Efficacy and safety of sirolimus in the treatment of vascular anomalies: A systematic review

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ABSTRACT

Objective: The management of vascular anomalies is complex and requires a multidisciplinary team with a combination of medical, surgical, and intervention treatments. Medical treatment is limited and has conflicting results. Off-label use of mammalian target of rapamycin inhibitors shows promising results. The objective of this study was to systematically evaluate the literature published about the efficacy and safety of sirolimus in the treatment of vascular anomalies.

Methods: A systematic review of the published literature was conducted using the PubMed database and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: There were 73 articles included: 2 randomized controlled studies, 2 nonrandomized prospective studies, and 69 retrospective case reports and case series. In total, 373 patients were included. Sirolimus was administered topically to 56 patients and orally to 317 patients. Sirolimus was highly effective in the treatment of vascular tumors associated with Kasabach-Merritt phenomenon (95.5% of the patients clinically improved and 93% had normalization of coagulopathy), venous malformations (size reduction was observed in 88.9% of patients), and lymphatic malformations (clinical improvement in 94.9% of patients). Topical sirolimus results were conflicting. Arteriovenous malformations were not improved by sirolimus.

Conclusions: Low-level evidence suggests that sirolimus can improve the prognosis of vascular anomalies, most notably vascular tumors associated with life-threatening coagulopathy and venous and lymphatic malformations. Further research is needed to establish the benefits of sirolimus in the management of vascular anomalies. (J Vasc Surg 2020;71:318-27.)

Keywords: Sirolimus; Vascular malformations; Vascular tumors; Vascular anomalies

Vascular anomalies are a heterogeneous group of rare vascular development disorders that include two broad categories: vascular tumors and vascular malformations.[1] Vascular tumors are characterized by increased neoplastic endothelial cell proliferation; vascular malformations result from errors in embryologic vasculogenesis involving capillaries, veins, arteries, lymphatics, or a combination of these.[2] Whereas vascular tumors may regress as the patient ages, vascular malformations increase in size and never regress on their own.[2,3] Accurate diagnosis is crucial for appropriate evaluation and management, often requiring multidisciplinary specialists. Classification schemes provide a consistent terminology and serve as a guide for pathologists, clinicians, and researchers.[2] The International Society for the Study of Vascular Anomalies classification was recently updated by the Society's Scientific Committee and Board at the last Assembly in Amsterdam, The Netherlands (May 2018).[1] Growth or expansion of vascular anomalies can cause clinical problems, such as disfigurement, chronic pain, recurrent infections, coagulopathies (thrombotic and hemorrhagic), organ dysfunction, and death. Individuals often experience progressive clinical symptoms with worsening quality of life. The management of vascular anomalies is difficult and challenging, given the broad spectrum and insufficient evidence from prospective clinical studies.

Somatic phosphatidylinositol 4,5-bisphospate 3-kinase, catalytic subunit alpha (PI3KCA) mutations are common in isolated lymphatic malformation, Klippel-Trénaunay syndrome, and other malformative syndromes.[4,5] The somatic mutations in the PI3K/mTOR pathway provide the molecular rationale for mammalian target of rapamycin (mTOR) inhibition treatment. The mTOR inhibitors, usually applied as immunosuppressive agents for preventing organ rejection in transplantation, have been used for vascular anomalies, given their antiproliferative and antiangiogenic and lymphangiogenic properties, with promising results.[6-8] Sirolimus inhibits mTOR, a serine-threonine kinase regulated by phosphoinositide 3-kinase (PI3K), which acts as a master switch in numerous cellular processes, such as cell growth and proliferation, cellular metabolism, autophagy, and angiogenesis and lymphangiogenesis. Off-label use of mTOR inhibitors was reported to be efficient

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in different types of vascular anomalies, with heterogeneous outcomes.

The objective of this study was to systematically evaluate the data published about the efficacy and safety of sirolimus in the treatment of vascular anomalies.

METHODS

Electronic databases were systematically searched for original articles referring to the use of sirolimus in vascular anomalies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for the systematic review design.[9]

Eligibility criteria. Inclusion criteria were all original reports (randomized controlled trial, prospective and retrospective case series, and case reports) describing treatment with sirolimus (topical or oral), alone or in association with other therapeutics, in any vascular anomaly (vascular tumors and vascular malformations), in humans, without age and sex restrictions. Duplicated publications, reports with insufficient information, and opinion and revision articles were excluded.

