Family Medicine & Primary Care Review 2022; 24(2): 168–171, https://doi.org/10.5114/fmpcr.2022.115879

#### REVIEWS

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ISSN 1734-3402, eISSN 2449-8580

# The role of sirolimus in the treatment of vascular anomalies

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A – Study Design, B – Data Collection, C – Statistical Analysis, D – Data Interpretation, E – Manuscript Preparation, F – Literature Search, G - Funds Collection

Summary Vascular anomalies are classified by the International Society for the Study of Vascular Anomalies (ISSVA). They result from an abnormal embryonic development of vessels, and in most cases, they are present at birth. A minority of VAs manifest at a later stage. They grow along with the child and may enlarge spontaneously during an infection. They often create aesthetic flaws, pain, impaired quality of life and require challenging treatment options that frequently do not provide patients with desired results. Part of these anomalies are classified as lymphatic. Proper diagnosis is based on radiological tests, including ultrasonography, computed tomography and magnetic resonance. It is vital to establish a correct diagnosis that precedes the appropriate treatment. The mammalian target of rapamycin (mTOR) inhibitor sirolimus is an effective treatment for difficult lymphatic anomalies. This article presents the current use of sirolimus and its antiproliferative properties that enables mTOR pathway inhibition, leading directly to stopping, reversing or minimising the effects of development of vascular anomalies. So far, it has been proven that sirolimus has a measurable effect on lymphatic malformations, is well tolerated, manageable and rarely produces adverse effects. Still, there are no guidelines for sirolimus care in patients with vascular anomalies as we lack prospective clinical trials.

Key words: sirolimus, therapeutics, lymphatic system.

Kopeć J, Gawłowska A, Kopeć E, Przewratil P. The role of sirolimus in the treatment of vascular anomalies. Fam Med Prim Care Rev 2022; 24(2): 168-171, doi: https://doi.org/10.5114/fmpcr.2022.115879.

# Background

Vascular anomalies (VA) cover a wide spectrum of heterogeneous disorders classified by the International Society for the Study of Vascular Anomalies (ISSVA). They result from an abnormal embryonic development of vessels, and in most cases, they are present at birth. A minority of VAs manifest at a later stage. They grow along with the child and may enlarge spontaneously during an infection. Lymphatic malformations (LM) are low-flow vascular anomalies. The incidence of LMs in the world is approximately 1.2-2.8/1,000 patients. Most of them

are benign, often diagnosed in the cervicocranial region; however, they can affect the vital organs and lead to various clinical complications. Apart from visual defects, the most common problems they cause are chronic pain, coagulopathy, breathing impairment and recurrent infections. The clinical appearance of patients with LMs may be diverse, ranging from a focal swelling to large diffusely infiltrating masses. Proper diagnosis is based on radiological tests, including ultrasonography, computed tomography and magnetic resonance. It is vital to establish a correct diagnosis that precedes appropriate treatment. There is no definite therapy for Vas, and all options need to be considered for each patient individually [1, 2].

Table 1. Vascular malformations classification								
Vascular malformations								
Benign tumours	Borderline tumours	Malignant tumours	Simple	Combined	Associated with other anomalies			
Infantile haemangioma • Endothelial cell prolifera- tion • GLUT-1 marker positive Congenital haemangioma • Excessive Angiogenesis with Capillary Lobules • GLUT-1 Marker negative	Haemangio- endotheli- oma Others	Angio-sar- coma Others	Venous Malformations (VM) Blue rubber bleb nevus Syndrome Glomuvenous Malformation Lymphatic Malformation (LM) Macrocystic Microcystic Mixed Cystic	CM + VM CM + LM CM + AVM LM + VM CM + LM + VM CM + LM + AVM CM + VM + AVM	Klippel – Trenaunay Syndrome CLOVES Syndrome			
Tufted Angioma			Capillary Malformation (CM) Teleangiectasia Nevus Simplex Others	CM + LM + VM +AVM	Sturge – Weber Syndrome			



Table 1. Vascular malformations classification								
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Benign tumours	Borderline tumours	Malignant tumours	Simple	Combined	Associated with other anomalies			
Spindle Cell Haemangioma			Arterio-Venous Malformation (AVM)		Parkes–Weber Syn- drome			
Epithelioid Cell Haemangioma • Others			Arterio-Venous Fistula (AVF) Hereditary Haemorrhagic Telangiectasia (HHT)		Others			

CM – capillary malformations, VM – venous malformations, LM – lymphatic malformations, AVM – arterio-venous malformations, AVF – arterio-venous fistula, HHT – hereditary haemorrhagic telangiectasia.

