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Sirolimus for Pediatric Cervicofacial Lymphatic Malformation: A Systematic Review and Meta-Analysis

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Objective: This study is a systematic review and meta-analysis of the efficacy and safety of sirolimus in the management of pediatric cervicofacial lymphatic malformations (LMs).

Data Sources: EMBASE, Medline, Scopus, and Cochrane databases were searched, along with the reference list of all included articles.

Review Methods: The study protocol was registered with PROSPERO and a systematic literature search strategy was designed and conducted with the aid of a medical librarian. All studies including case reports were included, with pooled analysis of raw data. A meta-analysis was conducted of magnetic resonance imaging (MRI), clinical, and airway outcomes.

Results: Thirteen case series and five individual case reports were included. Meta-analysis showed 78% (95% CI 57%–94%) of 62 patients had a reduction in LM volume, on MRI criteria, by 20% or more, and 32% (95% CI 11%–57%) had a reduction of 50% or more. Further meta-analysis showed 97% (95% CI 88%–100%) of 78 patients reported some clinical improvement on sirolimus. Sirolimus may be of particular value in management of airway LMs; out of 27 tracheostomy-dependent patients, meta-analysis showed 33% (95% CI 1%–78%) were decannulated after starting sirolimus. Individual patient meta-analysis on 24 individuals showed a statistically significant better response to sirolimus when initiated under the age of 2 years.

Conclusion: This review and meta-analysis support the efficacy of sirolimus in pediatric LMs of the head, neck, and airway. A large multi-center trial is needed to further explore its role and limitations.

Key Words: cystic hygroma, lymphatic malformations, pediatric, rapamycin, sirolimus, tracheostomy.

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INTRODUCTION

Lymphatic malformations (LMs) (formerly, "cystic hygromas") are congenital non-proliferative malformations of the lymphatic drainage pathways resulting in enlarged vascular and cystic spaces.[1] They can be simple or complex, the latter containing elements of other vasculature types, and may occur in isolation or in association with recognized syndromes. Simple LMs can further be classified as macrocystic, microcystic, or mixed.[2] They have an estimated incidence of between 1 in 6000 to 1 in 16,000 live births.[3] Seventy-five percent are found within the head or neck, and can cause serious morbidity, including speech impairment, dysphagia, and airway occlusion.[4]

The mainstay of treatment, to date, has been injection sclerotherapy alone or in combination with surgical resection. However, these strategies carry significant risks, which are increased in large or deep LMs.[5,6] Moreover, a sizeable proportion (13%–33%)[5,7] of large cervicofacial LMs prove refractory to these treatments.

Sirolimus (rapamycin) is a macrolide compound with inhibitory effects on mTOR (mammalian target of rapamycin), a protein kinase that mediates cell growth and proliferation pathways, and which may be implicated in LMs.[8] Recently, several case reports and case series have reported good responses of LMs to sirolimus treatment. The research question addressed by this systematic review and meta-analysis is the efficacy and safety of oral sirolimus in the treatment of pediatric cervicofacial LMs as compared to sclerotherapy or surgery.

METHODS AND MATERIALS

Study Parameters (PICOS)

The population of study is children (0–18 years) with cervicofacial LMs, the intervention is oral sirolimus, the comparison is with sclerotherapy and surgery, and the outcomes of interest are efficacy and safety. The study

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The systematic literature search and data extraction were conducted at the Noah's Ark Children's Hospital in Cardiff with the aid of the medical library team. Statistical analysis was conducted at University College London and the University of Bath.

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design is a systematic review and meta-analysis of case studies.

Search Strategy

The search strategy was designed with the aid of a medical librarian, and the protocol registered prospectively on the PROSPERO database (registration number CRD42022340823). The study was conducted and reported in line with PRISMA 2020 guidelines for systematic review. Searches were performed on the following databases: EMBASE, Medline, Scopus, and the Cochrane Library. The following key words were used: [rapamycin OR sirolimus], [lymphatic malformation* OR lymphangioma* OR cystic hygroma*], [paediatric* OR pediatric* OR neonat* OR infant* OR child*] (full search algorithm listed in Supplementary Table 1). Searches were conducted between January 13–February 10, 2022. The reference sections of included studies were then also searched by hand by two reviewers (YK/HJ).

