REVIEW ARTICLE

TREATMENT OF VASCULAR ANOMALIES WITH SIROLIMUS: AN UPDATED COMPREHENSIVE REVIEW

Paulo Miguel Santos*[1], Luís Loureiro[1,2], Andreia Pinelo[2]; Rui Machado[1,2]

[1] Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto (ICBAS-UP), Porto, Portugal
[2] Centro Hospitalar e Universitário de Santo António, Unidade Local de Saúde de Santo António, EPE, Porto, Portugal

* **Corresponding author:** up202006554@up.pt

Abstract

Background: *Sirolimus, an mTOR inhibitor, has transformed the management of complex slow-flow vascular malformations (VAMs), particularly those driven by PI3K/AKT/mTOR pathway activation. Evidence from prospective trials and real-world cohorts supports its use in venous, lymphatic and combined malformations, as well as in PIK3CA-related overgrowth spectrum (PROS) and PTEN hamartoma tumor syndrome (PHTS). However, sirolimus shows poor or absent benefit in fast-flow lesions such as arteriovenous malformations (AVMs).*

Methods: *This narrative review of the recent literature (2020–2025) was performed using PubMed, focusing on molecular mechanisms, clinical efficacy, safety, quality of life, therapeutic drug monitoring (TDM) and cost-utility of sirolimus in vascular anomalies.*

Results: *Sirolimus demonstrates high response rates in slow-flow malformations, with partial responses in approximately 60–85% of patients and clinically meaningful improvements in health-related quality of life (HRQoL). Lower trough levels (4–10 ng/mL) provide comparable efficacy with reduced toxicity. Adverse effects include oral mucositis, dyslipidaemia, fatigue and infections. In contrast, fast-flow malformations show negligible benefit, consistent with their distinct genetic architecture, which predominantly activates RAS/MAPK rather than PI3K/AKT/mTOR signalling.*

Conclusions: *Sirolimus is an effective targeted therapy for refractory slow-flow vascular malformations but should not be considered a universal treatment for all vascular anomalies. Future directions include molecularly guided therapy, rational combination regimens and integration with PI3K- and AKT-directed agents.*

Keywords: *sirolimus (MeSH), vascular anomalies (MeSH), immunosuppressive agents/adverse effects (MeSH); vascular malformations (MeSH); quality of life (MeSH.*

INTRODUCTION

Vascular anomalies comprise a heterogeneous group of congenital disorders of vascular development. The most recent ISSVA classification (2025) divides these into vascular tumours, vascular malformations and "Potentially Unique Vascular Anomalies" (PUVA), reflecting advances in clinical and molecular characterisation[(1)]. Among vascular malformations, the biological and therapeutical critically important distinction is flow status:

Slow-flow lesions – venous malformations (VMs), lymphatic malformations (LMs), and combined malformations.

Fast-flow lesions – arteriovenous malformations (AVMs) and fistulous arteriovenous anomalies.

Slow-flow malformations are frequently associated with somatic activating mutations in the PI3K/AKT/mTOR pathway, including mutations in TEK, encoding the endothelial receptor tyrosine kinase TIE2, which are highly prevalent in sporadic venous malformations[(2)], and PIK3CA mutations, which underpin PIK3CA-related overgrowth spectrum (PROS) and several complex overgrowth–vascular anomaly phenotypes [(3, 4)]. In addition, PTEN loss-of-function is responsible for PTEN hamartoma tumour syndrome (PHTS), a group of disorders in which vascular malformations are a frequent component [(5)]. These alterations converge on hyperactivation of mTOR signalling, providing a clear mechanistic rationale for mTOR inhibition.

In contrast, fast-flow AVMs are driven predominantly by mutations in genes such as RASA1, EPHB4, KRAS and MAP2K1, activating RAS/MAPK signalling rather than PI3K/AKT/mTOR [(3)]. This distinct molecular background explains the poor clinical response of AVMs to sirolimus observed in clinical practice and reported in expert series [(6, 7)].

Clinically, patients with slow-flow vascular malformations often experience chronic pain, swelling, functional impairment, disfigurement, recurrent infections and, in selected entities such as kaposiform haemangioendothelioma, life-threatening coagulopathies

including Kasabach–Merritt phenomenon[6-8]. These manifestations are associated with markedly reduced HRQoL[9,10]. Traditional management strategies, including surgery and sclerotherapy, may be insufficient or infeasible in extensive, multifocal or anatomically complex lesions, particularly with involvement of vital structures [11, 12].