LMs, particularly their microcystic forms, were often treated surgically. Excision of fragments of malformation ensured local control of the anomaly; however, this procedure may unfortunately be associated with complications. Less invasive options, such as embolisation and sclerotherapy, became more popular due to their high efficacy and tolerable adverse effects, and thus they are used most commonly in the case of macrocystic forms of LMs. Nonetheless, these options are often insufficient in the case of particularly extensive malformations. Obviously, in lifethreatening anomalies, early surgical intervention is still necessary, regardless of the complexity of the procedure; however, in other cases, systemic treatment is the most desirable solution.

In the last five years, more and more reports and large studies on the use of rapamycin in the paediatric population with VAs have been published. The clinical improvement in a majority of the patients and well-tolerated adverse effects presented in these publications encourage continuation of the development of rapamycin therapy in vascular malformations since it may be the first step to targeted treatment of these diseases.

Rapamycin (sirolimus) is a macrolide isolated from fungi Streptomyces hygroscopicus. Oral sirolimus has been commonly used to prevent rejection of kidney transplants. Sirolimus is a mammalian target of the rapamycin (mTOR) inhibitor. The mTOR pathway is responsible for protein synthesis activation, leading to numerous cellular processes resulting in e.g. angiogenesis. The mTOR inhibitor decreases VEGF, i.e. a key regulator in angiogenesis. Deregulation of the mTOR pathway has been observed in many other pathological mechanisms, leading to different genetic and neurological diseases or cancer. mTOR and the effects it has on angiogenesis are now being studied in terms of a potential mechanism involved in the development of vascular anomalies. mTOR is found in two protein complexes, i.e. mTORC1 - sensitive to rapamycin, mTORC2 - resistant to rapamycin. The mTORC1 phosphorylates are the known downstream targets of mTOR; the eukaryotic translation initiation factor 4E-binding protein (4EBP1) and the ribosomal protein S6 kinase 1 (S6K1) - mediators of cellular growth, protein synthesis, resulting in e.g. lymphangiogenesis. Upstream signalling of mTOR promotes the mTOR pathway and causes LM [3, 4]. Expression of the mTOR signalling pathway might play a key role in the pathogenesis of lymphatic anomalies.

mTOR inhibitors bring about positive therapeutic effects in the treatment of complex vascular malformations, especially lymphatic malformations in paediatric patients. Rapamycin is used in complicated LM cases, such as those which are progressive and difficult for surgical resection.

# **Clinical characteristics of patients**

As the subject is relatively new, the numbers of individuals enrolled in particular studies vary. Most reports are based on cases or small groups of up to 20 patients [1, 5–7]. Fortunately, some more extensive studies include groups of 40–60 subjects [8, 9], and literature reviews describe 70–150 individuals [1, 2]. Vascular anomalies occur predominantly in males [1, 2]. A majority of patients begin their therapy at the age of 2–13 years; however, there are older patients, as well as new-borns, and when starting sirolimus therapy, most are pre-treated with insufficient procedures applied being [1, 2, 5, 6, 8, 9]. Among the treated vascular anomalies, lymphatic malformations are the most common.

# Treatment with sirolimus – method and differences

Small differences exist in dosages since there are no evidence-based guidelines, neither for dosing nor for the duration of treatment of VAs. In most cases, treatment is based on experience and prevention of graft rejection in kidney transplantation. In most studies, the preferable way of sirolimus administration was the oral route. The most common starting dose is  $0.8 \text{ mg/m}^2$  of rapamycin in almost all cases. The drug is administered twice daily at 12-hour intervals. The dose is then adjusted to reach the expected blood level of the drug. Desired drug concentration levels range between 10 and 15ng/ml. All the patients receiving the therapy were subsequently assessed in different time frames, starting with weekly follow-ups at the beginning and monthly check-ups afterwards. They included thorough physical examination, blood tests, dose corrections depending on sirolimus blood levels, monitoring of adverse effects and treatment, as well as quality of life assessment. In some studies, dosing differed subtly. Due to a lack of specific guidelines, in a minority of studies, there were different starting doses, frequency of administration or sirolimus levels [1, 2, 5].

