Boletín Médico del
Hospital Infantil de México

PERMANYER

Check for updates

RESEARCH ARTICLE

Effectiveness and safety of topical sirolimus in children with angiofibromas and tuberous sclerosis complex

*Andrea Fernández de Lara-Arrieta[1], Silvestre García-de La Puente[2], Janett Flores-Pérez[3], Carmen Flores-Pérez[3], Rodrigo Lomelí-Valdez[4], Andrea Venegas-Andrade[4], and Carolina Palacios-López[4]**

[1]General Practitioner, Private Practice; [2]Department of Research Methodology, Instituto Nacional de Pediatría; [3]Department of Pharmacology, Instituto Nacional de Pediatría; [4]Department of Dermatology, Instituto Nacional de Pediatría. Mexico City, Mexico

Abstract

Background: *Tuberous sclerosis complex (TSC) is an autosomal dominant disease that can affect any organ with hamartomas. It is characterized by early-onset seizures and is associated with intellectual disability. The main dermatological findings include hypopigmented macules, shagreen patches, and angiofibromas, which appear in 81-96% of patients.* **Method:** *We conducted a quasi-experimental, before-and-after, open-label study in 10 patients with TSC and facial angiofibromas, aged 8-17 years, who were treated at the dermatology service of the Instituto Nacional de Pediatría in 2019 and 2020. All patients agreed to participate in the study and signed both consent and assent forms. All patients received treatment with 1% topical sirolimus for 6 months on the right side of the face, followed by 6 months on the left side of the face to assess recurrence. Each patient served as their own control. Measurements of baseline lesions were taken and followed monthly for 6 months. The changes in lesion size, measured in millimeters at each time point, were compared using repeated measures analysis of variance.* **Results:** *All children showed a decrease in the size and number of angiofibromas, as well as reduced erythema, from the 3rd month of treatment. Few recurrences were observed beginning at 4 months after discontinuation of the medication.* **Conclusion:** *Topical sirolimus is effective and safe for treating patients with angiofibromas and TSC.*

Keywords: *Tuberous sclerosis. Angiofibromas. Sirolimus. Children.*

Efectividad y seguridad del sirolimus tópico en niños con angiofibromas y complejo de esclerosis tuberosa

Resumen

Introducción: *El complejo esclerosis tuberosa (CET) es una enfermedad autosómica dominante y puede dañar cualquier órgano con hamartomas. Se caracteriza por inicio temprano de crisis convulsivas y se asocia con discapacidad intelectual. Los principales hallazgos dermatológicos incluyen las manchas hipopigmentadas lanceoladas, placas de Shagreen, y los angiofibromas, que aparecen del 81 al 96% de los pacientes.* **Método:** *Realizamos un estudio cuasi experimental, de antes y después, de etiqueta abierta, en 10 pacientes con CET y angiofibromas, en cara, de 8-17 años, que fueron atendidos en el servicio de Dermatología del Instituto Nacional de Pediatría, durante 2019 y 2020. Los pacientes aceptaron participar en el estudio y firmaron carta de consentimiento y asentimiento informado. Todos ellos recibieron tratamiento con sirolimus tópico al 1%, 6 meses en el lado derecho de la cara, y 6 meses en el lado izquierdo de la cara; para valorar recidivas, se tomó*

***Correspondence:**
Carolina Palacios-López
E-mail: caroderma@yahoo.com.mx

Date of reception: 03-07-2024
Date of acceptance: 10-12-2024
DOI: 10.24875/BMHIM.24000091

Available online: 14-05-2025
Bol Med Hosp Infant Mex. 2025;82(2):115-120
www.bmhim.com

como control al mismo paciente. Se realizaron mediciones de las lesiones basales y cada mes durante 6 meses. El cambio en el tamaño de las lesiones (en mm) en cada medición, se comparó mediante ANOVA de mediciones repetidas. **Resultados:** *Todos los pacientes presentaron disminución del tamaño, número de angiofibromas y eritema a partir del tercer mes de tratamiento, y se presentaron pocas recidivas a partir del cuarto mes de suspender el medicamento.* **Conclusiones:** *El sirolimus tópico es eficaz y seguro para tratar a los pacientes con angiofibromas y CET.*

Palabras clave: *Esclerosis tuberosa. Angiofibromas. Sirolimus. Niños.*

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant systemic disease that can affect any human organ with lesions known as hamartomas. It is caused by pathogenic variants in the tumor suppressor genes TSC1 and TSC2, which encode hamartin and tuberin, respectively. These genes are located on chromosomes 9q34 and 16p13.3, respectively. The hamartin-tuberin complex downregulates mTORC1[1].