Study Inclusion Criteria

Criteria for inclusion in this review were all clinical studies assessing the response of common LMs to sirolimus in pediatric populations (defined as age 0–18 years old). Macrocystic, microcystic, and mixed LMs were included. Studies of other vascular anomalies (VAs), such as complex LMs, Kaposi's haemangioendothelioma, venous malformations, mixed venous-LMs, and VAs associated with syndromes, were excluded. Cellular, genetic, and animal studies were excluded.

Study Evaluation

Two reviewers (YK/AH) evaluated each study for design quality and risk of bias using the Newcastle-Ottawa scale for assessing the risk of bias in non-randomized studies of interventions.[9] Data was extracted and subsequently analyzed using Excel (Windows, WA, USA). Statistical analysis was conducted by expert statisticians (RM and TB) using "R" statistical software meta package (The R Foundation, Bell Laboratories). A random effects model was assumed with a Freeman-Tukey double arcsine transformation for the meta-analysis of the reduction in LM volume, clinical improvement, and airway outcomes. Correlation of age of initiation of sirolimus with outcome was assessed via the Mann–Whitney-*U* test. Safety data was reported narratively due to heterogeneity of data. Heterogeneity for each meta-analysis was reported using the I^2 index, with <25% considered low heterogeneity, 25%–50% moderate heterogeneity, and >50% high heterogeneity.[10]

RESULTS

Search Results

Searches yielded 406 results, of which 62 were duplicates. Conference abstracts, reviews, and genetic studies were excluded. This process is summarized in the PRISMA flow diagram in Figure 1. Individual case reports of sirolimus use in pediatric cervicofacial LMs were included.

No randomized-control trials were found. Eight prospective case series were identified. Two of these (Adams et al. 2016,[11] Sandbank et al. 2019[12]) were excluded as they enrolled both adult and pediatric patients, and it was not possible to extract the pediatric data. Two (Tian et al.,[13] Ji et al.[14]) were excluded as the data for cervicofacial LMs could not be extracted. One (Maruani et al.[15]) was excluded as it omitted simple non-venous LMs. Therefore, three prospective case series were included in the review (summarized in Table I). One of these studies, Ozeki et al.,[17] included adults and children but only the pediatric data was extracted for this review. Ten retrospective case series[19–28] and five individual case reports[29–33] of sirolimus use in cervicofacial LMs were also included; these are summarized in Table II. Assessment of risk of bias for all included studies is shown in Table III. Statistical assessment for publication bias was not conducted as the included studies were all case series with no intervention effect reported. Searches of trial registries did not yield any completed unpublished studies; however, given that all the published studies showed a neutral-to-positive effect of sirolimus, there is a high risk that publication bias is present.

Study Settings and Participants

Case series were reported from Canada, the USA, Europe, China, and Japan. All patients had common LMs which were judged to be significant due to size, location, or associated side effects such as hemolysis, and many had failed multiple previous therapies.

Outcome 1: Radiological Improvement

Volume reduction on MRI evaluation was the primary outcome in all three prospective studies[16–18] and three retrospective studies.[19,23,25] A meta-analysis for proportions showed 77.9% of 62 patients experienced at least a 20% reduction in volume (95% CI: 57.1%–94.1%, I^2 0.49), and 31.8% of 59 patients experienced at least a 50% reduction in volume (95% CI: 10.9%–56.5%, I^2 0.61). Forest plots are shown in Supplementary Figures 1 and 2, respectively. In four of the six studies above, no concurrent surgery or sclerotherapy was given. A sensitivity meta-analysis looking at only the prospective studies (lowest risk of bias) showed 86.1% of 35 patients had at least a 20% reduction in volume (95% CI: 69.8%–97.7%, I^2 0, forest plot shown in Supplementary Figure 3). In this group, no patients received concurrent surgery or sclerotherapy whereas undergoing sirolimus therapy.

Outcome 2: Clinical Improvement

Two prospective studies[16,18] reported some improvement in patient function, or reduction in symptom severity, in all patients on sirolimus (a combined N. 30). This was loosely defined as either clinician-observed or patient-reported improvements in swelling, function, lymphatic ooze, or pain. The third study (Ozeki et al.[17]) did not report clinical improvement data. No concomitant

