time to response: 8 days	14	• Increased ALT/AST (Grade III)
		3	F/14	• Chest tube • Pleurodesis • Celecoxib	• Chylous pleural effusion	• Lung	Same as above	• Drainage decline; removal of chest tube • Time to response: 8 days	2	• Mucositis (Grade III)
		4	M/7 mos	• VATS×2 • Pleurodesis • Chest tubes	• Chylous pleural effusions	• Lung	Same as above	• Drainage decline; removal of chest tube • Time to response: extubated 15 days after starting sirolimus	>12	• Hypercholesterolemia (Grade I) • Increased AST (Grade II) • Increased ALT (Grade III) • Neutropenia (Grade III)

(*continued*)

Table 3. (Continued)

Study	*Study type*	*MLN S#*	*Sex/age years*	*Previous Tx*	*Main symptoms*	*Anatomical site*	*Sirolimus dose*	*Outcomes*	*Tx (mos)*	*AEs*
Lagrèze[23]	Case report	1	M/23	• None	• Retrobulbar microcystic lymphangioma	• Right orbit muscle cone	• Dose: 1 mg BID • BTDA: 5–10 ng/mL	• Substantial clinical and radiological improvement • Symptom regression	6	None
Rossler[24]	Case reports	1	M/16	• YAG laser therapy of the soft tissue lesion at the left flank • Lymphatic drainage and compression stockings • Antibiotics	• Lymphatic leakage • Local infection • Pain	• Left flank, subcutis, skin, iliopsoas muscle, and scrotum	• Dose: 0.8 mg/m^2 OD • BTDA = 10–15 ng/mL	• Lymph leakage was reduced dramatically after 2 weeks • Drainage had completely subsided after 4 weeks • With cessation of treatment, lymph leakage recurred, and acute cellulitis developed	≥36	None
		2	M/18	• Surgery • YAG laser therapy	• Infection • Pain	• Subcutis and cutis at the left axilla, arm, and thoracic wall	• Dose: 0.8 mg/m^2 BID • BTDA = 10–15 ng/mL	• Complete resolution of lymphatic drainage • Reduced vesicle volume • Time to response: 2 weeks	36	None
Strychowsky[25]	• Hospital case review 2012–2016	1	NA/17	NA[a]	NA	• Buccal mucosa • Anterior base of tongue	• Dose: 0.8 mg/m^2 BID • BTDA: 10–15 ng/mL	• Improved LM bulk • Modest reduction in vesicle bulk • Decreased infections	4	• Mouth sores • Nausea
		2	NA/6	NA	NA	• Left parotid extended into submandibular and submental areas	• Same as above	• Moderate improvement in LM bulk • Decreased infections	30	• Diarrhea • Elevated triglycerides and cholesterol
		3	F/15	NA	NA	• Cervicofacial • Tongue and pharynx	• Same as above	• Moderate improvement in LM bulk and vesicle size • Decreased infections	36	• Dermatologic reactions • Headache • Joint pain • Neutropenia • Irregular menstrual bleeding
		4	NA/8	NA	NA	• Cervicofacial • Anterior tongue	• Same as above	• Modest improvement LM bulk • Improved vesicle size • Decreased infections	34	• Eczema • Elevated cholesterol and triglycerides • Mouth sores • Elevated transaminase
		5	F/18	NA	NA	• Cervicofacial • Anterior tongue	• Same as above	• Modest improvement LM bulk • Improved vesicle size	23	• Irregular menstrual bleeding
		6	NA/7	NA	NA	• Left facial region	• Same as above	• Decreased infection • Modest improvement LM bulk and vesicle size	24	• Elevated transaminase • Neutropenia

(*continued*)

Table 3. (Continued)

Study	Study type	MLN S#	Sex/age years	Previous Tx	Main symptoms	Anatomical site	Sirolimus dose	Outcomes	Tx (mos)	AEs
		7	NA/6	NA	NA	• Bilateral cervicofacial, ventral, and dorsal tongue	• Same as above	• Modest improvement on LM bulk • Improved mucosal vesicle size	25	• Mouth sores • Elevated transaminase
		8	NA/22	NA	NA	• Cervicofacial • Neck, floor of mouth, and tongue	• Same as above	• Modest improvement LM bulk • Improved vesicle size	18	• Mouth sores • Fatigue
		9	NA/34	NA	NA	• Ventral and dorsal aspects of tongue • Oropharyngeal airway	• Same as above	• Modest improvement LM bulk • Improved vesicle size • Decreased infection	15	• Elevated triglycerides • Headache • Mouth sores
Triana[26]	• Hospital case review 2014–2918	1	F/10 months	• None	• Cervicofacial right mass and macroglossia • Capillary malformation lower lip	Neck and tongue	• Dose: 0.8 mg/m^2 BID • BTDA: 4–12 ng/mL	• Partial disappearance of symptoms • Reduction in lesion size	12	• None
Zhang[15]	• Prospective, open-label • Beijing Children's Hospital 2018–2020	7[b]	NA/Overall age range: 14 days to 14 years	NA	• Lymphatic malformations (unspecified)	• Cervicofacial	• Dose: 0.8 mg/m^2 BID • BTDA: 4–13 ng/mL	• Fair, good, or excellent response for 4/7 patients (fair=≥20% improvement) • No or minimal response in 3/7 patients • 20% volume reduction on average	8 (median)	• Upper respiratory infection (most common) • No discontinuations due to adverse events
Zobel[27]	• Retrospective hospital review 2004–2019	6[b]	NA/mean age: 4 years	• Sclerotherapy: 3 MLM subjects • Surgical resection: 4 MLM subjects	• Microcystic lesion (unspecified)	NA	• Dose: 0.8 mg/m^2 BID • BTDA: 10–15 ng/mL	• 3/4 patients who received a full 3-month course of sirolimus and who had efficacy data available experienced at least some improvement (≥25%) in lesion volume. • All 3 responders experienced noticeable improvement MLM disease burden • 1 of the 3 experienced >50% improvement	3	• Nausea resulting in study discontinuation in 1 subject • Another subject received a short course of sirolimus before expiring (reason not provided)