The presence of angiofibromas in tuberous sclerosis can have significant repercussions for patients, with both physical and psychological implications. Angiofibromas are commonly found in school-aged patients with TSC. Although they rarely pose a life-threatening risk, they often become a source of stigma for these patients, affecting their self-esteem, social interaction, and consequently, their quality of life. Due to their potential to become disfiguring, various therapeutic options have been considered, including radiosurgery, cryosurgery, electrofulguration, CO_2 laser, and chemical peels, most of which are painful. Angiofibromas present as multiple erythematous or skin-colored papules in centrofacial areas, primarily on the nose and surrounding regions[1].

The accidental observation of facial angiofibroma regression in a patient with TSC who received oral sirolimus after a renal transplant has led to the development and increasing use of this drug through topical application. Sirolimus is a macrolide consisting of a ring with lactonic and lactam-like groups derived from the fermentation products of *Streptomyces hygroscopicus*. The disappearance of angiofibromas has been observed with its use[2].

The concentrations of topical sirolimus, the vehicle used, and the dosage vary among different studies. The use of topical sirolimus has been reported in active ingredient concentrations ranging from 0.003% to 1%, with the most common concentrations being 0.1% and 0.2%[3,4].

At the *Instituto Nacional de Pediatría*, 105 patients were registered from 2005 to 2017, all of whom were evaluated in the dermatology service outpatient clinic.

There is no consensus on management, with most treatments being painful, and multiple sessions are often required to achieve satisfactory results. Topical sirolimus represents a therapeutic option to achieve a sustained response in preventing the appearance of new angiofibromas.

The objective of this study was to analyze the effectiveness and safety of topical sirolimus in the treatment of children with angiofibromas and TSC. The study was approved by the Institutional Project Review Committees of the *Instituto Nacional de Pediatría* in Mexico City, with registration number 2019/003.

Method

After obtaining approval from the Research Ethics Committee, Biosafety Committee, and Research Committee of the *Instituto Nacional de Pediatría*, parents of the patients completed the informed consent form, and children provided assent letters (for children aged 6-18 years). Ten patients diagnosed with TSC were recruited. Patients with potential pregnancy, autoimmune conditions, or those taking oral sirolimus were excluded.

A quasi-experimental, open-label before-and-after study was conducted. The study included patients with angiofibromas and TSC treated at the dermatology service of the *Instituto Nacional de Pediatría* from 2019 to 2020, aged 8-17 years, who agreed to participate and signed both informed consent and assent letters.

Patients who met the selection criteria underwent baseline photography, lesion counting, documentation of lesion locations, and measurement of the largest lesions' diameters. Subsequently, they received the compounded sirolimus preparation with instructions to apply it once daily on the right side of the face for 6 months, followed by discontinuation on that side and initiation on the left side for another 6 months. Patients attended monthly follow-up appointments for photography and evaluation of lesion number and size. In addition, lesion resolution and sirolimus-related adverse events were assessed. After the initial 6-month treatment period, lesion recurrence was also evaluated.

Sirolimus solution (1 mg/1 mL) and CeraVe moisturizing lotion were used. The 1% sirolimus compounded