Against this background, sirolimus has emerged as a targeted systemic therapy capable of modifying disease manifestations in slow-flow lesions and certain vascular tumours, filling an important therapeutic gap[6, 7].

MECHANISM OF ACTION

Sirolimus (rapamycin) is a macrolide compound initially developed as an immunosuppressant. It exerts its effect by forming a complex with the intracellular protein FKBP-12, which selectively inhibits mTOR complex 1 (mTORC1) [13]. Inhibition of mTORC1 leads to decreased phosphorylation of downstream effectors such as p70S6 kinase and 4E-binding protein 1 (4EBP1), thereby attenuating protein synthesis, cellular growth and proliferation [13, 14].

From the perspective of vascular anomalies, several mechanistic aspects are particularly relevant:

Pathway specificity: Lesions driven by hyperactivation of PI3K/AKT/mTOR signalling (e.g. TEK/TIE2-mutant VMs, PIK3CA-mutant PROS, PTEN-deficient PHTS) are biologically primed to respond to mTORC1 blockade [2-5].

Cytostatic rather than cytotoxic effect: Sirolimus typically suppresses endothelial and stromal proliferation without eradicating malformed vascular structures, which explains the frequent recurrence or worsening of symptoms following treatment discontinuation [13].

Incomplete pathway inhibition: mTOR complex 2 (mTORC2), which phosphorylates AKT at Ser473 and contributes to cytoskeletal organisation and cell survival, is not directly inhibited by acute sirolimus exposure [13]. Over time, partial mTORC2 inhibition may occur in some cell types but remains incomplete, predisposing to pathway escape and "AKT rebound".

Anti-angiogenic and anti-lymphangiogenic effects: By reducing VEGF production and downstream signalling, sirolimus exerts anti-angiogenic and anti-lymphangiogenic effects that are particularly relevant in venous and lymphatic malformations [14, 15].

These mechanistic considerations align strongly with the slow-flow specificity of sirolimus efficacy and the lack of consistent benefit in fast-flow AVMs, whose pathobiology is dominated by RAS/MAPK activation [3, 7].

METHODS

A narrative review of the literature was conducted using PubMed by a single reviewer. The search strategy combined the terms "sirolimus", "vascular anomalies", "venous malformations", "lymphatic malformations", "PIK3CA", "PTEN", "mTOR" and "overgrowth" and was limited to publications from January 2020 to March 2025.

Eligible articles included randomised clinical trials, prospective and retrospective cohorts, paediatric series, molecular–genetic studies, systematic reviews focusing on efficacy or safety, HRQoL investigations, TDM analyses and cost-utility evaluations. Study size and real-world clinical applicability of findings were determining factors in assessment of relevance. No language restrictions were applied.

The primary objective was to synthesize updated evidence on the efficacy, safety and optimisation of sirolimus in slow-flow vascular anomalies, while clearly delineating its lack of efficacy in fast-flow lesions. Secondary objectives included summarising data on HRQoL, TDM and the emerging landscape of targeted therapies that may compete with or complement sirolimus.

RESULTS

1. Efficacy of Sirolimus in Slow-Flow Vascular Malformations

Multiple lines of evidence consistently support the efficacy of sirolimus in slow-flow malformations, albeit with differing criteria for reporting of response type, utilizing a combination of the following variables: symptomatic response, HRQoL improvement, and lesion size or volume alterations in imaging studies. Whilst future studies would greatly benefit from standardized reporting of response type, we advise cautious interpretation of currently available evidence. A summary of the main results of each study is detailed in Table I.

1.1 Prospective trials and large cohorts

A nationwide Phase IIB trial in the Netherlands evaluated low-target sirolimus levels (4–10 ng/mL) in children and adults with refractory slow-flow vascular malformations [16]. Partial response was achieved in 79.1% of patients, and treatment was associated with clinically meaningful symptom improvement. Importantly, this study demonstrated that lower trough levels were as effective as historical targets (10–15 ng/mL), but with fewer severe adverse events [16].

The VASE Phase III European trial, the largest prospective study to date (n=132), reported clinical improvement in 85% of patients, frequently within the first month of treatment[17]. Subgroup analysis suggested that patients with PIK3CA-mutant lesions responded more rapidly but also experienced faster recurrence after drug discontinuation, a pattern consistent with strong pathway dependence and the cytostatic nature of therapy[17]. Interestingly, sirolimus also allowed for feasibility of conventional interventional techniques such as surgery and sclerotherapy in 15% of patients initially considered unsuitable for these procedures[17].

