Infectious Complications of Vascular Anomalies Treated with Sirolimus: A Systematic Review

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September 25, 2023

Abstract

Background and Objectives: Initially developed as immunosuppressive agents, mTOR inhibitors are currently used widely in the management of vascular malformations and tumors. The incidence of infectious complications in the vascular anomalies (VA) population is not well defined. The goal of this systematic review was to better define the types and severity of reported infectious complications in patients with VAs treated with mTOR inhibition. Methods: This was a systematic review conducted following PRISMA guidelines evaluating all research articles focused on infectious complications in patients with VAs treated with sirolimus or everolimus. Thirty articles including 1181 total patients and 315 infections (in 290 unique patients) were ultimately included. Results: The majority of infections were viral upper respiratory (n=137, 54%), followed by pneumonia (n=52, 20%), and cutaneous infections (n=20, 8%). There were 6 total infection-related fatalities, which all occurred in patients younger than 2 years. Only 1 case of *Pneumocystis jirovecii* pneumonia (PJP) was reported. This was in an infant with KHE who was also treated with steroids and did not receive PJP prophylaxis. Almost 1/3 (n=95, 32%) of infectious complications were graded 3 to 4 according to CTCAE criteria. Details of patient age, subtype of VA, and timing of infection were lacking from many reports. Conclusions: Most infectious complications reported in patients with VA on mTOR inhibitors were viral respiratory infections and non-severe. Bacteremia, infectious fatalities, and PJP are exceedingly rare. Future studies are needed to clarify the spectrum of infectious risks in VA patients and to provide guidance for infection prevention.

INTRODUCTION

Vascular anomalies (VAs) are a collection of rare disorders resulting from abnormal development, structure, and function of the vasculature.[1-3] VAs can cause pain, coagulopathy, disability, and disfigurement,[4-8] and some VAs are associated with overgrowth of bone, muscle, or fatty tissue.[1,4] In 2011, Hammill, et al. published the first report of successful treatment of complicated VAs with sirolimus, an inhibitor of mammalian target of rapamycin (mTOR).[9]Following this study, several clinical trials and case series have demonstrated the efficacy of sirolimus in treating certain types of VAs, especially VAs with lymphatic components.[10-13] As a result, sirolimus has become a central component of treatment strategies for VAs.[14,15]

Many VAs are driven by post-zygotic, somatic variants of genes in the mTOR pathway, especially PIK3CA and TEK.[3] The mTOR pathway controls cell proliferation, adhesion, migration, metabolism, and survival.[16] Gain of function variants in this pathway can lead to overgrowth of veins, capillaries, and lymphatic vessels that constitute VAs. The mTOR pathway is also integral to the immune response, and mTOR inhibitors were initially developed and continue to be used primarily as immunosuppressant agents.[17] Likely as a result

of this immunosuppressive effect, some patients with VAs treated with sirolimus have developed serious infections.[18] However, the reported rates of infections across studies have varied widely, from 16%[19] to 42%.[20] Because of the known inhibitor effect on T cell function, many centers also advocate for *Pneumocystis jirovecii* prophylaxis while taking the agent. Clinicians must determine which patients might be at higher risk of serious infections, how to respond to symptoms of infection in these patients, whether patients require antibiotic prophylaxis, and how to counsel patients about the potential risks of taking sirolimus. To date, no systematic review has assessed the types and severity of reported infectious complications in patients with VAs treated with sirolimus. In this systematic review, we describe all reported infectious complications of sirolimus in patients with VAs to provide evidence to guide clinical decisions.

METHODS

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting results,[21] posing the question: "What are the reported infectious complications of mTOR inhibitors when used to treat VAs?" We did not register this review protocol.

Inclusion and Exclusion Criteria

This review is inclusive of all research articles presenting original data that reported infectious complications of mTOR inhibitors (sirolimus/rapamycin or everolimus) in the treatment of VAs. We did not restrict inclusion based on the year of publication. For inclusion, patients reported in the study had to have (1) been diagnosed with a VA, (2) received sirolimus or everolimus, and (3) had a reported infectious complication. Exclusion criteria included articles that (1) did not report original data (e.g. review articles and commentaries), (2) did not report infections, (3) were not available in English, or (4) were abstracts, trial protocols, or dissertations. We included studies of both children and adults with VAs.