Study selection. Two authors (C.F. and V.F.) worked independently and identified all the eligible articles for further review by performing a screening of abstracts and titles according to the predefined criteria. Nonagreement in any article was discussed with a third author for the final decision.

Search strategy. The electronic database MEDLINE through PubMed was searched on July 27, 2018. The following search terms were used: (((((((("vascular"[All Fields] OR "arteries"[All Fields] OR "arterial"[All Fields] OR "capillaries"[MeSH Terms] OR "capillaries"[All Fields] OR "capillary"[All Fields] OR "veins"[MeSH Terms] OR "veins"[All Fields] OR "venous"[All Fields] OR "lymphatic"[All Fields] OR "arteries"[MeSH Terms] OR "arteriovenous")))) AND (("abnormalities"[All Fields] OR "anomalies"[All Fields] OR "malformations"[All Fields] OR "congenital abnormalities"[MeSH Terms] OR ("congenital"[All Fields] AND "abnormalities"[All Fields])))) OR ("vascular malformations"[MeSH Terms] OR ("vascular"[All Fields] AND "malformations"[All Fields]) OR "vascular malformations"[All Fields] OR"lymphatic abnormalities"[MeSH Terms] OR "vascular anomalies"[All Fields] OR "kasabach-merritt" OR "lymphedema" OR "lymphangioma" OR "hemangioendothelioma" OR "hemangioma" OR "low-flow malformation" OR "high-flow malformation"))))) AND (("sirolimus"[MeSH Terms] OR "sirolimus"[All Fields] OR "mTOR"[All Fields] OR "rapamycin"[All Fields] OR "rapalogs")).

Data extraction. Data were extracted to a Microsoft Excel spreadsheet database (Microsoft, Redmond, Wash). The data included publication metrics (name of first author, publication year and country), study design, type of vascular anomaly (using the classification system of the International Society for the Study of Vascular Anomalies, pathology complications), number of patients and characteristics of patients (sex, age, number and size of lesions), treatment information (sirolimus dose, blood level, cointerventions, treatment duration, adverse effects, efficacy), criteria used for clinical benefit, and follow-up.

RESULTS

In the initial database search, we identified 414 articles. After title and abstract reading by two reviewers (C.F. and V.F.), 84 studies were selected for full-text reading. After full-text reading, 73 studies were included for final analysis: 2 randomized controlled studies, 2 nonrandomized prospective studies, 22 case series, and 47 case reports (Fig). Topical sirolimus was studied in nine articles (two randomized controlled studies, one nonrandomized prospective study, three retrospective case series, and three case reports). Oral sirolimus was studied in 64 studies (1 nonrandomized prospective study, 19 retrospective case series, and 44 case reports). The flow diagram is detailed in the Fig. The distribution of study designs for each subtype of vascular anomaly and topical or oral sirolimus is detailed in Table I.

Characteristics of patients

The selected articles included a total of 373 patients: 162 patients with vascular tumors and 211 patients with vascular malformations. Vascular anomaly classification and epidemiologic data are detailed in Table II.

Treatment

Sirolimus was administered topically to 56 patients and orally to 317 patients. The median duration of treatment was 8.5 months (0.23-216.0 months). The time delay until first clinical response was reported in 56 patients. Of these, 35.7% had clinical response in <7 days, 64.3% in <14 days, and 75% in <21 days. Disease progression after suspension of sirolimus therapy was reported in 19 patients.

The dose level was available for 194 patients (81 patients with vascular tumors and 113 patients with vascular malformations). In the vascular tumors group, the most frequently prescribed doses were 0.8 mg/m^2 twice daily (43.2%), 5 mg/d (22.2%), and 0.05 mg/kg twice daily (13.6%). In the vascular malformations group, the dose most often prescribed was 0.8 mg/m^2 twice daily. In the pediatric patients (younger than 18 years), the most frequently prescribed dose schemes were 0.8 mg/m^2 twice daily (72.1%) and 0.05 mg/kg twice daily (9.1%). In the adult patients, the most frequently prescribed doses were 5 mg/d (62.1%) and 0.8 mg/m^2 twice daily (17.2%). Sirolimus blood levels were available for 178 patients (73 with vascular tumors and 105 with vascular malformations). In the vascular tumors group, the blood level goal ranges were most frequently 10 to 15 ng/mL (38.4%), 15 to 20 ng/mL (24.7%), and 5 to 15 ng/mL