1.2 Venous malformations and hematological function biomarkers

VMs comprise the most prevalent type of congenital VAs and experience with sirolimus use in these specific lesions has been significantly documented[18, 19]. A pooled odds-ratio

of 0.02 for dichotomous variables (clinical improvement, radiological response) across 6 studies indicated a high response rate and very low treatment failure rates in a recent meta-analysis, with no severe side-effects being attributed to sirolimus[18]. Similarly, clinical improvement was observed in 72% of patients (n=71/98) and adverse effects were comparable in a systematic review by Teng et al[19]. Notably, sirolimus may have an important therapeutic role in managing coagulopathy associated with extensive VMs as hematological parameters such as a normalization of fibrinogen levels, decrease in D-dimers and increase in hemoglobin concentration with diminished transfusion requirements were reported in both studies[18, 19].

Paediatric cohorts further support the efficacy of sirolimus in complex vascular anomalies. A Korean single-centre study reported an objective response rate of 60% (complete or partial response) in children with complex vascular anomalies, with vascular tumours responding more rapidly than malformations[20].

An Italian two-centre series of 14 paediatric patients with complex vascular anomalies treated with sirolimus showed overall improvement or stability in 86% of cases, reinforcing its role as a systemic option in refractory disease[13].

1.3 Topical formulations and PTEN-associated lesions

A Spanish paediatric series explored both oral and topical sirolimus in complex vascular anomalies. Oral sirolimus achieved an 85.7% response rate, whereas topical formulations achieved a 72.7% response rate in superficial lymphatic malformations, offering a non-invasive alternative for selected patients while minimising systemic exposure [21].

In a retrospective study of seven paediatric patients with PHTS and vascular anomalies, sirolimus led to significant clinical improvement in 86% of cases [22]. This supports the rationale for sirolimus in PTEN-associated vascular anomalies, in which mTOR hyperactivation is a core pathogenic mechanism[5, 22].

2. Lack of Efficacy in Fast-Flow Lesions

In stark contrast, the evidence for sirolimus in fast-flow AVMs is weak and largely negative. Clinical experience and expert reviews consistently report minimal or absent durable responses in AVMs treated with sirolimus, with little effect on flow dynamics, lesion progression or the need for embolisation or surgery [7, 11].

This disparity mirrors the genetic and signalling background of AVMs, which are predominantly driven by RAS/MAPK pathway mutations rather than PI3K/AKT/mTOR [3]. As such, sirolimus should not be considered a disease-modifying therapy for AVMs but may occasionally be used for symptom control in highly selected cases, with realistic expectations communicated to patients[7, 11].

3. Impact on Health-Related Quality of Life

Beyond anatomical response, improvements in HRQoL are among the most consistent findings in sirolimus-treated cohorts. A systematic review and meta-analysis showed that vascular malformations are associated with substantial decrements in HRQoL across physical, emotional and social domains [9].

More recently, a study specifically assessing HRQoL in patients with vascular malformations treated with sirolimus found clinically relevant improvements in physical, social and emotional functioning, with HRQoL scores approaching those of the general population in many adult patients [10]. These findings support the view that sirolimus provides not only structural and symptomatic benefits but also meaningful gains in daily functioning and psychosocial wellbeing.

4. Safety and Adverse Events

Sirolimus has a characteristic but generally manageable adverse event profile. Across trials and cohorts, the most frequently reported adverse events include: oral mucositis, dyslipidemia (hypertriglyceridemia and hypercholesterolaemia), fatigue, gastrointestinal complaints (nausea, diarrhoea), upper and lower respiratory tract infections and urinary tract infections.

A systematic review of the safety of oral sirolimus in paediatric diseases identified oral mucositis as the most common adverse effects, affecting approximately 20–30% of patients [23]. Both this review and prospective vascular anomaly cohorts report a clear relationship between higher trough levels (≥10 ng/mL) and the incidence of severe adverse effects, supporting the shift towards lower target ranges[16,23].