Search Strategy

A medical librarian (LHY) searched the literature for records including the concepts of VAs, sirolimus, rapamycin, everolimus, and infection. This search strategy included broad categories (e.g. vascular anomaly, vascular malformation, vascular tumor), types of VAs (e.g. hemangioma, lymphatic malformation, hemangioendothelioma), and syndromes (e.g. CLOVES, Sturge-Weber Syndrome, Klippel-Trenaunay Syndrome). We included disorders listed in the International Society for the Study of Vascular Anomalies classification of vascular anomalies. The librarian created search strategies using a combination of keywords and controlled vocabulary in Embase.com 1947- , Ovid Medline 1946- , Scopus 1823- , and Cochrane Central Register of Controlled Trials (CENTRAL). All search strategies were completed November 11, 2022 with no added limits. Book chapters, conference papers, editorials, and systematic reviews were removed when possible. A total of 3,874 results were found. 302 duplicate records were deleted after using the de-duplication processes described in "De-duplication of database search results for systematic reviews in EndNote,"[22] resulting in a total of 3,572 unique citations included in the project library. Fully reproducible search strategies for each database can be found in Appendix 1.

Screening and Data Abstraction

We utilized Covidence® web-based systematic review software for screening the studies. All screenings were performed in duplicate, and any disagreements were reconciled through group discussion. Four authors (BAS, EG, RMK, and CB) and one additional staff member collaboratively screened the studies in a two-stage format. First, RMK and EG screened titles and abstracts. In this stage, only studies that included patients with VAs treated with an mTOR inhibitor were accepted. Second, RMK, EG, CB, and another staff member completed a full text review to confirm that included studies reported on infections in this population. In this stage, we indicated reasons for exclusion based on the following: duplicates, wrong intervention, wrong study design or publication type, infection not reported, wrong patient population, or text unavailable in English. We only included studies that explicitly reported infections, because the absence of reporting infections does not necessarily mean that patients did not experience infections. It is possible that case reports or case series

failed to report infections if this was not the focus of their report, or if the infection was minor. At the end of screening, all eligible studies were reviewed by BAS, a pediatric hematologist oncologist with expertise in treating VAs. Two authors (BAS and CB) abstracted data in duplicate from all included studies, reviewed the other's abstraction, and resolved differences through discussion.

Critical Appraisal

One author (SCC) performed critical appraisal of all included studies using JBI Research Institute critical appraisal checklists for randomized controlled trials, quasi-experimental studies, cohort studies, case series, and case reports.[23] We chose this collection of critical appraisal tools because it included checklists for the variety of study designs included in this review.

RESULTS

Study Characteristics

Our initial search yielded 3572 unique articles. Exclusions related to irrelevant content (n=3196), wrong patient population (n=125), infection not mentioned (n=113), wrong study design (n=64), wrong intervention (n=33), or text unavailable in English (n=11) (Figure 1). Thirty remaining studies were evaluated, of which most were case series or retrospective chart reviews (n=17, 57%). Studies were reported from geographically diverse populations, including 11 studies from Europe (37%), 9 studies from China (30%), and 7 studies from North America (24%) (Table 1). See Supplemental Table S1 for full details of each included study.

Patient Characteristics

These 30 studies reported on 1181 total patients, of which 290 patients had a total of 315 infections. Of note, one study only listed the number of infections without specifying whether any patient had more than one infection, so we counted each infection in this study as a unique patient to avoid underestimating the number of patients experiencing infections.[24] Patients in all included studies received sirolimus. Many studies lacked sufficient detail to determine key demographics of patients with infections. For example, age was not specified in 237/290 patients (82%). The remainder were younger than 1 year (n=16, 5%), 2 to 17 years (n=28, 10%), or older than 18 years (n=9, 3%). Similarly, sex was not specified for 268/290 patients (n=92%). The remainder were male (n=14, 5%) and female (n=8, 3%). Similarly, these studies lacked granular detail about the sites of VA disease (not specified in 83%) and whether sirolimus was held during infections (not specified in 81%). Patients with infections for whom they type of VA was reported (n=121/290) had a wide variety of VAs, with slow flow vascular malformations (n=60, 50%) and kaposiform hemangioendothelioma (KHE)/tufted angioma (n=24, 20%) most commonly reported. Given the limited granular reporting, 58% of participants did not have a specific VA diagnoses listed and instead were aggregated into the category "multiple VAs" (Table 2).