Sometimes, even a lower dose of sirolimus may offer the same therapeutic benefit while minimising adverse effects. This might be true, as there seems to be no association between serum levels and the grade of response [2].

#### **Response rate and response levels**

The criteria of treatment efficacy vary from one study to another [1]. They include clinical, radiological and/or laboratory response, quality of life-related or combined criteria. The clinical criteria may include a change in size, change in dermoscopy or photographs, an improvement in vital functions or pain level. The most favourable radiological evaluation is MRI. Laboratory results usually reflect the blood-clotting aspect of malformations. Quality of life forms are selected with reference to a patient's age.

There is no current standard for evaluation of rapamycin efficacy, and it is essential to standardise the response levels.

The percentage of patients with at least a partial response varies from 79% to 95% in larger groups. These are mostly a partial response, with few cases of a full response and progressive disease. The most common improvements concern pain levels, lesion size, normalisation of fibrinogen and D-dimer levels and bleeding. The most responsive anomalies were lymphatic or venolymphatic malformations.

In most patients starting treatment, the initial time required for achieving an improvement ranges from 1 to 90 weeks among studies.

The assessment time should be standardised among studies. For example, check-ups should be carried out after three, six and twelve courses of sirolimus. (1 course - 28 days) [7].

### Adverse effects and frequency

Despite its possible side effects and strict dosing requirements, sirolimus is well tolerated, and most adverse reactions are rare and manageable [1]. Even neonates tolerate the treatment well [6]. The most commonly reported adverse effects are gastrointestinal-like stomach ache, blood/bone marrow disorders - mostly anaemia or low platelet count, metabolic/ laboratory manifestations such as hypertriglyceridemia or hypercholesterolemia and mucositis. Less frequently observed adverse reactions may include neutropenia, elevated liver enzymes, nausea interfering with the quality of life and persistent lymphoedema. There are few cases of a sirolimus-associated infection. Some patients develop oral ulcers during treatment. A small number of patients interrupt the treatment because of the abovementioned neutropenia, elevation of liver enzymes, hyperkalaemia, persistent nausea or lymphoedema. In many cases, it is possible to resume the therapy.

Interventions in managing adverse effects may include simple responses such as a dose reduction, implementation of fibrates or statin treatment or a strict diet. However, all adverse effects should be consulted with a physician coordinating the treatment, as the patient receiving sirolimus should be under constant care. So far, there have been no reports of late neoplasms associated with sirolimus treatment.

Patients should be checked for long-term toxicities every six months for five years [7].

#### Other applications of the drug

Not all vascular malformations are life-threatening anomalies. Nevertheless, for those who require treatment for various reasons (cosmetic purposes, ulcerations, etc.), topical sirolimus along with adjuvant therapy can be an alternative [10]. This is

most recommended for capillary and capillary-lymphatic malformations. Patients using topical sirolimus may apply the treatment themselves. Topical rapamycin is effective in the case of many vascular malformations. This has been proven to be a safe alternative for superficial vascular malformations. In general, topical sirolimus may prove effective in reducing blebs, exudate and bleeding. The most common form of topical sirolimus is a rapamycin unguent at a concentration ranging from 0.1% to 1% [11, 12]. A study describing topical rapamycin interventions in 23 patients with SWS demonstrated the advantage of a treatment combining sirolimus and laser therapy. In this study, blood levels of sirolimus were monitored during the therapy. The average blood concentration of rapamycin was 0.69 ng/mL, and the intervention was generally well tolerated by all the subjects. The detected side effects were mild facial acne (the most common), small aphthous ulcers, herpes labialis, transient numbness of the upper lip and a slight and temporary stinging sensation in the treated area after the application of the cream [12]. In a study carried out in Minnesota including 18 subjects using sirolimus for VA treatment, all the patients reported an improvement. Half of the patients observed an improvement > 50%, and 72% of the patients showed at least a moderate improvement concerning mostly blebs and exudate [10]. Even though the treatment is relatively effective and safe, every superficial lesion should be seen by an experienced clinician to exclude the need for further diagnostics or more aggressive therapy. More studies are needed to evaluate the safety and efficacy of rapamycin treatment. There is an ongoing French clinical trial examining the topical use of rapamycin, i.e. Topical Sirolimus in Cutaneous Lymphatic Malformations (TOPICAL), sponsored by the University Hospital, Tours [11].