A specific concern has also been the risk of Pneumocystis jirovecii pneumonia (PJP) in patients receiving sirolimus. However, a systematic review and an international multicentre retrospective cohort found that the incidence of PJP in patients with vascular anomalies treated with PI3K/AKT/mTOR pathway inhibitors is very low, and that routine prophylaxis with trimethoprim–sulfamethoxazole does not significantly reduce serious infection rates compared with no prophylaxis[24, 25]. These data suggest that universal PJP prophylaxis is not mandatory and may be reserved for high-risk subgroups, such as patients receiving combination immunosuppression or those with severe lymphopaenia[24, 25].

5. Therapeutic Drug Monitoring

Given the narrow therapeutic window and inter-individual variability in pharmacokinetics, TDM is central to sirolimus therapy. A retrospective study in Chinese paediatric patients with vascular anomalies confirmed substantial variability in dose-to-concentration ratios, with younger children typically requiring higher mg/kg doses to achieve target trough levels [26].

While early experience favoured target trough levels of 10–15 ng/mL, accumulating data from the Dutch trial and other cohorts indicate that lower targets of 4–10 ng/mL are equally effective and associated with fewer severe adverse effects [16, 26]. This has important implications for long-term tolerability, especially in children.

Table 3 **Clinical Progression Features**

Article	Patients/ Typology	Main Results
Harbers VEM et al, 202316	68 patients, original article	-Partial response achieved in 79.1%, clinically meaningful symptom improvement. -Lower trough levels (4-10ng/mL) as effective as historical targets with fewer AEs.
Seront E et al, 202317	132 patients, original article	-Largest prospective study -Clinical improvement in 85%. -PIK3CA mutant lesions respond faster but faster recurrence after treatment discontinuation. -Window of opportunity for interventional techniques (e.g. sclerotherapy, surgery) after sirolimus therapy in 15% of candidates initially deemed ineligible.
Wang G et al, 202518	74 patients, meta-analysis	-Pooled OR 0.02 (clinical improvement, radiological response) across 6 studies indicate high response rate and low event failure rate. -No severe AEs reported due to sirolimus therapy. -Normalization of fibrinogen, decrease in D-dimer and increase in haemoglobin concentration. -Decrease in transfusion requirements.
Teng J et al, 202519	98 patients, systematic review	-Clinical improvement in 72%. -AEs profile comparable to previous literature. -Decrease in D-dimer levels, increase in haemoglobin concentration. -Transfusions were no longer necessary due to treatment.
Kim M et al, 202320	20 patients, original article	-Complete or partial response rate of 60% in patients with complex VAs. -Vascular tumours responded more rapidly than VAMs.
Oliveira CF et al, 202321	18 patients, original article	-Topical formulation of sirolimus achieved a 72.7% response rate in superficial lymphatic malformations vs. 85.7% with oral formulation.
Zabeida A et al, 202422	7 patients, original article	-Significant clinical improvement in 86% of patients with PHTS and VAs treated with sirolimus.
Stor MLE et al, 20243	4261 patients, systematic review	-AVMs are mainly driven by mutations in the RAS/MAPK pathway rather than PI3K/AKT/mTOR.
Shimano KA, 20227	NA, opinion article	- Sirolimus should not be considered disease-modifying therapy in AVMs - Sirolimus may be considered for symptom control in highly selected patients
Nguyen HL et al, 20189	692 patients, systematic review	-Patients with VAMs had lower SF-36 scores in bodily pain and mental health vs. general US population.
Harbers VEM et al, 202310	50 patients, original article	-Adults with VAMs had significatively lower SF-36 scores in all domains except mental health vs. general Dutch population. -6 months of sirolimus treatment improved HRQoL in 77.8% of children and 57.7% of adults.
Zhang et al, 202223	575 patients, systematic review	- The most commonly reported AEs was oral mucositis (20.52%) -Subgroup analysis revealed many AEs were significantly higher in the higher concentration group (>10ng/ml) vs low concentration group (<10ng/mL)
Navarro et al, 202424	1235 patients, systematic review	-Out of 1189 cases of VAs receiving mTOR inhibitors, 2 cases (0.2%) of PJP were reported: 1 with sirolimus. -PJP is a rare event and prophylaxis with TMP-SMX may be appropriate for subgroups of patients with risk factors.
Qiu T et al, 202325	307 patients, original article	-Prophylactic TMP-SMX did not increase the incidence of infection or improve tolerance of sirolimus monotherapy in patients with VAs.
Hu YH et al, 202426	67 patients, original article	-High variability in sirolimus trough concentrations in Chinese children with VAs (3.6-46.8ng/mL). -Patients with older age and higher body weight had lower trough concentrations.
Li GX et al, 202427	NA, original article	-In a 1-year interval, sirolimus treatment of VAs yielded a cost effectiveness ratio of 35410$AUD/QALY, considered a cost-effective intervention by most metrics.

