Treatment with oral or topical sirolimus in complex vascular anomalies in pediatrics. Experience in a third-level hospital

C. Fernández Oliveira[1], C. Martínez Roca[1], M. Gómez Tellado[2], M.P. Salvador Garrido[1], M. Outeda Macías[1], I. Martín Herranz[1]

[1]Pharmacy Department, [2]Pediatric Surgery Department. Complexo Hospitalario Universitario A Coruña (Spain).

ABSTRACT

Objective. The use of sirolimus in vascular anomalies is a special indication not authorized in its data sheet. The objective of this study was to increase the evidence of oral or topical use of sirolimus for this indication in the pediatric population.

Materials and methods. An observational, retrospective study of patients under 18 years of age treated with oral or topical sirolimus for vascular anomalies was carried out. Diagnosis and location of lesions, administration route and dosage of sirolimus, blood levels of sirolimus in patients who received oral treatment, treatment duration, response, and toxicity were collected.

Results. 18 patients – 7 with oral treatment and 11 with topical treatment – were included. With oral sirolimus, the overall response rate was 85.7%. Sirolimus was discontinued in 2 cases – as a result of full resolution and progression. 57.1% of patients had adverse effects, most of which were mild. Dyslipidemia was the most frequent adverse effect. Blood levels were monitored in all patients for dose adjustment purposes. With topical treatment, the overall response rate was 72.7%. Sirolimus was discontinued in 3 cases –due to progression in 2 cases and to stability in 1. 27.3% of patients had adverse effects, with itching standing out as the most frequent one.

Conclusions. The favorable results of sirolimus treatment in our patients seem to confirm its effectiveness and safety in vascular anomalies, which make it stand as a therapeutic option in pediatric patients. However, further research is required to establish the optimal treatment regimen, treatment duration, and potential long-term adverse effects.

KEY WORDS: Sirolimus; Vascular anomalies; Vascular malformations; Therapeutic drug monitoring; Pediatrics.

TRATAMIENTO CON SIROLIMUS ORAL O TÓPICO EN ANOMALÍAS VASCULARES COMPLEJAS EN PEDIATRÍA. EXPERIENCIA EN UN HOSPITAL TERCIARIO

RESUMEN

Objetivo. El uso de sirolimus en anomalías vasculares es una indicación especial no autorizada en ficha técnica. El objetivo de este estudio es incrementar la evidencia del empleo por vía oral o tópica de sirolimus en esta indicación en población pediátrica.

Método. Estudio observacional retrospectivo de pacientes menores de 18 años tratados con sirolimus oral o tópico para anomalías vasculares recogiendo: diagnóstico y ubicación de lesiones, forma de administración y dosificación de sirolimus, niveles sanguíneos de fármaco en los pacientes con tratamiento oral, duración del tratamiento, respuesta y toxicidad.

Resultados. Se incluyeron 18 pacientes (7 con tratamiento oral y 11 tópico). Con sirolimus oral, la tasa de respuesta global fue 85,7%. Se interrumpió sirolimus en 2 casos: por resolución completa y por progresión. El 57,1% experimentó algún efecto adverso, en su mayoría leves; siendo la dislipemia el efecto adverso más frecuente. La monitorización de niveles sanguíneos fue empleada en todos los pacientes para el ajuste de dosis. Con el tratamiento tópico, la tasa de respuesta global fue 72,7%. Se interrumpió sirolimus en 3 casos: progresión en 2 casos y estabilidad en 1. El 27,3% experimentó algún efecto adverso, siendo el prurito el más frecuente.

Conclusiones. Los resultados favorables del tratamiento con sirolimus en nuestros pacientes parecen confirmar la efectividad y seguridad del fármaco en anomalías vasculares y lo posicionan como una opción terapéutica en pacientes pediátricos. Aun así, parece necesaria mayor investigación que trate de aclarar, entre otros, el régimen óptimo del tratamiento, la duración del mismo y los potenciales efectos adversos a largo plazo.