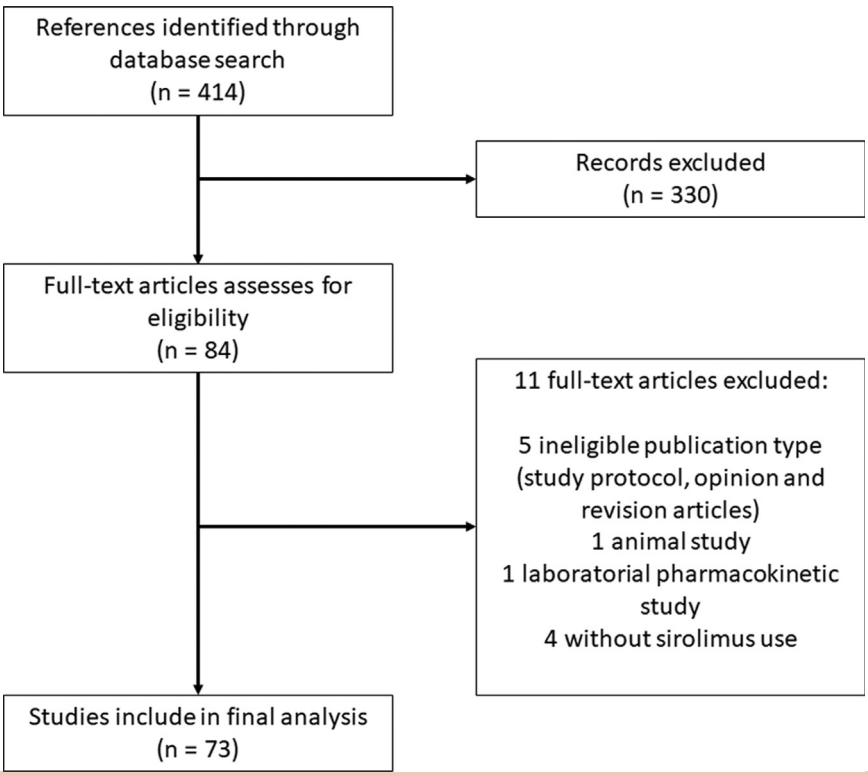

Fig. Flow chart of literature search results and details of included and excluded articles.

Table I. Description of studies included in the final analysis

	Randomized controlled studies	Prospective nonrandomized studies	Case series	Single case reports
Vascular malformations				
Oral sirolimus			7	20
Topical sirolimus	2	1	2	2
Vascular tumors				
Oral sirolimus			8	24
opical sirolimus				1
Malformations and tumors				
Oral sirolimus		1	4	
Topical sirolimus			1	

(15.1%). In the vascular malformations group, the target ranges were most frequently 5 to 15 ng/mL (43.8%) and 10 to 15 ng/mL (33.3%). In the pediatric patients, the blood level goal range was most frequently 10 to 15 ng/mL (38.3%) and 5 to 15 ng/mL (38.3%). In the adult patients, the blood level range was most frequently 15 to 20 ng/mL (62.1%) and 10 to 15 ng/mL (20.7%).

Regarding the systemic absorption of topically administered sirolimus, in one study of lymphatic malformations, sirolimus blood levels were undetectable or minimal (<0.25 ng/mL) in all patients at 1 week, 1 month, and 3 months of treatment.[10] In another study of capillary malformations, sirolimus blood levels were available in nine patients; sirolimus levels were below the lower limit of detection in seven patients, and two patients had detectable levels of 2.1 μg/L and 2.2 μg/L.[11]

Efficacy

Outcome definition and assessment of results were broadly heterogeneous among different studies, using a vast array of descriptive terminology. A systematic comparison of the results is not possible because of the inclusion of different pathologic processes in the same case series, with different clinical presentation and anatomic areas affected.