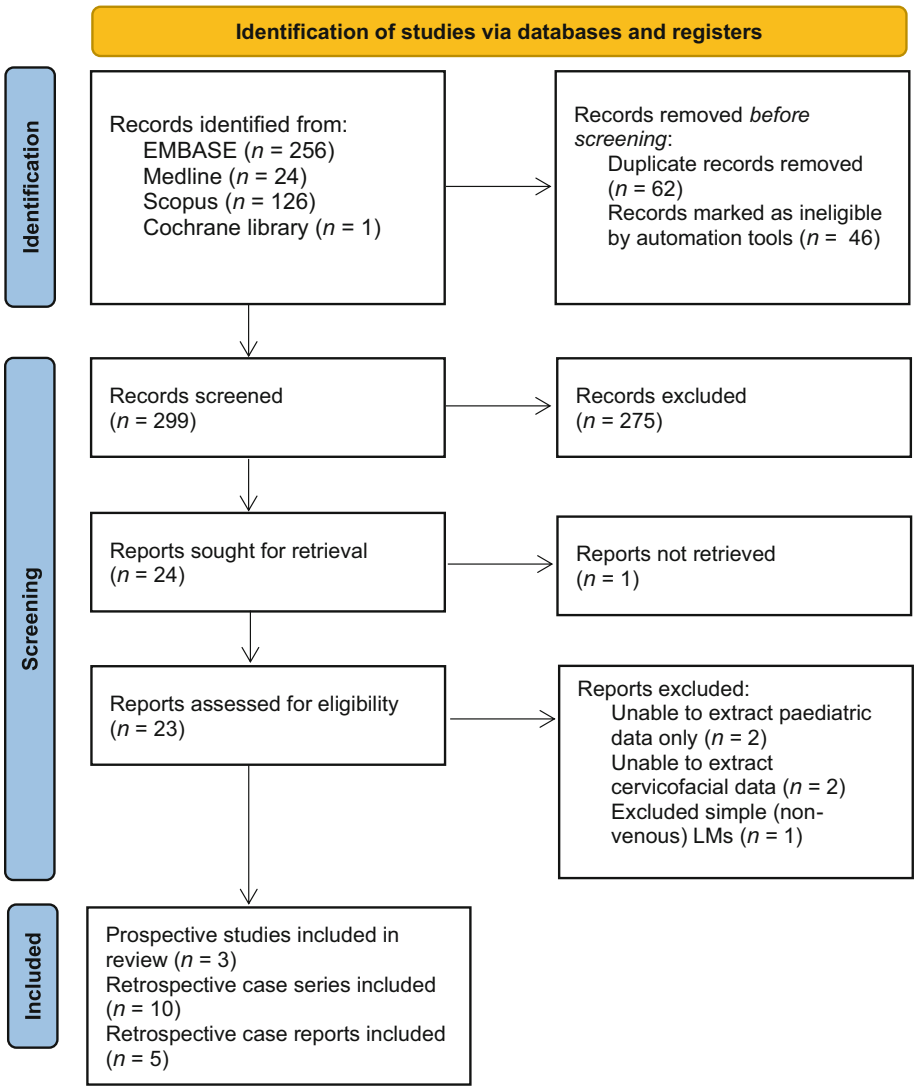

Fig. 1. PRISMA flow diagram of search results [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

surgery or sclerotherapy was given alongside sirolimus therapy in this group.

Of the nine retrospective case series that reported clinical improvement as an outcome,[19–27] meta-analysis showed 97% of patients experienced some clinical improvement (95% CI: 88%–100%, I^2 0.28, forest plot shown in Supplementary Figure 4). This outcome was subjectively determined by the clinicians and/or parents in most studies and ranged from complete resolution of the lesion to reduced pain and infectious episodes, without any reduction in bulk. A further five individual case reports[29–33] showed clinical benefit in four cases, again assessed subjectively by treating clinicians.

Airway Management

Meta-analysis of outcome data for patients with tracheostomy from six studies[19,21–24,27] showed, out of a combined N. 27, 33% (12 patients; 95% CI: 1%–78%, I^2 0.59, forest plot shown in supplementary figure 5) were decannulated whereas on sirolimus therapy, either alone or as an adjunct to surgery and sclerotherapy. Meta-analysis showed that a further 22% (eight patients; 95% CI: 0%–61%, I^2 0.50, forest plot shown in Supplementary Figure 6) had an improved tolerance of capping or speech valve use, with ongoing follow-up with a view to future decannulation. There was insufficient data reported to calculate a median duration of sirolimus treatment prior to decannulation.

In one series (Holm et al.[21]), 8 out of 13 patients were decannulated after a median 18 months of sirolimus treatment in combination with either sclerotherapy or surgery. Triana et al.[24] reported on seven neonatal patients who required either non-invasive ventilation (NIV) or intubation, due to LMs. After sirolimus monotherapy (N. 4) or sirolimus with concomitant surgery or sclerotherapy (N. 2), 6 out of 7 patients were successfully weaned off respiratory support, whereas 1 out of 7 progressed to a tracheostomy.