PALABRAS CLAVE: Sirolimus; Anomalías vasculares; Malformaciones vasculares; Monitorización farmacocinética; Pediatría.

INTRODUCTION

Vascular anomalies (VAs) are a heterogeneous group of rare conditions[1,2]. According to the International Society for the Study of Vascular Anomalies (ISSVA) classification, which was updated in 2018, they are divided into tumors

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Corresponding author: Dra. Carla Fernández Oliveira. Pharmacy Department . Complexo Hospitalario Universitario A Coruña. As Xubias, 84. 15006 A Coruña
E-mail address: carla.fernandez.oliveira@gmail.com

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and malformations based on clinical, biological, radiological, histological, and genetic characteristics[3]. Both tumors and malformations can give rise to complications as a result of local organ invasions, coagulopathies, or secondary infections. In addition, frequent symptoms such as pain, bleeding, lymphedema, or de-figuration impact quality of life[4]. Treatment should be individualized, and it may require combining surgical and radiological procedures as well as drugs – corticoids, propranolol, and antiangiogenics – with auxiliary therapies[5,6].

The genetic study of VAs is associated with mutations of the intracellular signaling pathways involving the mammalian target of rapamycin (mTOR), which causes uncontrolled activation of angiogenesis and lymphangiogenesis[7]. In 2010, the case of an infant with severe refractory kaposiform hemangioendothelioma successfully treated with oral sirolimus –an mTOR inhibitor– was published[8,9]. Subsequent experiences have been reported since then, with the development of a clinical trial to assess safety and effectiveness in pediatrics[10]. This trial, which consisted of 53 patients following 12 months of treatment, demonstrated that sirolimus was safe, with significant responses in microcystic and diffuse lymphatic malformations (LMs), capillary malformations, and venous and lymphatic malformations (VLMs)[10]. In order to avoid systemic exposure, and based on the previous knowledge of topical sirolimus in angiofibromas, VAs with a superficial component have been treated with topical sirolimus[11,12].

Since sirolimus was first marketed, authorized indications in Spain have included prophylaxis of rejection following renal transplantation and treatment of sporadic lymphangioleiomyomatosis with moderate condition or impaired pulmonary function in adults[13]. Therefore, its use in pediatric patients with VAs is special, and as such, it must take place under Spanish Royal Decree 1015/2009, with sirolimus being dispensed at Hospital Pharmacy Departments (PD)[14].

This case series was studied in order to increase the evidence available in the real life with the use of sirolimus in pediatrics. To our knowledge, this is the largest series in Spain exclusively consisting of pediatric patients with various types of VA.

MATERIALS AND METHODS

An observational, retrospective study of all patients under 18 years of age treated with sirolimus for VAs in a third-level hospital from January 2015 to January 2022 was carried out. The experience of this patient series is described, with demographic and clinical information. Patients were treated in the same order they were identified, with no control group.

Individuals eligible for inclusion were pediatric patients previously diagnosed with VA –according to the 2018 ISSVA classification[3]–, treated with oral or topical sirolimus, and with clinical follow-up taking place at the Cross-Disciplinary Pediatric Vascular Anomaly Consultation and the Pediatric Pharmacy Care Area. Patients whose guardians refused to sign the informed consent form to participate in the study, as well as patients not meeting inclusion criteria, were excluded.