The largest case series, that of Triana et al,[12] included 41 patients with vascular tumors, arteriovenous malformations, lymphatic malformations, venous malformations,

Table II. Description of the patients included in the final analysis

Vascular tumors	
Total	162
Angiosarcoma	1
Epithelioid hemangioma	17
PHACE	1
Kaposiform hemangioendothelioma	121
Infantile hemangioma	2
PMH	1
PTEN hamartoma	1
Retiform hemangioendothelioma	1
Spindle cell hemangioma	1
Tufted angioma	8
Not specified	8
Oral sirolimus	158
Topical sirolimus	4
Median age	19 months
<12 months old	50%
<18 years old	80%
Male	52.0%
Female	48.0%
Vascular malformations	
Total	211
Arteriovenous	4
Venous	18
Lymphatic	108
Capillary	45
Capillary-venous-lymphatic	19
Venous-lymphatic	9
Others	8
Oral sirolimus	159
Topical sirolimus	52
Median age	12.8 years
<12 months old	10%
<18 years old	80%
Male	46%
Female	54%

PHACE, Posterior fossa malformations, hemangioma, cerebral arterial anomalies, cardiac defects, and eye anomalies; *PMH*, pseudomyogenic hemangioendothelioma.

and unknown vascular malformations; the overall successful response rate was 80.4% (33/41) of cases, presenting improvement in radiologic imaging and reduction in symptoms at a median time of 10 (1-16) weeks. No patients had a complete response. Eight had no response (four arteriovenous malformations, one Gorham-Stout disease, one lymphatic malformation, one kaposiform lymphangiomatosis, and one unknown vascular tumor), and four were lost to follow-up. In the case series of Ji et al[13] that included 52 patients with kaposiform hemangioendothelioma, 37 with Kasabach-Merritt phenomenon, 96% (50/52) and 98% (50/51) of patients experienced improvement in symptoms at 6 and 12 months; all Kasabach-Merritt phenomena resolved, and there were no Kasabach-Merritt phenomenon complications or deaths during follow-up. After 6 months of treatment, 75% reduction in tumor size evaluated by magnetic resonance imaging was achieved in 46% of patients at 6 months and 71% of patients at 12 months of follow-up. Notably, patients without Kasabach-Merritt phenomenon showed a less pronounced response compared with patients with Kasabach-Merritt phenomenon (95% confidence interval, 40.87-53.80; $P < .001$). Adams et al[14] included 61 patients with vascular malformations and vascular tumors and reported outcomes concerning radiologic evaluation, functional impairment score (clinical measurement of disease), and health-related quality of life. Quality of life was assessed by the Pediatric Quality of Life Inventory 4.0 (3-18 years) and Infant Scales (≤2 years) and the Functional Assessment of Chronic Illness Therapy system (>18 years). Of 57 patients who completed 6 courses of treatment, 47 (83%) had a partial response; and of 53 patients who completed 12 courses of treatment, 45 (85%) had a partial response. Three patients (5%) had stable disease at the end of 6 courses, and no patient had stable disease at the end of 12 courses. Seven patients (12%) had progressive disease by course 6 and eight (15%) by course 12. No patients experienced a complete response. Only one patient at the end of course 12 had progressive disease related to quality of life. Concerning radiologic evaluation, no patient had a complete response. At the end of course 6, only one patient (2%) had progressive disease, and no patients progressed at the end of course 12. At the end of course 6, 35% had a partial response; and at the end of course 12, 52% had a partial response. Stable disease was found in 63% at the end of course 6 and in 48% at the end of course 12. Two studies[15,16] reported results using the Response Evaluation Criteria in Solid Tumors classification.[17] Tan et al[15] included eight patients, with two compete responses, three partial responses, two very good partial responses, and one minimal response. Stacchiotti et al[16] included 18 patients with 6% partial response, 75% disease stabilization, and 19% disease progression. Wang et al,[18] in eight patients, reported resolution of Kasabach-Merritt phenomenon in all patients and >25% size reduction by ultrasound evaluation in all patients. In the case series of Strychowsky et al[19] with 19 lymphatic malformations, significant size reduction was reported in 4 patients, moderate size reduction in 3 patients, and modest size reduction in 12 patients; improvement of skin and mucosal vesicles was reported in 14 patients, and 2 patients were able to have the tracheostomy closed.