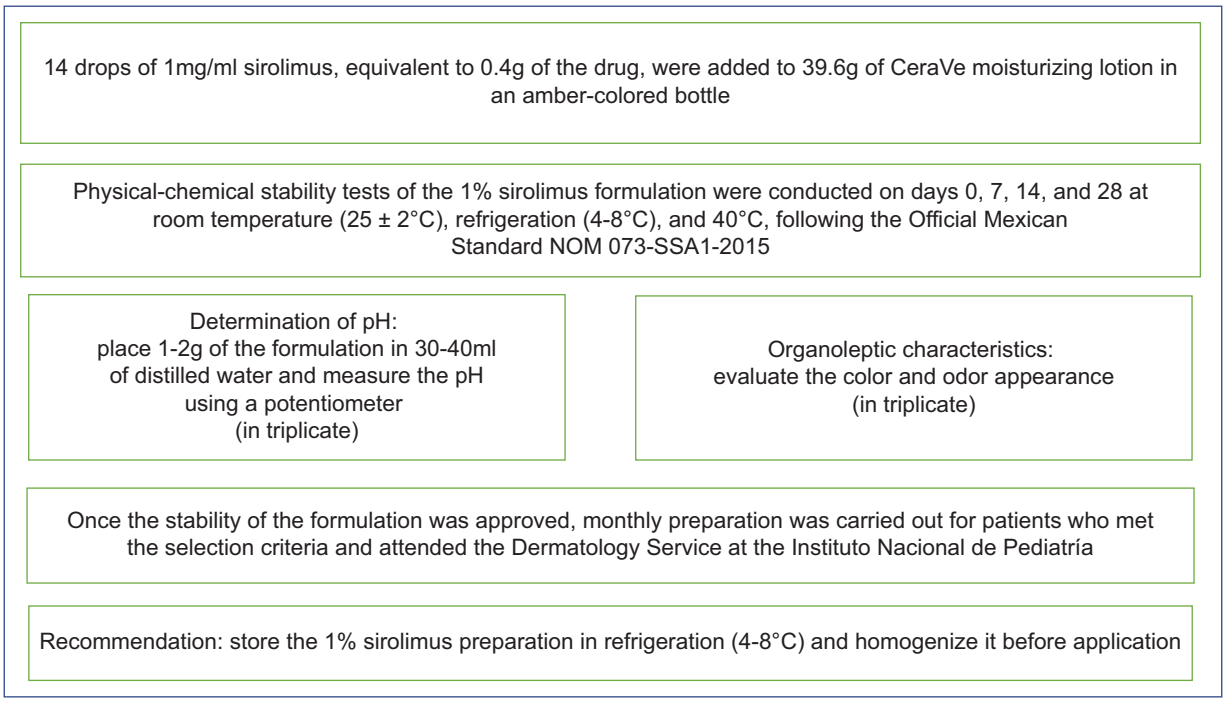

Figure 1. Preparation of the 1% sirolimus formulation.

formulation was prepared by incorporating 0.1 g of sirolimus into 19.9 g of CeraVe moisturizing lotion, which was then provided to patients. They transported it under refrigeration, and follow-up appointments were scheduled monthly. Details of the sirolimus preparation are recorded in figure 1.

Data analysis

The changes in the number and size of angiofibromas over the 6-month treatment period were analyzed using repeated measures analysis of variance, as were the recurrences after treatment discontinuation.

Results

Ten patients were included, with a median age of 15.5 years (range: 8-17 years). Six patients (60%) were male. All patients had numerous lesions of varying sizes. Table 1 shows the evolution of the lesions, demonstrating a decrease in both number and size from the 3rd month onward. Regarding recurrences, evaluation of the right side of the face 6 months after treatment discontinuation revealed new lesions appearing from the 4th-month post-treatment.

There was a positive correlation between age and the number of lesions, with older patients having more lesions ($r = 0.466$, $p = 0.038$). A positive correlation was also found between average lesion size and number of lesions, with larger lesions associated with greater lesion numbers ($r = 0.401$, $p = 0.08$). Conversely, a negative correlation was found regarding the percentage of resolved lesions, with older patients showing a lower percentage of resolved lesions ($r = -0.501$, $p = 0.024$).

The percentage of resolved lesions showed negative correlations with both the number of lesions ($r = -0.857$, $p < 0.001$) and lesion size ($r = -0.67$, $p = 0.001$). These findings suggest that early treatment initiation may be beneficial.

Regarding safety, two patients experienced local irritation during sun exposure, which resolved with sunscreen application, and treatment discontinuation was not required.

Discussion

TSC is a genetic, autosomal dominant disorder characterized by the formation of benign tumors in multiple systemic organs[4]. Facial angiofibromas are present as red or pink centrofacial papules, particularly in the nasofacial fold, cheeks, and chin. They develop in early childhood (6-8 years) and are present in over 80% of individuals with TSC (Figs. 2-5). These tumors, which contain vascular and connective tissue elements,

Table 1. Evolution of facial angiofibromas

Evaluated features	n	Month of treatment						p*
		1	2	3	4	5	6	
Number of lesions	20	113	113	94	74	47	53	< 0.001
Average size (mm)	20	39	39	34	30	24	20	< 0.001
Disappeared lesions	20	0	0	18	37	48	59	< 0.001
Recurrences Average number of lesions	10	0	0	0	0.3	2.7	6.5	< 0.001

*Repeated measures analysis of variance. Within-subjects effects.