Patients were identified based on the type of VA and location of lesions according to clinical and radiological criteria, previous treatments and administration route, posology, and sirolimus treatment duration. Baseline oral dose was 0.6-1 mg/m^2 every 12 hours –with dosage units being adjusted to facilitate administration of the oral solution– in patients under 12 years of age, and 1 mg every 12 hours in patients aged 12 or older –with subsequent pharmacokinetic-monitoring-guided adjustment. The pharmaceutical forms used were commercial oral solution specialties (1 mg/ml concentration) and tablets. Before systemic treatment initiation, all patients underwent a blood test with hemogram, biochemistry, coagulation, and serologies. Baseline topical dose was 1 application every 12 hours. The pharmaceutical form used was magistral ointment formulation (0.1% or 0.4% concentration) or toothpaste (0.1%) manufactured at the PD. Effectiveness was assessed according to the following criteria: 1) changes in lesion characteristics (size, color, consistency); 2) changes in functional capacity (pain, mobility limitation, frequency of bleeding and/or recurrent infections); 3) analytical progression, and 4) radiological progression. Safety was assessed based on the profile of the adverse reactions described in the clinical, medical, and pharmaceutical course reported in the electronic medical records. Treatment response was classified as complete response (CR) (disappearance of lesions and full resolution of clinical signs), partial response (PR) (decrease in lesion size and symptomatic improvement), lack of response (without changes in clinical signs or symptomatic improvement), and progression (increase in lesion size). In the subgroup of patients with pharmacokinetic monitoring of levels, minimum blood concentrations (minC) and the number of pharmacokinetic determinations were described.

In order to support clinical decision, level monitoring was previously requested by the physician in charge. The lower and upper thresholds for minC quantification were 2 and 35 ng/ml, respectively. The target therapeutic range was established at 5-15 ng/ml. Level interpretation and pharmacokinetic recommendation were based on the information collected in the patient's bibliography and clinical signs. In risk situations, the medical physician in charge was contacted by phone to inform them of the level found and take concerted action. Maximum time from sample extraction for monitoring purposes to report issuance was 24 hours.

The study protocol was approved by the Hospital's Research Ethics Committee, with record number 2020/577. Written informed consent was gathered from all participants.

RESULTS

18 patients met inclusion criteria, making up 2 independent series. The description of the population treated with oral and topical sirolimus is featured in Tables 1 and 2, respectively.

Systemic sirolimus

Since 2015, 7 pediatric patients with VA received oral sirolimus. All patients were Caucasian. 6 out of 7 were male, and median age at baseline was 4.2 years (range: 3 months-17 years). 3 patients had complex LMs (in 2 cases, they were large and caused significant functional and esthetic impairment [Patients 2 and 6]). 2 patients had large venous malformations (VMs) (with important clinical signs in the case of Patient 4: thrombophlebitis, pain, increased D dimer). 1 patient had mixed venous-lymphatic-capillary malformation (with an impact on dental esthetics). And 1 patient had kaposiform hemangioendothelioma with cervical involvement compromising the airway and requiring tracheostomy. In addition, patient 1 had an additional complication –Kasabach Merritt syndrome.

Sirolimus was the first-line treatment in 1 case, whereas the remaining patients had received at least one previous treatment with insufficient response or persistent disease. Clinical characteristics, previous treatments, and treatment response are featured in Table 1.

Regarding response, CR was achieved in 3 patients, PR in 3 patients, and progression in 1 patient. Sirolimus was discontinued in 2 patients –in 1 case as a result of progression (Patient 2), and in 1 case following full resolution of the pericardial and mediastinal disease radiologically (Patient 3). In light of the excellent progression of the disease and the achievement of a CR in Patient 1, future treatment discontinuation was considered. In terms of safety, 4 out of 7 patients had adverse effects (AEs). The most frequent AE was lipid profile alteration (2 patients), with spontaneous resolution. In 1 case, tolerance could not be assessed. In Patient 2, repeated infections compromised therapeutic compliance and required topical antibiotic cycles in alternation with sirolimus. The presence of mucositis in the oral cavity of Patient 4 eventually led to replacing the oral solution with tablets, which allowed tolerability and AE control to improve. None of the patients received prophylactic antibiotic treatment for opportunistic infections concomitant with sirolimus.

Baseline dose was 1 mg/m^2/12 h in 3 out of 7 cases, 0.7 mg/m^2/12 h in 1 case, and 0.6 mg/m^2/12 h in 1 case (under 12 years of age), and 1 mg every 12 hours in 2 out of 7 cases (12 years old and older). Median treatment duration was 1 year (range: 1 month-7 years), and the preferred pharmaceutical form was the oral solution. Pharmacokinetic monitoring of sirolimus was used in all patients. A median of 4 (1-14) monitorings/patient were carried out, and mean minC level was 10.8±6.8 ng/ml. At treatment baseline, monitoring showed supratherapeutic levels in Patient 2. They were related to the concomitant administration of azithromycin, which eventually led to definitive discontinuation as a result of lack of response.

