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Quality of life in children with complex vascular anomalies treated with sirolimus: A quasi-experimental study

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ABSTRACT

Introduction. Complex vascular anomalies have a severe impact on quality of life. Sirolimus is used off-label, but local evidence regarding its impact on health-related quality of life (HRQoL) is limited.

Objective. To evaluate the effect of sirolimus treatment in patients with complex vascular anomalies.

Population and methods. A single-group, quasi-experimental before-and-after study without a control group, conducted at a pediatric hospital. Patients aged 4 to 21 years with complex vascular malformations were included. HRQoL was measured using the PedsQL 4.0 questionnaire before starting sirolimus and at 6 months. Clinical characteristics, pain intensity and duration, and adverse events were recorded, and multivariate analyses were performed.

Results. A total of 39 patients were included (56.4% were female). At baseline, low HRQoL scores were observed. After 6 months of treatment, total scores increased from 64.6 (29.34-94.5) to 79.9 (55.43-98.91) in self-reports and from 65.2 (27.17-90.62) to 77.2 (46.73-93.47) in caregiver reports (p <0.005). Chronic pain, present in 21 patients (53.8%), was the main factor associated with a worse baseline HRQoL (−14.4 points; 95% CI −24.4 to −4.3; p = 0.0065) and decreased in 95% of patients. Adverse events, observed in 41%, were mild and did not require treatment discontinuation.

Conclusion. Treatment with sirolimus was associated with an improvement in HRQoL and pain in pediatric patients with complex vascular anomalies.

Keywords: *lymphatic vessels, anomalies; veins, anomalies; sirolimus; quality of life; vascular malformations, pharmacological treatment.*

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INTRODUCTION

Vascular anomalies (VA) comprise a heterogeneous group of conditions that include tumors and malformations, with wide clinical, anatomical, and genetic variability. Since the first classification proposed by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996, advances in molecular biology and diagnostic imaging have enabled greater precision in the characterization of these conditions and in understanding their pathophysiological mechanisms.[1]

Traditionally, the management of complex VAs has relied on surgical and interventional procedures, with few pharmacological alternatives. Over the past decade, the identification of somatic mutations that activate the PI3K/Akt/mTOR pathway has driven the development of targeted therapies. One of them is sirolimus, an mTOR inhibitor that has demonstrated clinical benefits in various international series.[2-5] Although its use is off-label, it has established itself as a relevant therapeutic option in selected patients.

Complex vascular anomalies typically follow a chronic course, with persistent symptoms such as pain, lymphorrhea, bleeding, recurrent infections, or functional impairment, which significantly impact physical, emotional, and social well-being. In this context, health-related quality of life (HRQoL) has become a fundamental component in assessing the overall impact of the disease and the response to interventions. Despite growing international evidence, information on HRQoL in pediatric patients with VA and on its evolution following sirolimus treatment is scarce in our setting.

In Latin America, access to targeted therapies and diagnostic opportunities may differ from the settings in which most published studies were conducted. These differences can influence clinical outcomes and perceptions of quality of life. Therefore, having local data that incorporates QoL measures is essential for contextualizing the impact of these conditions and assessing the applicability of international evidence to our population.

OBJECTIVES

The primary objective of this study was to evaluate the impact of sirolimus treatment in pediatric patients with complex vascular anomalies. Secondary objectives included analysis of clinical variables, pain intensity, and treatment-related adverse effects.

POPULATION AND METHODS DESIGN

A single-group, quasi-experimental before-and-after study without a control group.

Population

Patients aged 4 to 21 years who were treated at the interdisciplinary clinic for vascular anomalies at the Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan, in the Autonomous City of Buenos Aires (Argentina), between January 2017 and October 2023, and initiated sirolimus as part of routine clinical practice. The indication was established by the treating team for complex vascular anomalies with clinical and/or functional impact (significant disfigurement, persistent pain, lymphorrhea, recurrent infections, and/or functional limitations attributable to the lesion).