Vascular tumors

The searched literature identified 1 prospective nonrandomized trial and 35 retrospective case reports describing the effect of sirolimus on vascular tumors when it was administered orally.[12-16,20-49] Overall, 121 patients were diagnosed with kaposiform hemangioendothelioma, 17 with epithelioid hemangioma, 5 with tufted angioma, 1 with infantile hemangioma, 1 with angiosarcoma, 1 with infantile hemangioma associated with PHACE syndrome (posterior fossa malformations, hemangioma, cerebral arterial anomalies, cardiac defects, and eye anomalies), 1 with pseudomyogenic hemangioendothelioma, 1 with PTEN hamartoma, 1 with retiform hemangioendothelioma, and 1 with spindle cell hemangioma. The authors reported a decrease in lesion size in 90.1% of patients. Concerning kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon, 95.5% of the patients clinically improved and 93% had normalization of coagulopathy. Improvement was reported in an average of 13.7 days, and the mean follow-up was 13.4 months. Regarding epithelioid hemangioma (n = 17), clinical benefit was observed in 62.5% of patients.

Three retrospective studies described the benefits of topical sirolimus in the treatment of tufted angiomas.[10,50,51] A decrease in lesion size was reported for all patients, but no clinical benefit was described for the infantile hemangioma.

Vascular malformations

Capillary malformations. Four studies described topical sirolimus effect in the treatment of capillary malformations, and one study described oral sirolimus treatment.[11,52-55] In a phase 2, randomized, double-blind, placebo-controlled clinical trial by Marqués et al,[52] 23 patients tested topical sirolimus (1%) plus pulsed dye laser; the results suggested that topical sirolimus with pulsed dye laser was more effective than placebo or sirolimus alone or pulsed dye laser alone for the treatment of port-wine stains in patients with Sturge-Weber syndrome. Greveling et al[11] published a randomized controlled trial of 14 patients comparing pulsed dye laser, pulsed dye laser plus sirolimus, pulsed dye laser plus erbium:yttrium-aluminium-garnet laser plus sirolimus, and sirolimus monotherapy. The highest percentage skin clearance was achieved with pulsed dye laser alone, but there were no statistically significant differences between treatments. The dose of topical sirolimus used was 0.1%. Griffin et al[53] reported a single-patient study of topical sirolimus 0.5% and pulsed dye laser compared with retrospective previous treatments with laser alone, concluding that topical sirolimus showed significant improvement in color and texture of port-wine stains. Doh et al[54] evaluated the efficacy of 1% sirolimus plus pulsed dye laser. Three adjacent areas of cutaneous capillary malformation were selected in each patient and treated with pulsed dye laser, pulsed dye laser plus topical sirolimus for 1 week, and pulsed dye laser plus topical sirolimus for 8 weeks. Only six patients were included. There were no statistically significant differences in erythema and blanching rate among the treatments.

Skaro et al[55] published a clinical case of the regression of cutaneous and gastrointestinal telangiectasia and cessation of gastrointestinal bleeding with oral sirolimus, aspirin, tacrolimus, and liver transplantation in a patient with hereditary hemorrhagic telangiectasia.

Venous malformations. Ten case reports describe the effect of sirolimus orally for the treatment of venous malformations.[12,18,56-63] Efficacy was considered a nonspecified reduction in lesion size, which was observed in 88.9% of patients. The median age of patients in these reports was 12 years (1.4-23.0 years). Median follow-up was 24 months. Le Sage et al[10] described in their study that topical sirolimus for the treatment of verrucous venous malformation is not associated with any clinical benefit.

Lymphatic malformations. One prospective nonrandomized study and 17 retrospective studies described the treatment of lymphatic malformations with oral sirolimus.[14,19,26,32,41,48,56,61,64-73] The median age was 12.8 years (0-34 years); 20% of patients were younger than 1 year, and 90% were younger than 18 years. Nonspecified decrease in lesion size was reported in 77.8% patients, partial response in 22.2%, complete response in 3.7%, improvement of pleural effusion in 9.9%, decrease of skin exudate and vesicles in 16.5%, and improvement of pain in 4.9%. Disease progression was observed in 4.9%.

Three studies described the effect of topical sirolimus in the treatment of lymphatic malformations including seven patients in total.[10,74,75] One patient had no clinical benefit, four patients presented with decreased exudate, and two patients had a decrease in lesion size.