Infection Characteristics

The type of infection was reported for 81% of infections (n=255/315). Of these, most infections were reported as upper respiratory infections or "viral infections" (n=137, 54%), followed by pneumonia (n=52, 20%), and cutaneous infections (n=20, 8%). Within the pneumonia category, one patient was reported to have*Pneumocystis jirovecii*pneumonia (PJP).[25] This patient was 4 months old with a diagnosis of KHE with Kasabach-Merritt Phenomenon (KMP), receiving treatment with sirolimus at 0.05 mg/kg per dose twice a day with a trough goal of 8 to 15 ng/mL. At 2 months of age, this patient was treated with vincristine, prednisolone, and propranolol. At 3 months of age, the patient discontinued vincristine and propranolol, started sirolimus, and began a steroid wean. Four weeks after initiation of sirolimus therapy, the patient developed PJP. Sirolimus was temporarily held, and the pneumonia was treated successfully with sulfamethoxazole-trimethoprim and methylprednisolone. Notably, this patient had not received PJP prophylaxis. Four cases of bacteremia (1%) were reported. Common Terminology Criteria for Adverse Events (CTCAE) grading was reported for 91% of infections. Most infections were grade 1 to 2 (n=194, 66%), and 32% (n=95) were grade 3 to 4. Six patients (n=2%) had grade 5 infections (i.e., they died as a result of infection). Most patients

received antibiotic prophylaxis against PJP (n=175, 80%), while 42 (19%) did not receive prophylaxis. Of note, prophylaxis was not specified for 73 patients.

Characteristics of Fatal Infections

Six infectious deaths were reported in patients with VAs receiving sirolimus (Table 3). One patient received PJP prophylaxis, one did not, and 4 studies did not report prophylaxis status. All of these patients were 2 years or younger, and 5/6 patients were infants (< 12 months of age). Four patients had KHE with KMP, one patient had microcystic lymphatic malformation, and one patient had generalized lymphatic anomaly (GLA). These fatal infections occurred within 2 months of starting sirolimus in 4/6 cases. Five of these deaths resulted from pneumonia and one case did not specify the type of infection. One patient with viral pneumonia also had ileitis. The responsible pathogens included viral (adenovirus, metapneumovirus), bacterial (*Mycoplasma*), and unknown pathogens. Sirolimus was held at the time of infection in all cases. Co-administered steroids were not specified in 3/6 cases. Two patients were weaning off steroids at the time of the infection, and one patient did not receive any steroids. Deaths occurred 4 to 11 days after onset of infection. Further information on possible comorbidities was not reported.

Characteristics of Bacteremia Infections

Bacteremia was reported in 4 patients: 2 patients had KHE, 1 patient had a slow flow vascular malformation, and 1 patient did not have their disease specified in the manuscript (Table 4). Two of these patients had central lines, and 2 did not have central lines. One central line infection was caused by *Staphylococcus epidermidis* . The other central line infection did not specify the pathogen. For the two patients without central lines who developed bacteremia, one patient had methicillin-resistant *Staphylococcus aureus* and the other patient had *Pseudomonas aeruginosa* . These studies did not report whether the patients had other comorbidities or whether they were receiving concomitant immunosuppression, such as steroids.

Critical Appraisal

The most common deficiencies in reporting related to granularity of demographics and disease characteristics (Supplemental Table S2). Only 1 study specifically focused on reporting infectious complications, and this study provided granular details for characteristics of each infection (n= 12 patients and 15 infections). The remaining 29 studies aimed to report clinical outcomes of sirolimus treatment, and they provided less detail about infections. For example, fewer than 20% of studies reported the following characteristics specific to the participants with infections: age, sex, sites of VA disease, and whether sirolimus was held.