Topical sirolimus

Since 2020, 11 pediatric patients with superficial VAs received topical sirolimus. They were all Caucasian. 9 out of 11 were girls, and median age at baseline was 10.5 years (range: 11 months-16.9 years). 10 out of 11 patients had LMs, whereas 1 patient had VLM. The lesions were superficially located in the tongue in 5 out of 11 patients, in one of the fingers in 3 out of 11 patients, and in the knee, in the right leg and foot, and in the chin in the remaining 3 patients. Lesion size and deepness were variable, with the exact dimensions before and after topical treatment being unavailable for record purposes.

In 4 out of 11 patients, topical sirolimus was the first-line treatment. In all cases, sirolimus was used as a single therapy. Clinical characteristics, previous treatments, and treatment response are featured in Table 2.

Regarding response, 8 out of 11 patients had a PR, 2 out of 11 patients had progression, and 1 case could not be assessed owing to the short treatment duration. Sirolimus was discontinued in progression cases and in Patient 4*, who underwent a scheduled surgery. None of the patients where topical treatment failed were subsequently given systemic sirolimus. In terms of safety, 3 out of 11 patients had mild AEs, with administration-related itching being the most frequent (2 patients). Tolerance did not compromise therapeutic compliance in any case.

Baseline and maintenance posology was 1 application of ointment or toothpaste every 12 hours. Median treatment duration was 0.6 years (range: 15 days-1.37 years). Toothpaste was the pharmaceutical form used in tongue lesions, whereas 0.1% ointment was preferred in the remaining cases. 0.4% ointment was only used in the patient with a knee lesion.

DISCUSSION

Our experience supports the limited evidence that sirolimus is an effective and safe option in the treatment of VAs in pediatrics, and that topical sirolimus stands as a non-invasive therapeutic option in the management of superficial lesions. Our overall response rate with oral sirolimus was 85.7% (6 out of 7), and 72.7% (8 out of 11) with topical sirolimus, slightly below other series published[15-17].

Oral sirolimus proved highly effective in the only patient with vascular tumor, whereas results were variable in malformations –clinical improvement in 2 out of 3 cases with LM, stabilization and/or improvement in 2 out of 2 cases with VM, and excellent response in the only case of mixed malformation. In a phase II trial with

Table 1. Description and progression of patients treated with oral sirolimus.