Age at Initiation of Sirolimus

The largest prospective study, Zhang et al.[16] (N. 27) found no association between the age at which sirolimus

Table I.
Summary of Prospective Studies of Sirolimus in Pediatric Lymphatic Malformations (LMs).

Study	Design	*N*	Patient Demographics	Prior/ Concomitant rx	Dose	Duration of Treatment	Duration of Follow-Up	Effect	Safety
Zhang et al. 2021[16]	Prospective cohort	27	Mean age 2 years 3 months (range: 14 days–14 years) 56% female	No prior rx, nil concomitant.	0.8 mg/m^2 BD (0.5 mg/m^2 BD in neonates). Trough target 4–13 ng/mL No prophylaxis	Avg. duration 10 months (median duration 8 months) (6–27 months) 22/27 responded within 12 weeks	>6 months	85% (N. 23) reduction of lesion size by ≥20% (measured at 6 months) All patients reported symptom improvement No difference by age No airway data	27 adverse events, 3% (N. 1/27) grade 3 LRTI
Ozeki et al. 2019[17]	Prospective cohort	5 simple LMs (N. 20 overall, including different VA subtypes)	Mean age 3 years 2 months (range: 14 days–11 years) 60% female	3 prior sclerotherapy and traditional medicine, 1 propranolol, 1 nil prior No other rx during/8 weeks prior to sirolimus starting	Body surface area (BSA) ≥1.0 m^2 received 2 mg OD. BSA of <1.0 m^2 received 1 mg OD. Target trough 5–15 ng/mL PCP prophylaxis given	Mean duration 10 months (range 6–18 months)	Not available	80% (4/5) had reduction of lesion size by ≥20% (measured at 6 months) No airway data	3 adverse events 2/3 events were grade 3 (URTI, cellulitis). 1 was grade 1 (stomatitis)
Hammer et al. 2018[18]	Prospective cross-over trial	3 simple LMs (N. 19 overall, including different VA subtypes)	Mean age 10 years (range: 3–16 years) 60% female	All had prior surgery, 1 had prior sclerotherapy as well No other rx during/4 weeks prior to starting sirolimus	0.8 mg/m^2 BD. Target trough 10-15 ng/mL. Children ≥12 years received 2 mg/day No prophylaxis	Mean duration 25 months (range 13–34 months)	>12 months	66% (2/3) had reduction of lesion size on MRI 100% (3/3) reported clinical/symptomatic improvement (measured at 12 months) No airway data	Unable to extract specific safety data for these patients

Note some study populations included adult patients and/or other subtypes of VA; data pertaining to pediatric simple LMs only was extracted. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE): grades 1–2, mild to moderate; grade 3, medically significant but not life-threatening; grade 4, life-threatening; grade 5, death.

BD = twice daily; LRTI = lower respiratory tract infection; OD = once daily; PCP = pneumocystis pneumoniae; URTI = upper respiratory tract infection; VA = vascular anomaly.

TABLE II.
Summary of Retrospective Series and Case Reports of Sirolimus in Pediatric Cervicofacial Lymphatic Malformations (LMs).