Discussion

In this systematic review, we identified 315 infections in 290 patients with VAs undergoing treatment with sirolimus. Notably, serious infections, infection-related deaths, bacteremia, and PJP were infrequent. The vast majority of infections were respiratory infections, with 54% upper respiratory infections and 20% pneumonias. Overall, 25% of all patients reported in evaluable studies had an infection reported, and fewer than 10% of all reported patients had serious adverse events related to infections (CTCAE grade 3 or greater). Furthermore, it is unclear how many of these infections were attributable to sirolimus. For example, 54% of infections were upper respiratory viral illnesses. While sirolimus could theoretically increase the risk of developing these viral infections, such infections are also common in the general pediatric and adult population. Furthermore, cutaneous infections (or inflammation mimicking cutaneous infections) often occur on the skin overlying vascular malformations, and sirolimus is used to decrease the frequency of these flares.[26] As such, the 20 reported cutaneous infections could be related to the underlying VA, rather than as a result of sirolimus' immunosuppressive effects, and they might not actually represent infections.

All reported fatalities occurred in children 2 years of age or younger, and were most common in infants and related to pulmonary infection. These deaths generally occurred within 2 months of starting sirolimus. Furthermore, the majority of these deaths occurred in infants with KHE who also had KMP, a consumptive coagulopathy.[4] While these findings could underrepresent the true frequency of infection-related fatalities due

to insufficient reporting, they suggest that death is very infrequent, and infants with KMP or other complications are most at risk. Furthermore, they suggest that clinicians should maintain vigilance for respiratory infections and pneumonia in patients treated with sirolimus. These data also leave several questions unanswered. Future studies should address whether patients with KHE have a higher risk of infectious complications with sirolimus usage, whether concomitant steroid usage is a significant risk factor, and whether patients are at a higher risk of serious infectious complications soon after initiating sirolimus therapy. Furthermore, studies should evaluate whether KMP or other complications represent a selected patient population that is at increased risk of infection due to comorbidities.

Bacteremia was a very uncommon infectious complication. Of all 1181 patients reported in these studies, 0.2% of patients developed bacteremia. Furthermore, bacteremia accounted for 0.6% (4/315) of infections ever reported in this literature. Of these 4 cases, 2 patients had central lines that served as a likely nidus for infection. For the remaining 2 patients, there was no clear source of the infection reported in the studies. For patients without a central line, these data suggest that bacteremia is a rare occurrence and these patients do not routinely require blood cultures and antibiotics with febrile episodes. Patients with a central line, however, should continue to be evaluated for central line associated bacteremia with fevers, as is standard of care for all patients with an indwelling central catheter.

We only identified one patient who developed PJP while receiving sirolimus (0.08% of 1181 total patients reported in these studies), and this patient was an infant with KHE and KMP who was weaning off steroids. Steroids alone in infants can increase the risk of PJP, thus warranting PJP prophylaxis in this patient.[27,28] As such, PJP is an extremely rare event for patients with VAs receiving sirolimus. Although many patients in these studies likely received PJP prophylaxis, our findings should encourage a re-evaluation of the risks and benefits of PJP prophylaxis. Given the documented PJP in an infant, it would be reasonable to encourage prophylaxis for infants with VAs receiving sirolimus, especially if they have complicating factors like steroid treatment, KMP, or other comorbidities. However, these data suggest that PJP prophylaxis might not be warranted for many patients with VAs receiving sirolimus without significant comorbidities or concomitant immunosuppression. Future multicenter studies should aim to assess the incidence and risk factors of PJP using retrospective cohort studies, informatics queries, or claims data to better guide prophylaxis decisions.

This study should be interpreted in light of limitations. First, we excluded abstracts to avoid incomplete data or duplication with subsequent publications. However, abstracts could have contributed additional evidence of infectious complications. Furthermore, the frequency of published reports of infections does not necessarily represent the clinical experience with infections in this patient population. Reporting bias could result from either increased reporting of infections (overestimation) or decreased reporting of infections (underestimation). Furthermore, several key characteristics of infections were omitted from included studies. As such, we are limited in our ability to generate hypotheses about which patient characteristics might place patients at higher risk of infectious complications.