AEs: Adverse Events; HRQoL: health-related quality of life; NA: non-applicable; OR: odds-ratio; PJP: pneumocystis jirovecii pneumonia; QALY: Quality adjusted life years; TMP-SMX: Trimethoprim-sulfamethoxazole; VAs: vascular anomalies; VAMs: vascular malformations.

6. Cost-Utility

Economic evaluation is increasingly relevant in chronic, resource-intensive conditions. A cost-utility analysis from Australia concluded that sirolimus is cost-effective compared with supportive care in patients with complex vascular malformations, driven largely by gains in quality-adjusted life years (QALYs) and reductions in procedure-related costs [27]. These findings support the incorporation of sirolimus into treatment algorithms for appropriately selected patients.

DISCUSSION

This review underscores that sirolimus should not be regarded as a universal therapy for all vascular anomalies, but rather as a precision-directed treatment whose efficacy is tightly linked to the molecular and flow characteristics of the lesion.

Sirolimus in Slow-Flow and Fast-Flow Malformations

The robust efficacy of sirolimus in slow-flow lesions is biologically coherent:

TEK/TIE2, PIK3CA and PTEN mutations converge on PI3K/AKT/mTOR hyperactivation, making mTORC1 a rational therapeutic target [2-5];

Slow-flow lesions are typically low-grade proliferative but chronically dependent on pathway signalling, making cytostatic inhibition sufficient to reduce symptoms and lesion volume [6, 16];

Clinical response is observed across age groups and is accompanied by meaningful HRQoL gains [10, 13, 20].

In contrast, fast-flow AVMs exhibit a genetic landscape dominated by RAS/MAPK genes [3] and a haemodynamic profile in which shunting and abnormal vascular architecture are not primarily sustained by mTORC1 signalling. It is therefore unsurprising that clinical experience shows minimal or absent durable benefit from sirolimus [7, 11].

Recognising these boundaries has practical implications:

Sirolimus should not be presented to patients with AVMs as disease-modifying therapy;

Its use in AVMs, if considered, should be restricted to highly selected cases and framed as palliative or adjunctive, with transparent discussion of limited expectations, backed by currently low-level evidence.

Optimising Safety: Lower Targets and Therapeutic Drug Monitoring

The shift towards lower target trough levels (4–10 ng/mL) represents a major advancement in the safe long-term use of sirolimus [16, 26]. This strategy balances efficacy with reductions in severe adverse effects, particularly mucositis, infections and metabolic complications [16, 23]. TDM is essential, especially in children, where developmental pharmacokinetics introduce additional variability [26].

In our centre's experience, an initial 1mg PO i.d. dose is adequate for most adult patients, but this decision should be guided by target sirolimus trough levels and local centre expertise, especially in the pediatric population.

Sirolimus as a (Neo)Adjuvant Addition to Sclerotherapy

Sirolimus is firmly positioned as a suppressive rather than curative option for patients with refractory VMs that are not candidates for interventional techniques such as sclerotherapy and surgery. Chronic therapy with an acceptable adverse effects profile is thus justifiable in a population without alternative means of treatment. Temporary regression of venous malformations may open a window of opportunity for the aforementioned procedures and allow for earlier tapering/interruption of sirolimus.

A novelty technique utilizing a patented, intravenous compatible mTOR inhibitor embedded in a collagen matrix as an embolizing agent for sclerotherapy, has recently emerged [29]. This alternative administration route may allow for one-time exposure to sirolimus and limit its systemic toxicity, whilst preserving its cytostatic, therapeutic effect. No current evidence specifically utilizing sirolimus with this procedure exists, however.

Current Position of Sirolimus and Unresolved Questions

Sirolimus currently sits within a broader and rapidly evolving landscape of pathway-directed therapies:

Alpelisib, a selective PI3Kα inhibitor, has shown efficacy in PROS and other PIK3CA-driven disorders, offering deeper proximal pathway inhibition at the expense of metabolic toxicity (e.g. hyperglycaemia) [3, 4].

AKT inhibitors and other agents targeting downstream or parallel nodes are in development and may be particularly relevant in lesions where mTORC1 blockade alone is insufficient [28].