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*
Demographic characteristics							
Age at diagnosis (years)/ sex	1.41/M	0.8/M	0.2/M	3.7/M	0.56/M	17/M	3/F
Age (years)/Body surface at sirolimus initiation (m^2)	2.8/0.83	1.2/0.5	0.2/0.25	12.6/1.37	5.4/0.9	17/1.66	4.2/0.67
Diagnosis	LAVT	LM	LM	VM	VM	LM	MM
Location	Cervical region	Right upper limb	Pericardium	Right lower limb	Lip and tongue	Cheek (infiltrates face muscles)	Left lower limb (large)
Treatment chronology	Clopidogrel (1st); Ticlopidine (2nd); Vincristine (3rd); ASA (4th); Sirolimus (5th)	Debulking (1st); Sirolimus (2nd); Debulking (3rd); Liposuction + Pressotherapy (4th)	Sirolimus (1st)	ASA (1st); Pressotherapy (2nd); Endovascular laser x2 (3rd); Sirolimus (4th)	Endovascular laser x3 (1st); Surgical resection (2nd); Sirolimus (3rd)	Surgery (1st); Sirolimus (2nd)	Sclerotherapy (1st); Pressotherapy (2nd); Heparin (3rd); Rivaroxaban + Sirolimus (4th)
Sirolimus start/end	01/15-End of study	12/15-12/16	08/20-09/21	11/20- End of study	01/21- End of study	01/21- End of study	01/22- End of study
Pharmaceutical form	Oral solution	Oral solution	Oral solution	Oral solution > Tablets	Oral solution	Tablets	Oral solution
No. of monitorings	14	6	13	1	2	2	1
Baseline dosage (mg/m^2/12 h)	1	1*	1	0.7	0.6	0.6	0.6
minC (ng/ml) **– dose and posology** (mg/m^2/12 h)	12.67-1 12.56-1 7.74-1 8.13-1 9.21-1 11.81-1 12.02-1 10.88-1 11.91-1 12.11-1 12.9-1 12.15-1 9.19-1 12.63-1	26.19-1* 10.2-0.25* 9.57-0.5 10.79-0.5 7.35-0.5 7.7-0.5	34.74-1 27.72-1 20.92-0.5 14.86-0.4 14.49-0.4 14.73-0.4 5.37-0.4 5.5-0.5 3.84-0.6 4.8-0.8 6.74-0.8 4.93-0.8 3.48-0.8	4.69 -0.7	3.1-0.6 6.61-0.8	7.33-0.6 7.12-1.2 (mg/ m^2/**24 h**)	3.2-0.6
Progression							
Size/color/consistency	Highly fav.	Unfav.	Highly fav.	Highly fav.	Stable	Fav.	Highly fav.
Pain/Mobility limitation	Highly fav.	Unfav.	Stable	Highly fav.	Fav.	Fav.	Highly fav.
Bleeding/Infections	Highly fav.	Highly unfav.	Fav.	Highly fav.	Stable	Fav.	Highly fav.
Analytical progression	Stable	N/A	Stable	Fav.	N/A	N/A	Highly fav.
Radiological progression	Highly fav.	N/A	Highly fav.	N/A	N/A	N/A	N/A
Response	CR	DP	PR	CR	PR	PR	CR
Adverse effects	Hyperchol.; Neutropenia; Anemia	Recurrent infections	Hyperchol.; Hypertrigly.	Oral mucositis	-	-	-
Progression following treatment discontinuation	N/A	Drainages and intralesional doxycycline. Good progression with subsequent pressotherapy. Liposuction required.	Control ultrasonography following discontinuation with no recurrence observed.	N/A	N/A	N/A	N/A

**Plasma levels of sirolimus related to the concomitant administration of azithromycin.*
AAS = Acetylsalicylic acid; minC = Minimum blood concentration; Unfav. = Unfavorable; Fav. = Favorable; Hyperchol. = Hypercholesterolemia; Hypertrigly. = Hypertriglyceridemia; M = Male; F= Female; LM = Lymphatic malformation; MM = Mixed malformation; VM = Venous malformation; N/A = not applicable; DP = Disease progression; CR = Complete response; PR = Partial response; LAVT = Locally aggressive vascular tumor. End of study = January 2022.

Table 2. Description and progression of patients treated with topical sirolimus.