Combined vascular malformations

Capillary-lymphatic-venous malformation. One prospective nonrandomized study and three retrospective studies included 18 patients with capillary-lymphatic-venous malformation, with nonspecified reduction in lesion size in all patients.[14,48,61,76] The median age of the patients was 8.3 years (3.7-13.0 years). The median treatment duration was 16.5 months (12-27 months). Information about worsening or growth of the malformation after suspension of sirolimus was available in only two patients, with no recurrence after 6 months of suspension of treatment.

Lymphatic-venous malformation. One prospective nonrandomized study and five retrospective studies included nine patients with lymphatic-venous malformation.[14,41,61,77-79] Eight patients had a nonspecified reduction in lesion size and one had a complete response. The median age was 5.25 years (0.03-11.0 years). The median treatment duration was 1.1 year (0.4-4.4 years).

Arteriovenous malformations. Triana et al[12] included four patients with arteriovenous malformations in their retrospective series without any clinical benefit in any of the patients.

Other vascular anomalies. One patient with vascular anomaly associated with CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and skeletal deformities)[80] and one patient with PTEN-associated vascular anomaly were treated with sirolimus with partial response. One patient with unknown pancreatic vascular anomaly had no clinical response to sirolimus.[32]

Safety

The side effects most frequently reported were oral mucositis (31.9%), dyslipidemia (16.5%), leukopenia (12.3%), gastrointestinal symptoms (10.2%), and rash/eczema (8.2%).

Infectious complications were reported in 5.5% of patients with oral sirolimus treatment; two cases of fatal pulmonary infection developed in two patients (1 month and 6 months of age) with kaposiform hemangioendothelioma.[24] Prophylaxis with trimethoprim-sulfamethoxazole was reported in 29.4% of patients. Infectious complications were reported in 2.5% of patients under antibiotic prophylaxis compared with 5.2% of patients without prophylaxis.

Bias

Vascular anomalies are a heterogeneous group of pathologic processes with different levels of severity, which makes it difficult to define a "gold standard" treatment. The variability of the patients described in the different articles is therefore a limitation for statistical inference of clinical, radiologic, and laboratory benefit. Most studies available are retrospective reviews without control or adjustment for confounding variables. In 64 patients, there was no information about other treatments or therapeutics applied. In the studies that specify concomitant or previous therapeutics, 41.6% of patients received treatment with corticosteroids, 33% with chemotherapy (vincristine and others), 23% with surgery, 17% with embolization, 14.2% with interferon, 10.5% with propranolol, and 8.7% with radiation therapy, which limits any definitive considerations of the true effect of sirolimus treatment.

There is also the possible occurrence of publication bias. The systematic publication of studies with favorable results may interfere with the results of this review.

DISCUSSION

The treatment of vascular anomalies is complex and requires a multidisciplinary team with medical and surgical treatment capabilities. There is no consensus for management of these pathologic processes. Treatment frequently includes surgical excision and débridement, laser, sclerotherapy, and embolization; different schemes of medical therapy include aspirin, vincristine, propranolol, and sildenafil, with varying grades of efficacy. Treatment of vascular tumors is complex. The most frequent vascular tumors are the infantile hemangioma and congenital hemangioma, which most often regress spontaneously and do not require specific therapy. The standard treatment of the more aggressive vascular tumors, including kaposiform hemangioendothelioma complicated with Kasabach-Merritt phenomenon, is vincristine and prednisolone.[81] Small asymptomatic vascular malformations should be monitored, but lager symptomatic lesions warrant treatment as they can be associated with pain, recurrent infection, and compression of adjacent organs. Wiegand et al[82] published a systematic review in August 2018 that included 71 patients with lymphatic malformations, venous-lymphatic malformations, and capillary-lymphatic-venous malformations. Sirolimus led to a partial remission of disease in 60 patients, 3 patients had progressive disease, and the outcome of 8 patients was not reported.

In the articles evaluated in this review, there was broad heterogeneity in the definition of outcomes and the evaluation of clinical, hematologic, and radiologic response. Systematic evaluation of outcomes is limited by the broad clinical manifestations of the diverse disease processes of the different vascular anomalies and the anatomic area affected.