Exclusion criteria

Patients with medical contraindications to sirolimus (e.g., severe renal or hepatic impairment, severe uncontrolled dyslipidemia, uncontrolled immunodeficiency, or significant active infection) were excluded, those for whom safe outpatient follow-up with the required clinical and biochemical monitoring could not be guaranteed (based on a joint assessment by the treating team and Social Services, for patient safety reasons), and cases where treatment was refused by the patient and/or the responsible adult, as applicable.

Sample size

No *a priori* sample size calculation was performed. Convenience sampling was used, with all eligible patients who initiated sirolimus during the study period consecutively enrolled. The final sample analyzed consisted of 39 patients.

Intervention

The initial dose was 0.8 mg/m^2 every 12 hours, administered as tablets or an oral suspension. Plasma sirolimus levels were monitored at 15 and 30 days, and then every three months, to maintain levels between 5 ng/ml and 12 ng/ml. The minimum treatment duration was 6 months.

Variables analyzed

Age, sex, type, and location of the vascular anomaly (according to the 2018 ISSVA classification), history of tracheostomy or previous surgeries, presence and intensity of pain (Wong-Baker scale), and HRQoL.

Operational definitions (indication criteria)

The decision to prescribe sirolimus was made based on clinical judgment, with the clinical goal of improving quality of life. To this end, the presence of clinical/functional impairment attributable to the vascular anomaly was considered, defined operationally as persistent or progressive symptoms and/or a care burden affecting activities of daily living, as assessed by the interdisciplinary team during the initial interview with the patient and their family. This impact included, depending on the case, pain, bleeding, and/or lymphorrhea, recurrent infections, functional impairment of the affected organ (e.g., gait/mobility or eating/swallowing), and psychosocial repercussions.

Instruments

HRQoL was measured using the Pediatric Quality of Life Inventory™ (PedsQL) 4.0 Generic Core Scales, Spanish version for Argentina (self-report age-based and caregiver report), which assesses physical, emotional, social, and school domains. Scores were converted to a 0–100 scale (higher values indicate better HRQoL). For the administration and subgroup analysis of the PedsQL, the instrument's age categories were used. The 4 patients aged 19 to 21 were assessed using the 13–18-year-old version and included in that category in the stratified analysis. This instrument was used in accordance with its terms of use and with authorization obtained through the ePROVIDE distribution system (Mapi Research Trust) for the Spanish version (Argentina).[6-8]

The Wong-Baker scale was used to assess pain in patients aged 5 and older.

Methodology

The instruments were administered by the same operator in all cases, through separate interviews with children and caregivers. A unified database with prospective data collection and retrospective analysis was used.

Statistical analysis

In the descriptive phase, percentages, means, medians, and ranges were calculated for each variable type. In the analytical phase, chi-square, Student's t, or Wilcoxon tests were performed depending on the distribution, and multivariate analysis was conducted using linear regression. The Wilcoxon signed-rank test was used to compare HRQoL scores before and after treatment.

The study report was written in accordance with the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) guidelines for nonrandomized quasi-experimental studies. A participant flow diagram based on TREND was included (*Figure 1*).

Ethical considerations

Protocol approved by the institutional committee of Hospital Garrahan. Informed consent was waived because this was an observational study based on routine clinical practice, in which the use of sirolimus was based on clinical criteria unrelated to the research. The data were analyzed anonymously, in accordance with the Declaration of Helsinki and current regulations on the protection of personal data.