[a]Most had previous treatments, including sclerotherapy and surgical debulking. Individual patient data were not available.

[b]Only grouped data were presented.

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BTDA; blood level target of sirolimus dose adjustments; CO_2, carbon dioxide; F, female; GI, gastrointestinal; LM, lymphatic malformation; M, male; MLM, microcystic lymphatic malformations; MLN, Medicare Learning Network; NA, not available; OD, once daily; PD, progressive disease (increase in lesion size, symptoms, or decreased QoL assessment); QD, daily; QoL, quality of life; PR, partial response (reduction of ≥20% in size of the vascular lesion or improvement of symptoms or QoL); S, sirolimus; S, subject; VATS, video-assisted thoracoscopic surgery; YAG, yttrium aluminum garnet.

The compounding process for topical sirolimus was briefly described in 4 studies—1 study used a commercially available oral solution in a standard hydrophilic ointment,[7] 2 studies used a rapamycin petroleum formulation,[17,18] and 1 study used the commercial oral solution.[19] In one of these studies, rapamycin powder was used in the compounding of the petroleum formuation.[17]

Oral administration. For the 37 subjects treated with oral sirolimus (Table 3), treatment provided clinically meaningful relief in 31 subjects. In 1 study that included a total of 6 children with micro LM, 2 subjects were excluded from the efficacy analysis because they did not receive the full course of treatment.[27] As a result, 35 subjects were included in our oral sirolimus efficacy analysis for oral treatment yielding a responder rate of 89% (31/35). Subjects' oral treatment duration varied considerably among subjects ranging from 2 months[22] to more than 3 years.[24]

For most subjects, oral sirolimus resulted in reductions in lesion bulk size, pain, infections, and lymphatic leakage. In addition, oral sirolimus mitigated chylous pleural effusions in 4 subjects with diffuse micro LM affecting the lungs permitting chest tube removal.[22] In these subjects, responses occurred as early as 8 days after the start of treatment.

Adverse events

Topical application. With topical administration, the most common adverse event reported was transient irritation or burning at the application site. Application site reactions occurred in 5 of 7 subjects with safety data available. For 1 subject, the application site reaction resulted in a reduction in dosing frequency from twice to once daily.[7]

Oral administration. In 1 study,[13] blood and bone marrow toxicities were noted in about a quarter of the 57 subjects with vascular anomalies treated with sirolimus; however, the toxicity analysis in that study did not identify how many of the 5 micro LM subjects from that study included in our analysis were affected. Among the 18 orally treated subjects in our analysis with individual safety data available, 5 experienced liver enzyme elevations, 4 dyslipidemia, and 6 mucositis/mouth sores. The risk for these systemic events appeared to decline with sirolimus dose reduction.[22]

Treatment discontinuations. Treatment discontinuations (permanent) due to adverse events linked to sirolimus therapy occurred in 4 subjects (8%; 4/52) across 3 studies. All were treated with oral sirolimus. In Adams et al.,[13] 1 subject was discontinued because of grade 2 (moderate) nausea and a second for persistent grade 3 (severe) lymphedema. In Hammill et al.,[22] the toxicity was not specified for the 1 subject who discontinued due to adverse events. In Zobel et al.,[27] 1 subject with micro LMs discontinued treatment due to ''intolerable'' nausea.

Discussion

Micro LMs represent therapeutically challenging congenital vascular lesions.[28] There is no universally accepted gold standard of care and there are no FDA approved therapies. Current interventional treatment modalities such as surgery or sclerotherapy may be infeasible or have only transient efficacy for many patients with micro LM.[2,29] These clinical gaps in the management of micro LMs have spurred the search for novel treatments to improve outcomes and reduce symptom burden. Recent insights into the pathogenesis of micro LMs have provided an opportunity to examine treatments, such as mTOR inhibitors, that better target the underlying pathogenesis of this disorder.

This systematic review examined the published literature on the role of sirolimus in the treatment of micro LMs. Limited prospective clinical trials have been conducted to specifically examine the role of sirolimus in the treatment of micro LMs, and no trials have been identified that use a placebo control.