	*Pat. 1**	*Pat. 2**	*Pat. 3**	*Pat. 4**	*Pat. 5**	*Pat. 6**	*Pat. 7**	*Pat. 8**	*Pat. 9**	*Pat. 10**	*Pat.11**
Demographic characteristics											
Age at diagnosis (years)/sex	1.6/F	11.4/M	6.2/F	1.6/F	0.9/M	10.5/F	9.3/F	16.1/F	3.1/F	1.7/F	13/F
Age at sirolimus initiation (years)	8.8	13.2	11.3	8.1	0.95	10.5	11.3	16.7	8.3	3.5	16.9
Diagnosis	VLM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Location	Right knee	Tongue dorsum	Upper limb phalanx	Right leg and foot	Cheek	Upper limb phalanx	Tongue dorsum	Tongue base	Tongue and right submaxillary region	Upper limb phalanx	Tongue
Treatment chronology	Surgical removal x3 (1st); CO_2 laser (2nd); Sirolimus (3rd)	Sirolimus (1st)	Surgical removal (1st); Sirolimus (2nd)	Surgical removal (1st); Sirolimus (2nd)	Surgical removal (1st); Sirolimus (2nd)	Sirolimus (1st)	Sirolimus (1st)	CO_2 laser (1st); Sirolimus (2nd)	CO_2 laser (1st); Submaxillary removal (2nd); CO_2 laser (3rd); Sirolimus (4th)	Sirolimus (1st)	CO_2 laser x2 (1st); Sirolimus (2nd)
Sirolimus start/end	05/20-10/21	11/20-End of study	12/20- End of study	12/20-07/21	12/20- End of study	02/20- End of study	06/21- End of study	07/21- End of study	10/21-12/21	10/21- End of study	01/22- End of study
Pharmaceutical form	0.4% ointment	0.1% toothpaste	0.1% ointment	0.1% ointment	0.1% ointment	0.1% ointment	0.1% toothpaste	0.1% toothpaste	0.1% toothpaste	0.1% ointment	0.1% toothpaste
Progression											
Size/color/ consistency	Unfav.	Stable	Fav.	Fav.	Stable	Fav.	Fav.	Fav.	Unfav.	Stable	N/A
Pain/Mobility limitation	Unfav.	Stable	Fav.	Stable	Unfav.	Fav.	Highly fav.	Fav.	Unfav.	Stable	N/A
Bleeding/ Infections	Unfav.	Stable	Fav.	Stable	Unfav.	Stable	Stable	Fav.	Unfav.	Stable	N/A
Analytical progression	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Radiological progression	Unfav.	N/A	Fav.	Fav.	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Response	DP	PR	PR	PR	PR	PR	PR	PR	DP	PR	N/A
Adverse effects	-	-	Itching	-	Flaking Itching	-	-	-	Irritation	-	N/A
Progression following treatment discontinuation	Laser sclerosis scheduled.	N/A	N/A	Stable lesion without sirolimus.	N/A	N/A	N/A	N/A	January 2022 in a disease extension study.	N/A	N/A

Unfav. = Unfavorable; Fav. = Favorable; M = Male; F = Female; LM = Lymphatic malformation; VLM = Venous and lymphatic malformation; N/A = not applicable; Pat. = Patient; DP = Disease progression; CR = Complete response; PR = Partial response; End of study = January 2022.

pediatric patients, 77.8% had a favorable response, and more than 20% showed reduction in lesion volume. The response rates were higher in the cases of LM, VM, kaposiform hemangioendothelioma, and mixed malformations (p-value <0.05)[18].

Topical sirolimus was used in superficial LMs. Following initiation, 4 out of 11 patients showed clinical improvement, and 4 out of 11 patients remained stable (mean treatment duration: 9.8 months). Radiologically speaking, improvement was evident in 2 patients. In 5 cases, the lesions were located within the oral cavity, and in 4 out of 5 cases, the clinical and radiological progression of the lesions was favorable and/or highly favorable using the toothpaste. In the only case of mixed malformation, progression was unfavorable. In a retrospective case series, 3 out of 4 patients with LM showed decrease in lesion size after 3 months. (11) In an 18-patient series (venous-lymphatic-capillary malformations (n=11), vascular tumors (n=3), LMs (n=2), and VMs (n=2)), 100% of the patients had clinical improvement, and in 50% of them, response was highly favorable. Blisters and lesion exudate were the symptoms that showed the greatest benefit[16].

Safety is crucial in pediatrics, since this is a vulnerable population with little evidence regarding the use of sirolimus in VAs. In the long-term, Rössler found that the most severe toxicity cases occurred in children under 3 years old who had received treatment for over 1 year and who had risk factors related to the location of the