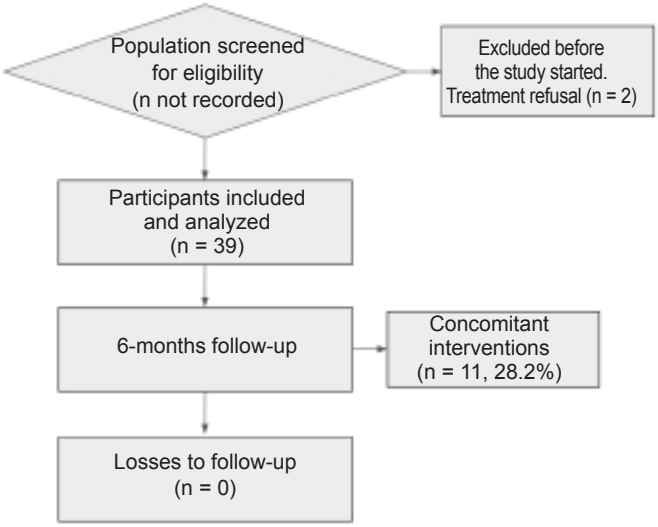
RESULTS

Figure 1 presents the flow diagram of participants (evaluated, included, and analyzed) in accordance with the TREND guidelines.

The baseline characteristics of the study population are detailed in *Table 1*. A total of 39 patients were included, with a median age of 12 years (range 4-21); 56.4% were female. The diagnoses, in order of frequency, were the spectrum of PIK3CA-related overgrowth syndromes (PROS) (28.3%), venolymphatic malformations (20.5%), lymphatic malformations (20.5%), fibroadipose vascular anomaly (12.8%), venous malformations (7.7%), Gorham-Stout disease (5.1%), generalized lymphatic anomaly (2.6%), and kaposiform lymphangiomatosis (2.6%). The most common sites were the lower limbs (33.3%), the head and neck (30.7%), the trunk (20.5%), generalized lesions (10.2%), and the upper limbs (5.1%). 15.4% of patients had undergone a tracheostomy; 48.7% had previously received sclerotherapy, and 38.5% had undergone surgery.

At the start of follow-up, the median total HRQoL score was 64.56 (range 29.34–94.5) in the self-report and 65.21 (range 27.17–90.62) in the caregiver report (*Table 2*). In the univariate analysis, the presence of chronic pain at baseline was significantly associated with a worse baseline HRQoL ($p = 0.01$). In contrast, injury location, sex, tracheostomy, and previous interventions showed no significant associations. In the multivariate analysis, chronic pain at baseline remained independently associated with a worse baseline HRQoL, with an average decrease of 14.4 points in the total PedsQL score (95% CI −24.4 to −4.3;

Figure 1. Chronic pain before and after sirolimus administration



Note: Given the observational nature of the study, there was no systematic record of the total number of patients evaluated who did not begin treatment (e.g., due to an alternative clinical indication or difficulties accessing care).

Table 1. Baseline characteristics of the patients

Population characteristics	N = 39	%
Male/female	17/22	43.6/56.4
Age, years, median (range)	12 (4-21)	
Age at admission, years: 4	3	7.7
5-7	8	20.5
8-12	13	33.3
13-18*	15	38.5
Diagnosis:		
PROS Spectrum	11	28.3
Venolymphatic malformations	8	20.5
Lymphatic malformations	8	20.5
FAVA	5	12.8
Venous malformations	3	7.7
Gorham-Stout	2	5.1
Generalized lymphatic anomaly	1	2.6
Kaposiform lymphangiomatosis	1	2.6
Primary location:		
Lower limbs	13	33.3
Head and neck	12	30.7
Trunk	8	20.5
Generalized	4	10.2
Upper limbs	2	5.1
Chronic pain	21	53.8
Pain intensity, median (range)	8 (2-10)	
Tracheostomy	6	15.4
Previous sclerotherapy	19	48.7
Previous surgery	15	38.5

Diagnoses were classified according to the ISSVA 2018.[1]
** Includes 4 patients aged 19–21 years, assessed using the 13–18-year-old version of the PedsQL for subgroup analysis.*
FAVA: fibro-adipose vascular anomaly; PROS: PIK3CA-related overgrowth syndromes.