In this context, sirolimus is likely to remain a foundational agent, particularly given its relatively favourable long-term safety profile and broad availability. Future strategies may involve combination or sequential therapy with PI3K or AKT inhibitors, genotype-driven treatment allocation, and dynamic treatment de-escalation once disease control is achieved.

Key areas for future research include:

Defining the optimal duration of sirolimus therapy and strategies for safe tapering

Identifying biomarkers of response and resistance

Exploring alternative means or administration and adverse effects profile

Identifying the ideal timeframe for interventional techniques in eligible lesions after sirolimus therapy

Clarifying long-term effects on growth, metabolism and immune function, especially in children

Integrating patient-reported outcomes and HRQoL metrics into routine clinical decision-making [9, 10].

CONCLUSION

Sirolimus has emerged as a safe, effective and biologically rational therapy for refractory slow-flow vascular malformations, including venous and lymphatic malformations, complex combined lesions, PROS and PHTS-associated anomalies. Its efficacy is grounded in the correction of PI3K/AKT/mTOR pathway hyperactivation and translates into high response rates, symptom relief and substantial improvements in HRQoL.

However, sirolimus does not provide meaningful benefit in fast-flow arteriovenous malformations, whose pathobiology is dominated by RAS/MAPK signalling. As such, it should not be used as a disease-modifying therapy in AVMs.

Future management of vascular anomalies will increasingly rely on precision medicine, integrating detailed clinical classification, high-resolution imaging, genetic testing and pathway-directed therapies. Within this framework, sirolimus is likely to remain a cornerstone for slow-flow malformations, complemented by emerging PI3K and AKT inhibitors and evolving interventional techniques.

Further research should be guided by a standardized response type evaluation and integration of HRQoL metrics, with greater cohorts, multicentre prospective studies proving to be essential in determining optimal treatment duration and administration and comparison of novelty procedures.