lesion[19]. In a systematic review, the most frequent AE was oral mucositis (31.9%). Other AEs included dyslipidemia, leukopenia, gastrointestinal symptoms, and rash/eczema[15]. In the largest trial published, 78.5% of the AEs were mild to moderate, with mucositis being the most frequent (37.3%), and pneumonitis and respiratory infection being the most severe[18]. In a retrospective review, 55% of the patients had mucocutaneous AEs[20]. In our population, oral sirolimus was well tolerated, and dyslipidemia was the most frequent AE (2 out of 7 patients). Rare AEs such as interstitial pneumonitis and *Pneumocystis carinii* pneumonia have also been described, which challenges the need for prophylactic cotrimoxazole[21,22]. In our study, none of the patients required prophylaxis against opportunistic microorganisms, and in the only case with infections as an AE (Patient 2), sirolimus was discontinued. In topical treatments, similarly to our patients, the evidence supports that sirolimus is well tolerated, even in large areas[16]. In our series, AEs occurred in 3 out of 11 patients, but they were limited to local irritation and/or rash.

Sirolimus dose and pharmacokinetic range are not uniform in the experiences published. The most frequent posology is 0.8 mg/m^2 every 12 hours in pediatrics, and 5 mg/day in adults[15]. Measuring blood concentrations allows the therapy to be adequately controlled. However, there is no specific recommendation in pediatrics, and application is based on the experience available in renal transplantation patients and in Adams et al.'s clinical trial[10]. In a study carried out in children with VA, the target level was 10 ng/ml, and the doses required to achieve such level were 0.7-1.6 mg/m^2 every 12 hours in patients under 2 years of age, whereas 1.8mg/m^2 doses every 12 hours were needed in older children[23]. These differences may result from the low expression of CYP3A4 in neonates, whose maturation occurs in the first 6 months of life, with significant changes in the first weeks. Therefore, a specific posology was proposed according to the weeks of life[24]. In our series, the baseline dose in patients under 12 years old was 1 mg/m^2/12 h in 3 out of 5 cases. In all patients, monitoring was key to adjust dosing and adapt levels to the therapeutic range. The dose required to maintain levels ranged from 0.4 to 1 mg/m^2/12 h. In our only infant case (Patient 3), baseline dosing and posology (1 mg/m^2/12h) proved excessive and required subsequent rigorous adjustment. In our opinion, the posology proposed by the US group would have probably been more adequate in this patient[24]. Topically treated patients from our population were not monitored as a result of the minimum systemic absorption published[25]. In various series of topical treatment cases, levels, when measured, were undetectable or below 2.5 ng/ml[11,16]. Treatment duration remains undefined, ranging from 0.23 to 216 months in the various experiences published[15]. In topical treatments, benefits are evidenced in the first 3 months, which means extending treatments in the absence of improvement throughout this period seems unjustified[11].

Few studies assess quality of life improvements. In Ji et al.'s clinical trial, quality of life improved in 79.4% of all orally treated patients[18].

VAs are a heterogeneous group of conditions with a complex pathological process and various severity degrees, which prevents reference treatments from being defined. There is no consensus in the therapeutic management of these conditions, nor are there any standardized criteria in terms of use, posology, follow-up, or treatment duration. The evidence available is based on phase II clinical trials and case series, which means further research is required to establish long-term risks and benefits. New evidence will also be key in designing a clinical protocol establishing the most adequate administration route according to the characteristics of the lesion, the optimal posology, the most appropriate follow-up model, the treatment duration recommended, AE management, and safety profile.

The most significant limitation of this study lies in its observational, retrospective, descriptive nature, based on a review of medical records. Furthermore, medical records do not feature the comparative progression of superficial lesion sizes, which means the magnitude of changes following treatment cannot be established.

In conclusion, topical sirolimus as a magistral 0.1%-0.4% ointment is a safe treatment with an overall response rate of 72.7% in superficial VAs. In complex cases, oral administration of sirolimus may prove necessary. Our results support its use in lymphatic, venous, and mixed malformations, as well as in kaposiform hemangioendothelioma, with an adequate symptomatic and radiological response, and with the support of pharmacokinetic monitoring for posology adjustment purposes. Anyhow, further research is required to define an evidence-based clinical protocol in pediatric patients, since this will allow the administration route, posology, and optimal duration of sirolimus treatment to be established.

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