Study Name	Design	N.*	Mean Age (Range) Months	Sex	Dose	Duration of Treatment	Effect	Safety
Strychow-sky et al. 2018[19]	Retrospective case series	16	80 (2–216 months)	Not available for children only	0.8 mg/m^2 BD, target trough initially 10-15 ng/mL, reduced to 7–13 ng/mL. PCP prophylaxis given	Mean 19.2 months, range 4–41 months	All experienced improvement in clinical symptoms and function Of 6 with tracheostomies, all 6 tolerated capping/speaking valve, 1 eventually decannulated	10% (N. 2) needed IV antibiotics for cellulitis. 89% (N. 14) experienced grade 1–2 side effects. 1 patient developed alopecia
Gao et al. 2021[20]	Retrospective case series	15	27.6 (3 days–48 months)	53% F	0.8 mg/m^2 BD, target trough level 10–15 ng/mL. 3 months continuous then alternating monthly No prophylaxis	Unclear	13% (N. 2) complete response of lesion clinically, 87% (N. 13) partial response All patients reported significant improvement in associated symptoms No tracheostomy data	19 adverse events reported; 11% (N. 2) were grade 3–4
Holm et al. 2021[21]	Retrospective case series (multi-centre)	13	59 (1–216 months)	46% F	0.8 mg/m^2 BD (1 patient received 0.4 mg/m^2 BD), target trough levels 2–15 ng/mL No prophylaxis mentioned	Mean 22 months (range 5–67 months)	62% (N. 8) decannulated after median 18 months' treatment. Further 15% due to be decannulated. 8% (N. 1) no reduction in bulk but reduced pain and infection. 15% no response	8% (N. 1) grade 4 SE; necrosis at site of pigtail catheter. 70% grade 1–2 Ses (viral infections, dermatitis, hypophophataemia, recurrent fevers of unknown source)
Durand et al. 2021[28]	Retrospective case series	12	Not available for cervicofacial	Not available for cervicofacial LMs	0.8 mg/m^2 BD, or 3 mg/m^2 OD for children ≥3 years. Target range 5–10 ng/mL PCP prophylaxis was given	Not available for cervicofacial	Mean reduction in volume of 58% on MRI, no clinical data reported No tracheostomy data	For the whole series (N. 25) Grade 1–2 only; 28% oral mucositis, 8% hyperlipidaemia
Tole et al. 2021[22]	Retrospective case series	8	72 (1–204 months)	Not available for cervicofacial LMs	0.8 mg/m^2 BD, or 2.5 mg/m^2 for children >5 years, target trough level 5–15 ng/mL No mention of prophylaxis	Not available for cervicofacial	Clinically 50% (N. 4) significant response, 12.5% (N. 1) moderate response, 37.5% (N. 3) no response Of 3 tracheostomy patients one tolerated capping	Not available specifically for the H&N pts (10% infections overall out of 38 pts, 56% mouth ulcers, 76% hyperlipidaemia
Wu et al. 2021[23]	Retrospective case series	8	12 (2–36 months)	62% F	0.8 mg/m^2 BD, target trough level 10-15 ng/mL No prophylaxis given	16 months (range 12–19 months)	100% had some improvement in clinical appearance and function (sucking and breathing) 87.5% had ≥40% reduction of LM size on MRI. 3/3 traches decannulated	1 case of grade 3 LRTI 75% oral mucositis, 25% GI symptoms, 12.5% each eczema, neutropaenia, dyslipidaemia

(Continues)

TABLE II.
Continued

Study Name	Design	N.*	Mean Age (Range) Months	Sex	Dose	Duration of Treatment	Effect	Safety
Triana et al. 2019[24]	Retrospective case series	7	All term neonates	57% F	0.8 mg/m^2 BD, target trough initially 10–15 ng/mL, reduced to 4–12 ng/mL. No prophylaxis given	16 months (range 3–46 months)	14% (N. 1) complete resolution of the LM, 86% (N. 6) reduction of LM size and improvement in symptoms 6/7 weaned off resp. support, 1 needed tracheostomy	28% (N. 2) sporadic elevation GGT, 14% (N. 1) hyperlipidaemia, resolved spontaneously without dose reduction
Zobel et al. 2021[25]	Retrospective case series	6	Not available for cervicofacial LMs	Not available for cervicofacial LMs	0.8 mg/m^2 BD, target trough 10–15 ng/mL. No prophylaxis given	Not available for cervicofacial LMs	N.4 had more than 3 months sirolimus 100% had some clinical improvement N. 3 had MRI—1 patient had >50% reduction in volume	1 patient discontinued sirolimus due to nausea. 1 patient died shortly after starting sirolimus, implied to be due to patient's general condition
Amodeo et al. 2017[26]	Retrospective case series	3	14 (2.5–23 months)	33% F	0.4–0.8 mg/m^2 BD target trough level 10–15 ng/mL No prophylaxis given	Not available	All (N.3) had significant reduction LM size clinically and radiologically. 0/1 decannulated	33% (N. 1) had mild hyperlipidaemia
Alemi et al. 2015[27]	Retrospective case series	2	2.5 (1–4 months)	Not reported	Dose not specified No prophylaxis given	17.5 months (range 11–24 months)	Both patients had significant reduction LM size and improved function. 0/1 decannulated, 1 avoided tracheostomy	None
Harbers et al. 2021[29]	Case report	1	Infancy	F	Target serum levels 4-10 ng/mL for 6 months	21 months	Reduction in lesion size, improved eating	Not extractable for this case
Chouchene et al. 2021[30]	Case report	1	48 months	F	0.75 mg/kg BD for 6 months	6 months	Volume reduction of >50%; patient gained mouth closure	Not reported
Honnorat et al. 2020[31]	Case report	1	1 day old (34 weeks' gestation)	F	0.1 mg/kg/day BD, initial target 12–20 ng/mL, reduced to 5.7–19 ng/mL. Adjunctive use alongside four rounds percutaneous sclerotherapy	14 months	Gradual and ongoing reduction in lesion size and symptoms. Tracheostomy decannulated age 2 months	3 mild infectious episodes with no interruption to sirolimus. Transient dyslipidaemia with spontaneous resolution
Gaffouri et al. 2018[32]	Case report	1	Not supplied	F	0.8 mg/m^2 BD. Target trough 10–15 ng/mL.	1 month	No response—continued LM growth	None reported
Fetoui et al. 2019[33]	Case report	1	24 months	F	0.4–0.8 mg/m^2 BD. Target trough 10–12 ng/mL.	8 months	Reduction LM size >80%—gained ability to close mouth, eat solid food, speak clearly	Pulmonary infection of uncertain severity