CONCLUSION

Sirolimus has become a mainstay of treatment for patients with VAs, and many patients receiving sirolimus for VAs have also been reported to develop infectious complications. Although most infections were minor, one-third of reported infections were serious. However, reports of bacteremia and infectious fatalities are exceedingly rare, and only 1 episode of PJP has been reported in this patient population. In the future, multicenter studies should aim to further characterize the infectious complications of sirolimus for treatment of VAs. This future work will be essential to provide guidance to clinicians and families on how to best monitor and manage these patients.

CONFLICT OF INTEREST STATEMENT –

Dr. Sisk serves as a consultant for Novartis pharmaceuticals. Otherwise, the authors do not have any conflicts of interest pertinent to the current study.

ACKNOWLEDGEMENTS –

N/A

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Tables and Figures

Table 1. Study Characteristics

Table 2. Patient and Infection Characteristics

Table 3. Characteristics of Fatal Infections (n=5)

Table 4. Characteristics of Patients with Bacteremia

Figure 1. PRISMA Flow Diagram

Table 1. Study Characteristics

Study Characteristic (n=30)	**n (%)**
Study Design	

Study Characteristic (n=30)	**n (%)**
Randomized Controlled Trial	1 (4)
Randomized Observational Phase Trial	1 (4)
Non-Randomized Experimental Study	4 (13)
Cohort Study	3 (9)
Case Series / Retrospective Chart Review	17 (57)
Case Report	4 (13)
Country	
China	9 (30)
Europe	11 (37)
North America	7 (24)
Europe and North America	1 (3)
Japan	1 (3)
Middle East	1 (3)

Table 2. Patient and Infection Characteristics

Patient Characteristics (n=290)	**n (%)**	
Types of Vascular Anomalies	**Types of Vascular Anomalies**	**Types of Vascul**
Vascular Tumors		
KHE/Tufted Angioma [a]	24 (8)	
Epithelioid Hemangioendothelioma	8 (3)	
Vascular Malformations		
Complex Lymphatic Anomaly [b]	7 (2)	
PIK3CA-Related Overgrowth Spectrum	18 (6)	
Slow Flow Vascular Malformation	60 (21)	
Arteriovenous Malformation	3 (1)	
Blue Rubber Bleb Nevus Syndrome	1 (<1)	
Multiple Vascular Anomalies	169 (58)	
Type of Infection [c] (n=315 total infections)	**Type of Infection [c] (n=315 total infections)**	**Type of Infectio**
Upper Respiratory Infection / "Viral Infection" [d]	137 (54)	
Pneumonia [e]	52 (20)	
Cutaneous Infection	20 (8)	
Gastroenteritis	14 (5)	
Urinary Tract Infection/Pyelonephritis	7 (3)	
Lymph Gland Infection	11 (4)	
Bacteremia	4 (1)	
Osteomyelitis/Septic Arthritis	3 (1)	
Meningitis	2 (<1)	
Herpes Reactivation	2 (<1)	
Infectious thrombophlebitis	1 (<1)	
Culture Negative Sepsis	1 (<1)	
CMV	1 (<1)	
CTCAE Grade of Infections [f]	**CTCAE Grade of Infections [f]**	
1 to 2	194 (66)	
3 to 4	95 (32)	
5	6 (2)	
Sirolimus Trough (Target or Actual) [g]	**Sirolimus Trough (Target or Actual) [g]**	
2 to 5	21 (9)	
5 to 10	49 (20)	

Patient Characteristics (n=290)	**n (%)**
5 to 15	5 (2)
10 to 15	159 (65)
>15	11 (4)
Antibiotic Prophylaxis [h]	**Antibiotic Prophylaxis [h]**
Penicillin	1 (<1)
PJP Prophylaxis	175 (80)
None	42 (19)