#### Conclusions

The use of sirolimus in systemic therapy of vascular malformations has been examined in many studies. Although we need more studies to be carried out on larger groups of patients, the drug is recognised as an effective therapeutic option in the treatment of complex vascular anomalies. There are ongoing clinical studies concerning the use of the medication. There is a great need for international guidelines regulating and unifying dosage, duration, evaluation and control of the treatment. Some trials are ongoing at the time [13]. Long term-toxicities are also yet to be determined. It has been proved so far that

Table	Table 2. Selected Tapamych studies based on study group size						
Select	Selected rapamycin studies*						
No.	Year	Title	Authors; DOI	Distinctive features			
1.	2016	Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascu- lar Anomalies	Adams D.M., Trenor C.C., Hammill A.M. 10.1542/peds.2015-3257	Original article Phase II trial study Evaluation of treatment protocol			
2.	2018	Treatment of Lymphatic Malformations with the mTOR Inhibitor Sirolimus: A Systematic Review	Wiegand S, Wichmann G., Dietz A. 10.1089/lrb.2017.0062	Systematic review Analysis of 20 studies – 71 patients Treatment protocols			
3.	2019	Analysis of mTOR pathway expression in lymphatic malformation and related diseases	Hori Y., Ozeki M., Hirose K. 10.1111/pin.12913	Original article expression pattern of mTOR pathway 18 patients with lymphatic anomalies			
4.	2019	Oral and Topical Sirolimus for Vascular Anomalies: A Multicentre Study and Review	Sandbank S., Molho-Pessach V., Farkas A. 10.2340/00015555-3262	Retrospective review Large study group 150 cases of VAs treated with siroli- mus analysed			
5.	2020	Treatment of superficial vascular anomalies with topical sirolimus: A multicenter case series	Dodds M., Tollefson M., Castelo- Soccio L. 10.1111/pde.14104	Original article Efficacy and tolerability of topical formulations of sirolimus Retrospective review treatment with topical sirolimus 18 patients			

Some patients present no response to the treatment or maintain stabilisation of the disease, whereas others go into complete remission, and in many cases, it is necessary to maintain drug administration for the beneficial effects to last. Most of the time, a partial response is observed. Further studies of VA genetics and overexpression of the mTOR pathway may lead to identification of patients with lesions susceptible to targeted therapy. This could result in improving efficacy, lessening the frequency of adverse effects and identifying the lesions receptive to sirolimus only.

Before targeted therapy is developed, recent findings of research on rapamycin analogues may be helpful. Rapalogs are supposed to provide a highly selective pharmacological inhibition of mTORC1 and reduce the impact on mTOR2 activity, which can lead to treatment that would eliminate long-term rapamycin side-effects [14]. Our department manages patients with LMs, applying all varieties of the abovementioned methods. The authors work at the Paediatric Surgery Centre focused (among others) on the treatment of vascular anomalies. Due to the recent new registration of Rapamycin in the treatment of lymphatic malformations in Poland, we have started administering the drug to selected patients using an internal treatment protocol. We are planning to register and start a study protocol in the near future.

Surgical treatment of complex vascular anomalies is often very difficult if not impossible in many cases. Rapamycin can be a useful tool for disease control, pain relief, prevention of functional disability and improving esthetical aspects. When combined with other well-established methods like sclerotherapy or laser therapy, it may complement the therapeutic range of nonsurgical treatment procedures applied in the disease.

Source of funding: This work was funded from the authors' own resources. Conflicts of interest: The authors declare no conflicts of interest.

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Tables: 2 Figures: 0 References: 14

Received: 17.12.2021 Reviewed: 27.12.2021 Accepted: 10.02.2022

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