As of July 2021, clinicaltrials.gov showed only 3 active clinical trials examining the role of sirolimus for the management of LM. Due to the paucity of prospective, controlled trials, our review relied primarily on case studies and case reviews. We identified 52 patients across 16 studies who were treated with sirolimus for the management of micro LMs. Most patients (90%) demonstrated a clinically meaningful response to sirolimus treatment, with notable reductions in, or elimination of, the micro LM lesions over time. Indeed, time to discernable onset of action was reported to occur as early as 2 weeks after the start of therapy in some studies. In addition, improvements continued during follow-up that ranged from 2 months to 3 years, implying long-term maintenance treatment may be needed to prevent disease progression. About half the studies reviewed reported changes in specific micro LM associated symptoms, with sirolimus treatment yielding improvements in such manifestations as lymphorrhea, bleeding, pain, and skin discoloration.

Our findings confirm and extend the results of broader retrospective reviews of sirolimus in micro LM and vascular malformations.[2,30–32] The findings of these previously published reviews also highlighted a potentially important therapeutic role for sirolimus in a broad array of vascular and LMs and tumors. As in our review, most patients in these reviews displayed a clinically relevant response to sirolimus therapy.

In our review, topical sirolimus was associated with transient application-site reactions. Yet the risk for an application-site reaction may not be uniform across all topical formulations. Individuals using the liquid formulation directly may experience greater irritation and skin breakdown due to the formulation's excipient content. In addition, topical formulations derived from sirolimus pills can contain an alcohol residue remaining from the dissolving process. This residue may promote skin irritation and degradation. Topical sirolimus derived from a powder formulation, however, possesses neither of these liabilities and thus may be less irritating when applied topically. Because of the potential variation in application-site reactions across formulations, it is important to use the least reactive topical products.

However, developing a commercial topical sirolimus formulation faces important challenges. The chemical instability and poor solubility of sirolimus present significant stability and penetration challenges for compounded sirolimus. Furthermore, the high molecular weight of the sirolimus molecule restricts transepidermal delivery to the diseased tissue. Sirolimus has a molecular weight of 914 Daltons, almost two-fold higher than the generally accepted value of the 500 Dalton Rule, which states that the molecular

weight of a compound should be under 500 Daltons to penetrate the skin.[33,34] At least partially because of these challenges, topical sirolimus is not commercially available, thus requiring compounding at a local pharmacy or shipping from a retail compounding pharmacy. Local compounding may result in variability in the formulation's concentration, potency, stability, quality and perhaps, increased patient costs as compounding is not covered under most insurance. Yet, these drawbacks should be balanced against the risk for systemic side effects and the need for regular blood testing with the long-term use of oral sirolimus for micro LMs.

In all the studies using the oral formulation identified in our review, blood testing was conducted to maintain sirolimus blood levels within a pre-specified blood level range, most commonly 10–15 ng/mL. Adverse events identified in our review were generally mild or moderate, manageable, and consistent with those previously reported with sirolimus treatment.[35,36] Treatment discontinuations (permanent) resulting from adverse events were uncommon, occurring in only 4 patients (8%; 4/52) treated with oral sirolimus across 3 studies.[13,22,27]

Nonetheless, due to the limited scope of our review, potential adverse events associated with sirolimus therapy require careful treatment monitoring. In 1 study reviewed, a significant number of oral sirolimus-treated patients experienced blood and bone marrow abnormalities. The sirolimus label warns of the potential for other serious adverse events such as angioedema, acute kidney injury, and interstitial lung disease.[13,36]

Our review, and others using similar methodologies, has important inherent limitations that affect the generalizability of the findings. Most of the studies cited in this review were case studies and case reviews. Many authors and centers may be prone to publish only positive outcomes for such studies. In addition, these studies assessed efficacy broadly by tools such as, QoL, and recorded a response as complete or partial, so it is difficult to assess the magnitude and relevance of differences in clinical responses across studies because of variability in the outcome measures used. Even responses to topical sirolimus may be difficult to generalize since the quality of compounded products was not standardized and likely varied considerably. Importantly, the overall sample size was small—a total of 52 patients with micro LMs. This small sample size may have resulted from the relative paucity of studies directly and specifically investigating mTOR inhibitors in micro LM or from our stringent selection criteria that required studies to specifically state that the patients included were diagnosed with a micro LM treated with sirolimus, which may have resulted in some studies being omitted from the search results. Finally, there was considerable heterogeneity in study conditions, processes, and outcome assessments, an expected source of variability that clouds the interpretation of retrospective, systematic reviews.

Conclusion

Data from the current retrospective review suggest a potentially important role for sirolimus as an effective and safe treatment option in the management of micro LMs. Due to the retrospective nature of this review and the heterogeneity of the studies included, the current findings, although intriguing, can only be considered heuristic. Yet findings such as these are sufficiently compelling to provide an impetus for future prospective, controlled studies.

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Authors' Contributions

All individuals who meet authorship criteria are listed as authors. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, and revision of the article.

Author Disclosure Statement

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