Abbreviations: KHE, kaposiform hemangioendothelioma; CMV, cytomegalovirus; PJP,*pneumocystis jirovecii* pneumonia. [a] In KHE category, 11 patients with Kasabach Merrit Phenomenon (KMP), 12 patients in which KMP was not specified, and 1 patient with Tufted Angioma.[b] In Complex Lymphatic Anomaly category, 4 patients with Generalized Lymphangiomatosis, 2 patients with Gorham Stout Disease, and 1 patient with Central Conducting Lymphatic Anomaly.[c]More than one infection was noted for some patients, so number of infections exceeds number of reported patients. Additionally, the type of infection was not specified for 60 patients.[d] URI/"Viral Infections" includes reported cases of Flu and COVID-19. [e] Pneumonia category includes 5 bacterial pathogens (including 1 *pneumocystis jirovecii* pneumonia), 8 viral pathogens, and 39 unspecified pathogens.[f] Grade of infection was not reported for 20 infections. [g] While some reported actual trough prior to infection, the vast majority of studies reported the goal range of troughs maintained during treatment. Of note, 16 participants counted in the "2 to 5" range were actually reported at "2 to 6". Similarly, in the "5 to 10" range, 25 were actually reported as "4 to 12" and 8 were reported as "4 to 13". Sirolimus dosing was not specified for 45 patients. [h] Antibiotic prophylaxis was not specified for 72 patients.

Table 3. Characteristics of Fatal Infections (n=5)

Study	**Age**	**Sex**	**Type of Vascular Anomaly**	**Location of Vascular Anomaly**	**Type of Infection**	**Co-Administered Steroids**	**Sirolimus dose, trough, or target trough**	**Duration of Infection before Death**	**Time after starting sirolimus**
Wang, Z. et al. (2019).[29]	6 months	Male	Multifocal KHE with KMP	Right shoulder, chest, lung, right axilla, chylothorax	N.S.	N.S.	N.S.	N.S.	N.S.
Wang, Y. et al. (2020).[30]	1 month	Male	KHE with KMP	Right neck	Bacterial vs fungal pneumonia	Steroid wean	0.7 mg/m2/d, q12 hours	8 days	2 weeks
Rossler, J. et al. (2021).[18]	3 months	N.S.	Microcystic LM	Face	Viral pneumonia - metapneumovirus	N.S.	6.9 ng/ml	4 days	2 months

Study	Age	Sex	Type of Vascular Anomaly	Location of Vascular Anomaly	Type of Infection	Co-Administered Steroids	Sirolimus dose, trough, or target trough	Duration of Infection before Death	Time after starting sirolimus
	2 years	N.S.	GLA	Lung, bowel, spleen	Viral pneumonia and ileitis – adenovirus	N.S.	8 ng/ml	6 days	24 months
Ying, H. et al. (2018).[31]	3 months	Female	KHE with KMP	Face	Pneumonia – unknown pathogen	No	0.1 mg/kg	10 days	2 months
	6 months	Male	KHE with KMP	Forearm	Pneumonia – mycoplasma	Steroid wean	0.1 mg/kg	11 days	1.5 months

Abbreviations: KHE, kaposiform hemangioendothelioma; KMP, Kasabach Merrit Phenomenon; PJP,*pneumocystis jirovecii* pneumonia; GLA, generalized lymphatic anomaly; LM, lymphatic malformation; TMP-SMX, trimethoprim-sulfamethoxazole; PCN, penicillin; N.S., not specified.[a] In KHE category, 11 patients with), Note – Sirolimus was held in all cases.

Table 4. Characteristics of Patients with Bacteremia

Study	Age [a]	Type of Vascular Anomaly	Location of Vascular Anomaly
Hammill 2011[9]	10 months old	KHE with KMP	Abdomen, back, chest, left leg, pelvis, retroperitone
Rossler 2021[18]	2 years old	KHE	Retroperitoneal with mediastinal extension
Sandbank 2019[32]	N.S.	N.S.	N.S.
Maruani 2021[20]	N.S.	Slow flow vascular malformation	N.S.

KHE, kaposiform hemangioendothelioma; KMP, Kasabach Merrit Phenomenon; PJP, *pneumocystis jirovecii* pneumonia; N.S., not specified; MRSA, methicillin-resistant *staphylococcus aureus* . [a]Hamill et al. reported age at start of treatment, rather than age at time of infection. Rossler et al. reported age at time of diagnosis. The patient described in Hammill et al. was female. Other studies did not report sex of affected patient.