*Note some study populations included adult patients, other subtypes of VA, and/or non-cervicofacial LMs; only data pertaining to pediatric simple cervicofacial LMs has been included in this table; therefore, the N. in this table may vary from the overall N. of a given study.

BD = twice daily; GI = gastro-instestinal; GGT = gamma-glutamyl transferase; LRTI = lower respiratory tract infection; OD = once daily; PCP = pneumocystis pneumoniae; VA = vascular anomaly.

TABLE III.
Risk of Bias in Included Studies.

Article Name	Selection (Out of 4)	Comparability (Out of 2)	Outcome (Out of 4)	Overall Risk of Bias
Zhang et al. 2021[16]	**	-	**	Moderate
Ozeki et al. 2019[17]	**	-	**	Moderate
Hammer et al. 2018[18]	***	-	**	Moderate
Strychowsky et al. 2018[19]	*	-	**	High
Gao et al. 2021[20]	*	-	**	High
Holm et al. 2021[21]	*	-	**	High
Durand et al. 2021[28]	*	-	**	High
Tole et al. 2021[22]	*	-	**	High
Wu et al. 2021[23]	*	-	**	High
Triana et al. 2019[24]	*	-	**	High
Zobel et al. 2021[25]	*	-	**	High
Amodeo et al. 2017[26]	*	-	**	High
Alemi et al. 2015[27]	*	-	**	High
Harbers et al. 2021[29]	*	-	**	High
Chouchen et al. 2021[30]	*	-	**	High
Honnorat et al. 2020[31]	*	-	**	High
Gaffuri et al. 2018[32]	*	-	**	High
Fetoui et al. 2019[33]	*	-	**	High

The Newcastle-Ottawa score tool[9] was followed with the addition of an overall judgement of risk of bias by the review authors. * 1 out of 4 stars, ** 2 out of 4 stars.

was started and its effectiveness. In a retrospective series of 12 cases, Durand et al.[28] reported a statistically significant greater reduction in LM volume when sirolimus was started under 2 years of age, whereas Tole et al.[22] (N. 8) reported a statistically significant greater reduction in LM volume when sirolimus was started under 4 years of age. Individual data on age and MRI response was available for 24 patients; pooled analysis of individual patient data showed a significantly greater response to sirolimus initiated at or under 2 years of age ($p = 0.02$, Mann–Whitney-U test).

Adverse Events

Side effects were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) score which grades side effects 1–5, with grade 1 defined as mild self-limiting events, grade 3 as events needing hospitalization, and grade 5 as death.[34]

Patient-specific safety data was available for two out of three prospective studies[16,17]; Ozeki et al.[17] reported 2 grade 3 events out of N. 5 patients (1 upper respiratory tract infection, 1 cellulitis), and 1 grade 1 event (stomatitis). Zhang et al.[16] reported 1 grade 3 event out of N. 27 (lower respiratory tract infection) and 26 grade 1–2 events, with the most common being oral mucositis, respiratory tract infections, liver function test derangement, and hypercholesterolemia.