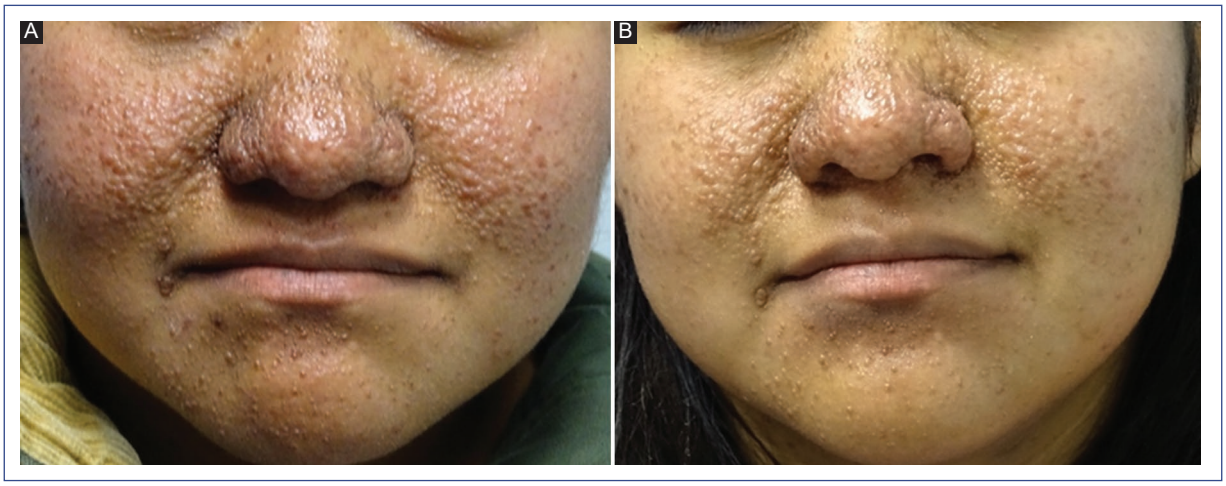

Figure 2. A and **B:** a 15-year-old adolescent with tuberous sclerosis and angiofibromas shows decreased lesion size and disappearance of small angiofibromas after 12 months of treatment with 1% sirolimus lotion. Note the absence of erythema.

constitute major criteria for TSC and commonly affect school-age children and adolescents, significantly impacting their self-esteem[4].

An ideal treatment for TSC has not yet been established; however, various procedures such as radiosurgery, cryosurgery, electrofulguration, CO_2 laser, and chemical peels are available. These treatments are often painful, invasive, and expensive[1,4].

The literature reports promising outcomes with topical sirolimus, which has been compounded at concentrations ranging from 0.001% to 1%. However, traditional preparation processes involve crushing and sieving sirolimus tablets and incorporating them into a vehicle (such as cold cream, polyvinylidene fluoride [PVDF] in ointment, gel, or petroleum jelly), resulting in poor cosmetic outcomes. Direct application of sirolimus solution (1 mg/mL) on angiofibromas resulted in intense irritation, necessitating a reduction in application frequency from twice daily to once daily. However, a compounded formula with sirolimus solution (1 mg/mL) mixed with emollients has been reported to be better tolerated by patients in previous studies[4,5].

Consequently, we used sirolimus oral solution (1 mg/mL) mixed with a moisturizing lotion, which significantly improved the organoleptic properties and cost of the formula. This formulation was prepared by the pharmacology department, and physicochemical stability tests were conducted on the 1% sirolimus formulation. The preparation requires refrigerated storage and has an optimal duration of 1 month.

In general, our patients showed improvement starting from the 3rd month of using 1% sirolimus in CeraVe moisturizing lotion, and this improvement persisted throughout both the initial 6-month application on the right cheek and the subsequent 6-month application on the left cheek. However, patients with large angiofibromas exhibited only