Table 2. Comparison of PedsQL 4.0 scores in healthy children, children with other chronic diseases, and children with vascular anomalies

Self-report	Healthy	BMT	COPD	HIV	Cancer	CKD	Heart disease	VA
Total	72.2 (14.21)	71.64 (17.13)	58.44 (15.8)	71.31 (17.07)	65.16 (15.45)	65.29 (19.96)	68.98 (15.22)	64.56 (29.34-94.5)
Physical	75.42 (15.93)	74.24 (17.08)	58.16 (19.84)	74.58 (18.05)	60.98 (19.44)	67.17 (1.32)	72.03 (15.84)	60.94 (9.3-100)
Psychosocial	71.20 (14.84)	70.10 (18.51)	58.76 (16.43)	69.52 (17.69)	67.57 (6.46)	64.07 (7.45)	67.32 (7.04)	69.16 (31.6-93.3)

BMT: bone marrow transplant; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; CKD: chronic kidney disease; VA: vascular anomalies.
Note: The values for children with chronic diseases and healthy children were taken from the instrument validation study conducted in Argentina: Roizen M, Rodríguez S, Bauer G, et al. Initial validation of the Argentinean Spanish version of the PedsQL 4.0 Generic Core Scales in children and adolescents with chronic diseases. Health Qual Life Outcomes. *2008;6:59. The HRQoL scores obtained in our cohort (vascular anomalies) were included in the last column for comparison with the groups in the original study.*

p = 0.0065), after adjusting for these variables. After 6 months of treatment with sirolimus, HRQoL scores increased to 79.89 (range 55.43–98.91) in the self-report and 77.17 (range 46.73–93.47) in the caregiver report ($p < 0.005$ in both cases), with no significant differences among age subgroups (*Table 3*). Regarding pain, 21 of the 39 patients (53.8%) reported chronic pain at baseline, with a median intensity of 8 on a scale of 0 to 10. After 6 months of sirolimus treatment, pain decreased in 95% of symptomatic patients. In 13 of the 21 patients, the pain resolved completely, while in 8 presented residual pain of lower intensity (*Figure 2).*

Adverse effects were observed in 41% of patients. The events reported included oral ulcers, headache, leukopenia, and diarrhea. All were self-limiting and did not require permanent discontinuation of treatment. In 11 patients (28.2%), sirolimus was combined with surgical procedures or other interventions.

DISCUSSION

The results of this study show that patients with complex vascular anomalies included in this series had a markedly impaired health-related quality of life (HRQoL) at the start of treatment.

At baseline, HRQoL scores (PedsQL total) were lower than those reported in the healthy pediatric population at the same hospital (mean 72.72; SD 14.21) and comparable to those reported in other complex chronic conditions managed at the institution, such as bone marrow transplantation (mean 71.64; SD 17.13), chronic obstructive pulmonary disease (COPD) (mean 58.54; SD 15.80), human immunodeficiency virus (HIV) (mean 71.31; SD 12.37), cancer (mean 65.16; SD 16.55), chronic kidney disease (mean 65.29; SD 19.96), and congenital heart disease (mean 68.98; SD 15.22) (*Table 2*). This internal comparison, conducted using the institutional database used for the Argentine validation of the PedsQL, reinforces the significant functional, psychological, and social impact of these conditions in childhood.[9]

The study population included patients with extensive malformations, chronic pain, functional impairment, and a history of multiple prior interventions, which partly explains the low baseline HRQoL scores.

After 6 months of treatment with sirolimus, a clinically significant improvement in the HRQoL was observed in both self-reports and caregiver reports. The magnitude of the increase in the total score (≈12-15 points) significantly exceeded the published thresholds for the minimum clinically important difference on the PedsQL in pediatric populations, suggesting a noticeable and meaningful change for patients and families.[10] The improvement was consistent across the physical and psychosocial domains and did not show significant variations by age group. These findings are consistent with previous studies that have documented clinical and functional benefits of sirolimus in vascular malformations, including reductions in lesion volume, control of lymphorrhea, functional improvement, and reduced risk of complications.[3-5]

Pain was identified as the primary determinant of baseline QoL. In the univariate analysis, it

Table 3. Health-related quality of life before and after sirolimus administration