In vascular tumor patients, sirolimus treatment was associated with clinical benefit in 90.1% of patients. Considering kaposiform hemangioendothelioma with life-threatening Kasabach-Merritt phenomenon, sirolimus was associated with resolution of coagulopathy in 93% of patients. Improvement was noted on average in 13.7 days. Consensus treatment guidelines from a multidisciplinary expert panel recommend corticosteroids and vincristine for first-line treatment of kaposiform hemangioendothelioma and tufted angioma.[81,83] Further research if needed to establish whether the association with sirolimus in combination with vincristine and corticosteroids improves results. Three clinical trials are in progress (ClinicalTrials.gov identifier: NCT03188068, NCT02110069, and NCT00975819).

In the treatment of capillary malformations, there is conflicting evidence of the benefit of topical sirolimus. One randomized controlled trial reported improved results with sirolimus plus laser. Another randomized controlled trial reported the highest percentage of skin clearance with pulsed dye laser alone.

Regarding venous malformations, sirolimus was associated with clinical benefit in most patients, with lesion size decrease in 88.9% of patients. Concerning lymphatic anomalies, oral sirolimus treatment was associated with clinical benefit in 94.9% of patients with decrease of lesion size. The results with topical sirolimus in these lesions are scarce and conflicting. In the mixed vascular malformation group, including capillary-lymphatic-venous

malformations and lymphatic-venous malformations, clinical benefit was observed in most patients. In contrast, the limited data available for arteriovenous malformations did not show any benefit of sirolimus treatment.

The duration of treatment is not well established, with a wide range of values in the data available (0.23-216.0 months). Recurrence or progression of disease was reported in 19 patients after sirolimus suspension. Further research is needed to establish the long-term benefits of sirolimus treatment. The first clinical improvement was observed in <7 days in 35.7% of patients, <14 days in 64.3% of patients, and <21 days in 75% of patients.

Safety is a major concern in the treatment of vascular anomalies as most patients require long-term treatment and are most often of pediatric age. The off-label use of sirolimus requires a thoughtful risk-benefit analysis and careful follow-up and report of possible effects. The most frequent side effects were oral mucositis, dyslipidemia, leukopenia, gastrointestinal symptoms, and cutaneous reaction. Infectious complications are a major concern, and there were two cases of fatal pulmonary infection associated with sirolimus used in the treatment of vascular anomalies. Antibiotic prophylaxis with trimethoprim-sulfamethoxazole is advocated by some authors, and in this review, the incidence of infection was 2.5% with prophylaxis compared with 5.2% in patients without prophylaxis. Further research is needed to establish the benefit of antibiotic prophylaxis. Thrombocytopenia is one of the side effects of sulfamethoxazole-trimethoprim, and its use in patients with coagulopathy associated with a vascular anomaly requires precaution.

Dose and blood level measurements were not uniformly reported among the studies found. The dose most often prescribed was 0.8 mg/m^2 twice daily in the pediatric patient (72.1%) and 5 mg/d in the adult patient (62.1%). In a model-based study, including data of 52 pediatric patients with vascular anomalies, the mean sirolimus dose to achieve the target of ~10 ng/mL for patients older than 2 years was 1.8 mg/m^2 twice daily (range, 0.8-2.9 mg/m^2), whereas it was 0.7 to 1.6 mg/m^2 twice daily for patients aged 3 weeks to 2 years.[84]

Because of the variety of anomalies included and the use of older nomenclature, the systematic data analysis is limited. Accurate classification is crucial for appropriate treatment of vascular anomalies. Multiple medical and surgical treatments are frequent, and there was no information about concomitant or previous treatments in 64 patients included. Further randomized controlled studies are required to establish the efficacy of sirolimus and the long-term adverse effects and to clarify which type of vascular anomalies benefit. At the moment, several clinical trials are recruiting patients to clarify these questions.

CONCLUSIONS

There is compelling low-level evidence that sirolimus can improve the prognosis of vascular anomalies, most notably vascular tumors associated with life-threatening coagulopathy and venous and lymphatic malformations. Further research is needed with randomized controlled studies to establish the benefits of off-label use of sirolimus in these complex pathologic processes.

AUTHOR CONTRIBUTIONS

Conception and design: CF, VF, JM, RA, DC, MR, JC, JF
Analysis and interpretation: CF, VF, JM, RA, DC, MR, JC, JF
Data collection: CF, VF
Writing the article: CF, VF
Critical revision of the article: CF, VF, JM, RA, DC, MR, JC, JF
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CF and VF contributed equally to this article and share co-first authorship.

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