Out of 70 patients in the retrospective case series,[19–28] there were 40 episodes of grade 2 side effects, 3 episodes of grade 3 side effects and 2 episodes needing intensive care treatment (1 chest infection, 1 cellulitis). One death was reported shortly after starting sirolimus; the authors suggest this was due to the general poor and deteriorating condition of that patient even prior to commencing sirolimus.[25]

Sirolimus Dosing and Surveillance

Eleven case series[16–26] administered sirolimus at a starting dose of 0.8 mg/m^2 BD adjusted to maintain target trough levels under 15 ng/mL, whereas 1 study[28] used the same starting dose but with a maximum trough limit of 10 ng/mL. Zhang et al.[16] used a starting dose of 0.5 mg/m^2 for neonates but followed the above regimen for older children. Ozeki et al.[17] administered 1 mg once daily to children with body surface area (BSA) <1.0 m^2, and 2 mg once daily for BSA ≥ 1.0 m^2, with target trough levels of 5–15 ng/mL. Duration of sirolimus treatment ranged from 4 to 67 months, with patients who experienced a response continuing it for between a year and 2 years in most cases. Several studies[16,19,20] described symptom recurrence upon cessation of sirolimus, with a good response upon restarting it. Those studies that reported their surveillance regimen checked full blood count, renal profile, bone profile, hepatic profile, and sirolimus levels monthly.[16,28]

Antibiotic Prophylaxis

Out of the included studies, three[17,19,28] gave all patients trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis* (PJP). Out of the total of 33 patients in these studies, 4 patients had grade 3–4 events during treatment. Ten studies did not use prophylaxis; of these, only eight studies reported safety data.[16,20,21,23–27] Pooled analysis of this data showed 6 grade 3–4 events out of N. 80.

DISCUSSION

This systematic review collates the evidence to date for sirolimus therapy for pediatric cervicofacial LMs. Meta-analysis of studies which reported MRI assessment of LM response to sirolimus showed that 78% (95% CI 57%–94%) of patients experienced a reduction in volume of 20% or more, and 32% (95% CI 11%–57%) experienced a reduction of 50% or more. Further meta-analysis showed 97% (95% CI 88%–100%) of 78 patients (retrospective data) reported some degree of clinical improvement, ranging from reduced pain, to improved swallow and speech, or reduced infections and lymphatic ooze. This subjective improvement was reported even by patients with minimal change in LM volume radiologically or clinically. However, it is important to caution that this outcome measure was very subjectively assessed and open to reporting bias from both the patients and clinicians as no blinding was applied.

Regarding sirolimus' safety profile in the included studies (N. 102 patients), there were 40 episodes of grade 1–2 complications, that is, resolved spontaneously or with outpatient medical management. The most common were oral mucositis, transient alterations in liver function, and rashes. Six patients needed hospitalization during their sirolimus course and two needed intensive care. The majority of these children resumed sirolimus upon resolution of the acute illness.

The established therapeutic options for LMs are sclerotherapy, with a variety of sclerosants, alone or alongside surgical resection. The literature for surgical resection of LMs suggests a 13%–33% recurrence rate, with a risk of permanent nerve injury of between 2%–6%.[5,25,35] The authors comment on the difficulty of complete excision within the cervicofacial region due to the risks of hemorrhage or nerve injury. Sclerotherapy case series report success rates of 54%–97%[6,25]; of note, patients required between 1 and 23 sclerotherapy treatments. Overall reported complication rate is approximately 5%. It is clear, therefore, that approximately one third of LM patients have recurrence despite surgery or sclerotherapy; sirolimus is an important option for these refractory cases (the majority of patients in this review). In some case series in this review, sirolimus was offered before surgery or before surgery or sclerotherapy, with outcomes comparable to the efficacy rates above. Comparing safety profiles of the treatment options, sirolimus does have a high rate of self-limiting side effects; however, it does avoid the risk of permanent nerve injury.

One area of debate is whether sirolimus is more effective when started at a younger age. Two case series[22,28] reported a greater response when sirolimus was initiated in patients less than 2 or 4 years of age. Analysis of individual data for 24 patients in this review suggests a statistically significant better response in children aged 2 or less. By contrast, the largest prospective study in this review, with N. 27, reported no significant difference by age of initiation of sirolimus[16]; one possible explanation for these conflicting results might be the young mean age (2 years 3 months) of patients in the prospective study, with possible underrepresentation of older age groups to allow for meaningful comparison.