	Baseline			After 6 months of treatment			*p*-value
Self-report							
Age	**All**	**Physical**	**Psychosocial**	**Total**	**Physical**	**Psychosocial**	
All	(n 34)	(n 34)	(n 34)	(n 28)	(n 28)	(n 28)	
	64.56	60.94	69.16	79.89	87.5	80	<0.005
	29.34-94.5	9.3-100	31.66-93.3	55.43-98.91	53.12-100	55-95	
5-7	(n 6)	(n 6)	(n 6)	(n 5)	(n 5)	(n 5)	0.06
	61.23	68.75	61.66	87.5	90	86.66	
	52.17-83.69	43.75-90.62	51.66-80	66.3-98.91	87.5-100	55-95	
8-12	(n 13)	(n 13)	(n 13)	(n 9)	(n 9)	(n 9)	
	67.39	71.87	71.6	79.34	84.37	80	<0.005
	39.9-94.5	31.25-100	32.5-91.66	73.91-93.47	62.5-100	71.76-90	
	(n 15)	(n 15)	(n 15)	(n 14)	(n 14)	(n 14)	<0.005
	65	59.37	68.33	77.72	82.81	79.13	
13-18*	29.34-89.13	9.3-90.62	31.66-93.3	55.43-93.47	53.12-100	56.66-91.66	
Caregivers							
Age	**All**	**Physical**	**Psychosocial**	**Total**	**Physical**	**Psychosocial**	
Todas	(n 39)	(n 39)	(n 39)	(n 32)	(n 32)	(n 32)	<0.005
	65.21	68.75	63.87	77.17	87.5	78.33	
	27.17-90.62	12.5-100	35-95	46.73-93.47	34.37-100	45-93.33	
2-4	(n 3)	(n 3)	(n 3)	(n 3)	(n 3)	(n 3)	0.25
	68.75	53.12	65.7	86.9	96.8	80.7	
	59.7-69.56	50-55	59.78-78.33	72.82-86.9	62.5-96.8	78.33-80.7	
5-7	(n 8)	(n 8)	(n 8)	(n 7)	(n 7)	(n 7)	<0.005
	63.03	75	63.33	82.6	87.5	78.33	
	55.55-82.6	43.75-84.37	48.33-81.66	65.21-89.13	78.12-96.87	53.33-85	
8-12	(n 13)	(n 13)	(n 13)	(n 9)	(n 9)	(n 9)	
	63.04	75	63.33	77.17	87.5	78.33	<0.005
	39.13-88.04	15.2-100	38.33-85	46.73-86.95	34.37-96.8	50-81.66	
13-18	(n 15)	(n 15)	(n 15)	(n 13)	(n 13)	(n 13)	
	65.21	65.62	61.66	76.08	81.25	71.66	<0.005
	27.17-90.62	12.5-93.75	35-95	48.91-93.47	56.25-100	45-93.33	

Note: PedsQL 4.0 questionnaire scores obtained before (T1) and after (T2) 6 months of treatment with sirolimus, based on patient self-reports and caregiver reports, broken down by age group. Total, physical, and psychosocial scores are included. Statistical analysis was performed using the Wilcoxon Signed-Rank test. The instrument used corresponds to the version validated in Argentina by Roizen et al. (2008).9

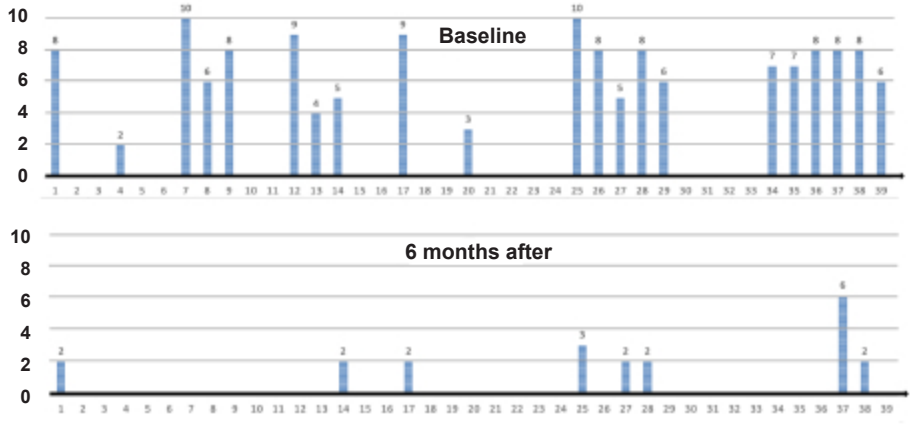
**For the PedsQL analysis by age subgroup, the 4 patients aged 19 to 21 were included in the 13-18 age category, as this corresponds to the version of the instrument used.*