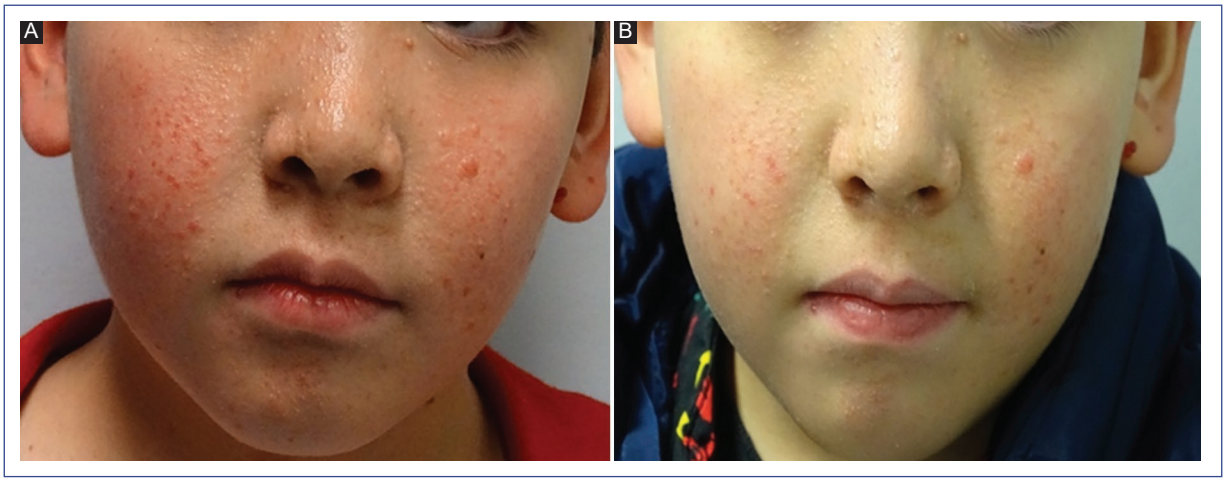

Figure 3. A and **B:** an 11-year-old boy with tuberous sclerosis and angiofibromas shows results after 1 year of treatment with topical sirolimus.

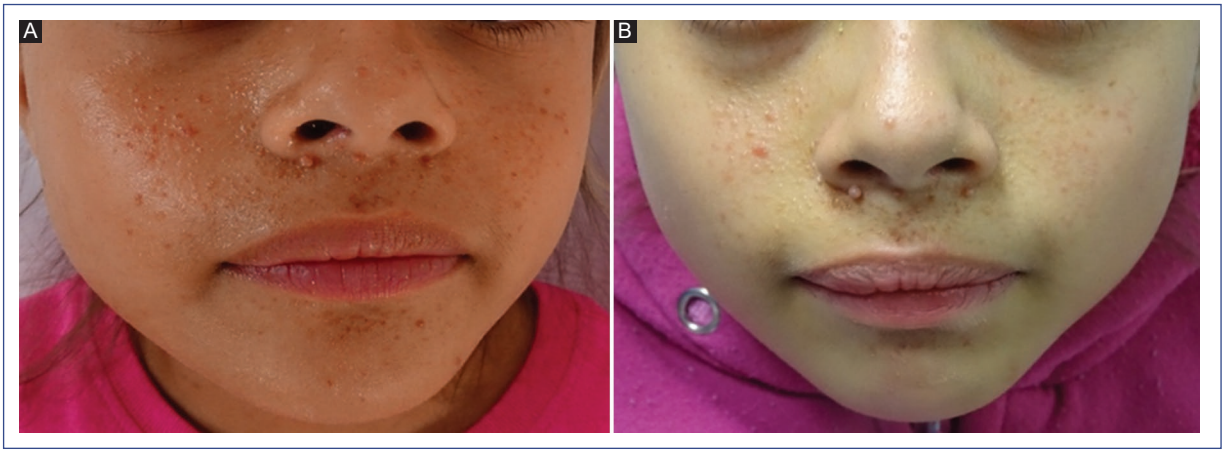

Figure 4. A and **B:** a 13-year-old girl with tuberous sclerosis and angiofibromas after 1 year of treatment with 1% sirolimus lotion.