REFERENCES

1. Goldenberg DC, Vikkula M, Penington A, Blei F, Kool LS, Wassef M, et al. Updated Classification of Vascular Anomalies. A living document from the International Society for the Study of Vascular Anomalies Classification Group. J Vasc Anom (Phila). 2025;6(2).
2. Soblet J, Limaye N, Uebelhoer M, Boon LM, Vikkula M. Variable Somatic TIE2 Mutations in Half of Sporadic Venous Malformations. Mol Syndromol. 2013;4(4):179-83.
3. Stor MLE, Horbach SER, Lokhorst MM, Tan E, Maas SM, van Noesel CJM, et al. Genetic mutations and phenotype characteristics in peripheral vascular malformations: A systematic review. J Eur Acad Dermatol Venereol. 2024;38(7):1314-28.
4. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet. 2006;7(8):606-19.
5. Eng C. PTEN: one gene, many syndromes. Hum Mutat. 2003;22(3):183-98.
6. Freixo C, Ferreira V, Martins J, Almeida R, Caldeira D, Rosa M, et al. Efficacy and safety of sirolimus in the treatment of vascular anomalies: A systematic review. Journal of Vascular Surgery. 2020;71(1):318-27.
7. Shimano KA, Eng W, Adams DM. How we approach the use of sirolimus and new agents: Medical therapy to treat vascular anomalies. Pediatric Blood & Cancer. 2022;69(S3):e29603.
8. Ji Y, Chen S, Zhou J, Yang K, Zhang X, Xiang B, et al. Sirolimus plus prednisolone vs sirolimus monotherapy for kaposiform hemangioendothelioma: a randomized clinical trial. Blood. 2022;139(11):1619-30.
9. Nguyen HL, Bonadurer GF, 3rd, Tollefson MM. Vascular Malformations and Health-Related Quality of Life: A Systematic Review and Meta-analysis. JAMA Dermatol. 2018;154(6):661-9.
10. Harbers VEM, Bouwman FCM, van Rijnsoever IMP, Verhoeven BH, van der Vleuten CJM, Schultze Kool LJ, et al. Magnitude and relevance of change in health-related quality of life in patients with vascular malformations treated with sirolimus. Front Med (Lausanne). 2023;10:1155476.
11. Akita S, Houbara S, Hirano A. Management of Vascular Malformations. Plastic and Reconstructive Surgery – Global Open. 2014;2(3):e128.
12. Horbach SER, van de Ven JS, Nieuwkerk PT, Spuls PI, van der Horst CMAM, Reekers JA. Patient-Reported Outcomes of Bleomycin Sclerotherapy for Low-Flow Vascular Malformations and Predictors of Improvement. CardioVascular and Interventional Radiology. 2018;41(10):1494-504.
13. Neirotti A, Barat V, Coppo P, La Selva R, Manicone R, Cotti R, et al. Therapy with sirolimus in vascular anomalies: the experience of two Italian centers on 14 pediatric patients. Front Pediatr. 2024;12:1434493.
14. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012;149(2):274-93.
15. Lee D-F, Hung M-C. All Roads Lead to mTOR: Integrating Inflammation and Tumor Angiogenesis. Cell Cycle. 2007;6(24):3011-4.
16. Harbers VEM, Zwerink LGJM, Rongen GA, Klein WM, van der Vleuten CJM, van Rijnsoever IMP, et al. Clinical differences in sirolimus treatment with low target levels between children and adults with vascular malformations – A nationwide trial. Clinical and Translational Science. 2023;16(5):781-96.
17. Seront E, Van Damme A, Legrand C, Bisdorff-Bresson A, Orcel P, Funck-Brentano T, et al. Preliminary results of the European multicentric phase III trial regarding sirolimus in slow-flow vascular malformations. JCI Insight. 2023;8(21).
18. Wang G, Lu W, Zhu Y, Wang C, Yang X. Effectiveness and safety of sirolimus in the treatment of venous malformations: A meta-analysis of prospective studies. J Vasc Surg Venous Lymphat Disord. 2025;13(6):102284.
19. Teng J, Martini J, Kelly M, Tollefson M, Greer A. Sirolimus for Venous Malformations: A Systematic Review of Efficacy and Safety. Lymphatic Research and Biology. 2025;23(6):311-9.
20. Kim M, Hong KT, Park HJ, Kim BK, Choi JY, Kim HY, et al. Clinical effectiveness and safety of sirolimus in pediatric patients with complex vascular anomalies: necessitating personalized and comprehensive approaches. Front Pediatr. 2023;11:1304133.
21. Fernández Oliveira C, Martínez Roca C, Gómez Tellado M, Salvador Garrido MP, Outeda Macías M, Martín Herranz I. Treatment with oral or topical sirolimus in complex vascular anomalies in pediatrics. Experience in a third-level hospital. Cir Pediatr. 2023;36(2):60-6.
22. Zabeida A, Brzezinski JJ, Wasserman JD, Cytrynbaum C, Weksberg R, Zwicker K, et al. Sirolimus for vascular anomalies associated with PTEN hamartoma tumor syndrome. Pediatr Blood Cancer. 2024;71(11):e31282.
23. Zhang Z, Li Y, Zhang G, Yang K, Qiu T, Zhou J, et al. Safety Evaluation of Oral Sirolimus in the Treatment of Childhood Diseases:

A Systematic Review. Children (Basel). 2022;9(9).
24. Navarro M, Allemang-Trivalle A, Leducq S, Jonville-Bera A-P, Maurier A, Zejli T, et al. Indication for a Pneumocystis Prophylaxis Therapy in Patients with Vascular Anomalies Treated with PIK3/AKT/mTOR Pathway Inhibitors: Experts' Opinion and Systematic Review from the Literature. Dermatology. 2024;239(6):942-51.
25. Qiu T, Li Y, Gong X, Zhou J, Yang K, Zhang X, et al. Oral antibiotic prophylaxis for infection in patients with vascular anomalies receiving sirolimus treatment: a multicenter retrospective study. Orphanet J Rare Dis. 2023;18(1):121.
26. 26. Hu YH, Zhao YT, Guo HL, Li Y, Zhang YY, Wang J, et al. Therapeutic Drug Monitoring for Sirolimus in Children with Vascular Anomalies: What Can We Learn from a Retrospective Study. Pharmaceuticals (Basel). 2024;17(10).
27. Li GX, Sebaratnam DF. Cost-utility of sirolimus in the treatment of vascular malformations. Australas J Dermatol. 2024;65(8):e259-e62.
28. Kane G, Fernandez-Pineda I. Targeted therapies for vascular malformations. Front Med (Lausanne). 2024;11:1446046.
29. Restrepo-Espinosa V, Lee AI, Prozora S, Patel P, Nassiri N. In-human clinical experience with direct stick embolization of low-flow vascular malformations using a mammalian target of rapamycin inhibitor. J Vasc Surg Venous Lymphat Disord. 2025;13(2):101997.