was associated with poorer quality of life, and this association persisted in the multivariate analysis after adjusting for lesion location, sex, tracheostomy, and prior interventions, reinforcing its role as a relevant clinical marker of a higher disease burden.

From a clinical perspective, the reduction in pain observed following treatment may have been a main contributor to the overall improvement in QoL, given its impact on mobility, daily activities, school and social participation, sleep, and emotional well-being. In this regard, an intervention that reduces persistent pain may yield simultaneous benefits for the physical and psychosocial components of HRQoL, consistent with the pattern of improvement observed in patients and caregivers.

About safety, the observed adverse events were mild, self-limiting, and manageable, and did not require permanent discontinuation of treatment. This safety profile is consistent with international evidence and supports the use of

Figure 2. Chronic pain before and after sirolimus administration



Pain scores using the Wong-Baker scale (0 = no pain; 10 = the worst possible pain). The x-axis represents intensity, and the y-axis shows each patient's scores. Note the baseline scores and scores at 6 months of treatment with sirolimus for the 39 patients included in the study.

sirolimus in real-world settings, particularly within specialized interdisciplinary teams.

In a significant number of cases, sirolimus was used as part of a combined therapeutic approach, complementing interventions such as sclerotherapy or surgery. This strategy helped optimize clinical conditions before procedures and improve post-procedural function. In daily practice, sirolimus does not replace interventional therapies; rather, it enhances them by improving pain control, reducing inflammation, and stabilizing disease progression.

The use of the PedsQL 4.0, which has been validated in Argentina and administered in a standardized manner, enabled assessment of health perception across multiple domains and comparison of the impact of these conditions with that of other pediatric cohorts at the same hospital. This approach represents a significant contribution, as studies on vascular anomalies typically focus on anatomical or volumetric parameters. In contrast, the CVRS is a more sensitive indicator for capturing clinically significant changes in daily life.

Our results are consistent with those reported in international publications, which also demonstrate clinical, functional, and quality-of-life improvements in patients with complex vascular anomalies treated with sirolimus, across both pediatric and adult cohorts.[3,4] The alignment between local findings and international studies reinforces the consistency of the observed effect and lends external validity to our experience.

This study has limitations inherent to its before-and-after design, which does not allow for the establishment of definitive causal relationships between the intervention and the observed changes. The absence of a control group, the single-center design, and diagnostic heterogeneity should be considered when interpreting the results.

Despite these limitations, the improvement in HRQoL and the agreement between self-reports and caregiver reports reinforce the clinical relevance of the findings and support the utility of sirolimus as part of a comprehensive therapeutic approach in this population. Although this study focused on HRQoL and pain, in clinical practice, concomitant improvements were observed across other clinical components (e.g., reduction in lymphorrhea, bleeding, infections, and functional impact), which likely contributed to the benefits perceived by patients and families and should be evaluated in future studies.

CONCLUSION

In the study sample, patients with complex vascular anomalies had lower HRQoL (PedsQL) scores across all domains, as reported by both patients and caregivers. Pain was associated with worse baseline scores. After 6 months of treatment with sirolimus, quality of life and chronic pain improved significantly, with no serious adverse events, suggesting its utility as a therapeutic option within an interdisciplinary approach. ■

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