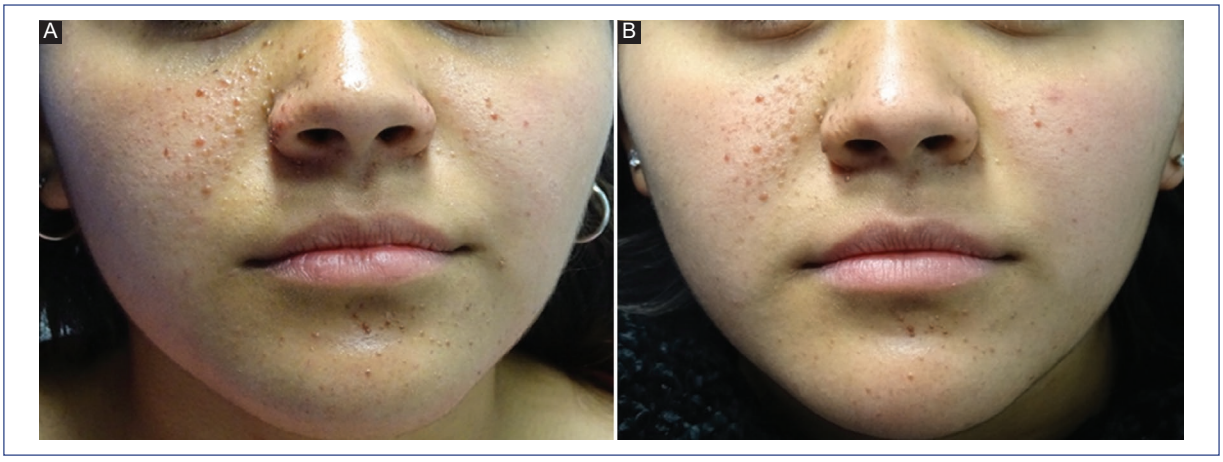

Figure 5. A and **B:** a 16-year-old adolescent, after 1 year of treatment with 1% sirolimus lotion. A decreased lesion size and disappearance of multiple angiofibromas can be observed.

a moderate response (40-80%). In addition, we found that children with smaller and fewer lesions showed a good response (80%) (Figs. 2-5). Therefore, while the efficacy and tolerability of 1% sirolimus in CeraVe moisturizing lotion have been demonstrated for small angiofibromas, this was not the case for larger lesions. This aligns with Foster's findings[5], which indicated a decrease in size and disappearance of smaller lesions but no significant change in larger lesions.

Multiple reports have demonstrated a good safety profile, with only six cases of local irritation reported: four related to the direct application of sirolimus oral solution (1 mg/mL) and two associated with the PVDF vehicle. In our study, we observed two patients with local irritation that resolved with sunscreen application. In studies monitoring systemic effects, no adverse effects have been reported, and sirolimus plasma levels have remained below detection limits, well below both therapeutic values and the toxicity range[2,5].

We consider 1% topical sirolimus to be a good treatment option for facial angiofibromas in children. While the ideal formulation has not been established, we found that 1% sirolimus in CeraVe lotion is highly effective in children, causing neither discomfort nor pain. Early initiation of treatment helps improve patients' self-esteem. However, in adolescents, ablative treatments with shaving and electrodesiccation can be used, followed by the application of 1% or 2% sirolimus. Long-term studies are needed to establish which treatment is most effective and have the lowest recurrence rate.

In our patients, the recurrence time after treatment cessation was 4 months. This information may guide treatment scheduling, allowing for planned treatment interruptions and resumption after this period.

It is important to emphasize that formulations, regardless of type, should be prepared by trained personnel under appropriate pharmacological laboratory conditions. Home preparation without proper controls should not be encouraged.

Conclusion

Topical sirolimus is an effective and safe treatment for facial angiofibromas in children with TSC, showing significant improvement, particularly in smaller lesions. The treatment has a good safety profile, with minimal side effects, mainly local irritation. While larger lesions showed a more moderate response, early treatment improved patients' self-esteem. Recurrence of lesions occurred about four months after discontinuation, suggesting the need for periodic treatment cycles. Further studies are needed to optimize dosage and treatment duration.

Acknowledgments

The authors thank the volunteers of the Instituto Nacional de Pediatría for their support in carrying out this project.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Salido-Vallejo R, Garnacho-Saucedo G, Velez A. Bases moleculares y aplicaciones farmacológicas de la vía de mTOR en dermatología. Elucidation of the mTOR pathway and therapeutic applications in dermatology. Actas Dermo Sifilográficas. 2016;107:379-90.
2. Balestri R, Neri I, Patrizi A, Angileri L, Ricci L, Magnano M. Analysis of current data on the use of topical rapamycin in the treatment of facial angiofibromas in tuberous sclerosis complex. J Eur Acad Dermatol Venereol. 2015;29:14-20.
3. Wataya-Kaneda M, Nakamura A, Tanaka M, Hayashi M, Matsumoto S, Yamamoto K, et al. Efficacy and safety of topical sirolimus therapy for facial angiofibromas in the tuberous sclerosis complex: a randomized clinical trial. JAMA Dermatol. 2017;153:39-48.
4. Malissen N, Vergely L, Simon M, Roubertie A, Malinge MC, Bassis D. Long-term treatment of cutaneous manifestations of tuberous sclerosis complex with topical 1% sirolimus cream: a prospective study of 25 patients. J Am Acad Dermatol. 2017;77:464-72.e3.
5. Foster RS, Bint LJ, Halbert AR. Topical 0.1% rapamycin for angiofibromas in paediatric patients with tuberous sclerosis: a pilot study of four patients. Australas J Dermatol. 2012;53:52-6.