Sirolimus has been suggested to be of particular value in managing LMs that cause airway compromise, suggested to be due to its effect on the microcystic components[19,21] which are the most resistant to surgery and sclerotherapy.[6,25,35] Meta-analysis of study data showed 33% (95% CI 1%–78%) of N. 27 patients were successfully decannulated whereas undergoing sirolimus therapy alone or combined with surgery or sclerotherapy, with another 22% (95% CI 0%–61%) gaining the ability to tolerate capping or speaking valves. However, it is important to note the small numbers and the wide confidence intervals accompanying these results. Other factors are likely to have contributed to the successful decannulation, including natural airway enlargement due to patient growth. However, Triana et al. (2019)[24] in their case series of neonatal patients with ventilator dependence due to large LM, found that 6/7 were able to avoid tracheostomy and wean off ventilation after starting sirolimus, 4/7 on sirolimus monotherapy. Encouragingly, a recent case report describes the successful use of maternal sirolimus for 6 weeks pre-delivery, to reduce the bulk of a large cervicofacial LM detected on antenatal ultrasound sufficiently to allow for oral intubation.[36] In these two studies, no significant patient growth or concomitant therapies took place, suggesting sirolimus played a significant role in the observed airway improvements.

Safety of any new therapy in pediatrics is of primary concern. In the wider literature, there are two reported deaths of infants receiving sirolimus for Kaposiform haemangioendothelioma (KHE) with Kasabach-Merritt phenomenon (KMP).[37] The cause of death was an atypical pneumonia, specific pathogen not identified. A further case[38] is described of severe *Pneumocystis jirovocii* pneumonia (PJP) in an infant also receiving sirolimus for KHE with KMP, necessitating extracorporeal membrane oxygenation; however, in this instance, the infant recovered and resumed sirolimus with good effect for two more years. In these cases, the aggressive, high-mortality nature of KHE with KMP was thought to have contributed to the immune compromise and significant morbidity, possibly exacerbated in two of the cases by the use of concomitant steroids. None of these cases had received PJP prophylaxis during initial sirolimus therapy. A retrospective review[39] of serious adverse events (SAEs, defined as CTCAE grade 3 or above) in 113 children treated with sirolimus, across 7 centers in 4 countries, reported two deaths from viral pneumonia, and a third patient who recovered but required a weaning tracheostomy. Overall, there were 17 SAEs in 14 patients, with respiratory infection being the most common. Of note, the incidence of SAEs appeared to be independent of the dosing regime used, with the majority of patients falling within target range at time of the SAEs. Sirolimus therapy is not without risk, and regular monitoring of patients clinically and biochemically (sirolimus levels, full blood count, renal and hepatic function, and triglycerides) is essential.

Two prior systematic reviews of this topic[40,41] were broader in scope than this review, including all age ranges and anatomical locations. Given the greater refractory rate of cervicofacial LMs, and the complexities

of managing the pediatric airway affected by LM, this review is the first to focus exclusively on pediatric cervicofacial LMs and particularly the effects on airway. Moreover, it is the first to use meta-analysis to allow a more robust pooling of the small studies available for this rare condition. The greatest limitation of the review is its reliance on small case series with high risk of bias (all included studies were Oxford level of evidence[42] 4). There is no level of evidence for a systematic review of case studies. Further limitations include the variable use of sirolimus within series, with some including only patients with LMs refractory to conventional treatment, and others offering sirolimus earlier in the treatment algorithm. No genetic testing was reported. The secondary outcome (clinical improvement) was very subjectively assessed, relying on clinician and/or carer perceptions rather than a scoring system or measurement. There is variation also in the duration of treatment and of follow-up, with a number of patients requiring a year or more of treatment, and this would need to be candidly discussed with patients and carers when discussing sirolimus as a therapeutic option.

Further research is warranted to explore the role and effect of sirolimus in LMs. A multi-center, multinational collaborative would be needed to generate enough data for this rare condition, with pre-study consensus regarding quantifying the extent of microcystic disease (to allow pre-, post- and inter-patient comparison) and regarding measures of clinical improvement.

CONCLUSION

There is evidence for the efficacy of sirolimus in ameliorating symptoms and morbidities associated with cervicofacial pediatric LMs including refractory LMs, but the dataset contains significant heterogeneity and risk of bias. This meta-analysis found that 78% (95% CI 57%–94%) of patients had an objective reduction in LM volume by 20 percent or more, with a higher proportion of patients (97%, 95% CI 88%–100%) reporting some subjective clinical improvement. Sirolimus may be beneficial in reversing or avoiding tracheostomy due to LMs, and individual patient meta-analysis suggested greater effect of sirolimus on LMs when initiated under 2 years of age. Sirolimus therapy does carry risks of significant side effects; however, with careful clinical and biochemical monitoring of patients, there is sufficient clinical data to justify its use in infants and children with LMs refractory to conventional management.

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