



Original article

Effectiveness and safety of liposomal rapamycin for the treatment of facial angiofibromas in tuberous sclerosis



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A B S T R A C T

Aim: Topical rapamycin is the pharmacological treatment of choice for facial angiofibromas in rare tuberous sclerosis disease. A new, more advanced, and complex formula was developed in our pharmacy service: rapamycin 0.4% liposomal formulation, with better organoleptic characteristics and a more favorable release profile of the active ingredient.

The purpose of this study is to evaluate the effectiveness and safety of liposomal topical rapamycin for the treatment of facial injuries in this rare disease.

Method: This was an observational, prospective, and multicenter study. Effectiveness was evaluated mainly through facial angiofibroma severity index (FASI), investigator's global assessment (IGA) scores, and dermatology life quality index (DLQI) questionnaire. To assess the safety profile of rapamycin, adverse reactions were reported, and blood tests and blood rapamycin levels were performed during treatment.

Results: Eleven patients were included, of which 8/11 (73%) patients obtained successful treatment according to FASI and IGA scores after 24 weeks of treatment. Statistical analysis demonstrated a significant improvement ($p < .05$) in FASI and IGA scores, erythema, and FA size after treatment with rapamycin liposomal formulation (FASI before treatment, median (interquartile range): 6.0 (2.0), FASI after treatment: 3.5 (2.0), $p = .0063$). Five patients also improved their quality of life after treatment. Regarding safety profile of rapamycin, the most common adverse reaction was mild pruritus and 2 patients reported erythema, who discontinued treatment prematurely. All hematological tests were normal, and blood rapamycin levels were undetectable.

Conclusions: After galenic improvements and clinical evaluations, the rapamycin liposomal formulation proved to be effective and safe for this therapeutic indication. This new formulation was included as a magistral formula in our hospital pharmacy service, now accessible for prescribing by dermatologists. Drug development in hospital pharmacy is often the only pharmacological alternative available to treat the symptoms of rare diseases, when treatment options are limited or inadequate.

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Efectividad y seguridad de sirólimus liposomal para el tratamiento de angiofibromas faciales en esclerosis tuberosa

R E S U M E N

Objetivo: El sirólimus tópico es el tratamiento farmacológico de elección para los angiofibromas faciales asociados a la enfermedad rara de la esclerosis tuberosa. En nuestro Servicio de Farmacia se desarrolló una nueva fórmula más avanzada y compleja: sirólimus liposomal al 0,4%, con mejores características organolépticas y un perfil de liberación del principio activo más favorable.

El objetivo de este estudio es evaluar la eficacia y seguridad del sirólimus tópico liposomal para el tratamiento de los angiofibromas en esclerosis tuberosa.

Método: Estudio observacional, prospectivo y multicéntrico. La efectividad se evaluó principalmente a través de la escala FASI (Facial Angiofibroma Severity Index), la escala IGA (Investigator's Global Assessment) y el

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cuestionario de calidad de vida en dermatología (DLQI). Para evaluar el perfil de seguridad de la formulación, se reportaron las reacciones adversas y se realizaron pruebas hematológicas y niveles sanguíneos de sirólimus durante el tratamiento.

Resultados: Se incluyeron once pacientes, de los cuales 8/11 (73%) obtuvieron un tratamiento exitoso según las puntuaciones FASI e IGA después de 24 semanas de tratamiento. El análisis estadístico demostró una mejora significativa ($p < 0,05$) en las puntuaciones FASI e IGA, el eritema y el tamaño de los AF después del tratamiento con la formulación liposomal de sirólimus (FASI antes del tratamiento, mediana (rango intercuartílico): 6,0 (2,0), FASI después del tratamiento: 3,5 (2,0), $p = 0,0063$). Cinco pacientes también mejoraron su calidad de vida tras el tratamiento. En cuanto al perfil de seguridad, la reacción adversa más frecuente fue prurito leve y dos pacientes refirieron eritema, por lo que suspendieron el tratamiento prematuramente. Todas las pruebas hematológicas fueron normales y los niveles sanguíneos de sirólimus fueron indetectables en todos los casos.

Conclusiones: Tras la optimización galénica y la evaluación clínica, el sirólimus liposomal demostró ser efectivo y seguro para esta indicación. Esta nueva formulación fue incluida como fórmula magistral en el nuestro servicio de farmacia, quedando disponible para su prescripción por parte de Dermatología. La elaboración de medicamentos en los servicios de farmacia hospitalaria es, en muchas ocasiones, la única alternativa farmacológica posible para tratar los síntomas de las enfermedades raras, cuando las opciones de tratamiento son limitadas o inadecuadas.

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Introduction

Tuberous sclerosis (TS) is a rare autosomal dominant disease with an incidence of 1 in 6000 to 1 in 10 000 individuals¹ in which a series of mutations occur in tumor suppressor genes (TSC1 and TSC2). This leads to deregulation of the mTOR pathway and uncontrolled cell proliferation, resulting in multisystem formation of benign tumors called hamartomas². These tumors can have different severity and locations, one of the most common being the kidneys. In addition, they can be affected by slight traumas that can also cause uncontrolled bleeding³.

The most common skin manifestation of TS is facial angiofibromas (FA). They constitute a fundamental diagnostic criterion for the disease since they are present in up to 80% of patients. FA appear at an early age and tend to stabilize in number and size in adolescence, which sometimes represents an esthetic and psychological problem for these patients^{4,5}.

Multiple treatments have been established for this skin condition. Physical treatments like radiofrequency, electrocoagulation, cryotherapy, dermabrasion, and laser therapy present certain problems because are invasive and painful and require anesthesia^{6,7}. The interest of mTOR inhibitors focuses pharmacological treatment on everolimus and sirolimus, and recent publications place topical rapamycin (sirolimus) as the most appropriate alternative. This molecule is a powerful mTOR inhibitor with immunosuppressive, antitumor, and antiangiogenic characteristics⁸.

We found multiple studies in the literature that ensure the effectiveness and safety of this pharmacological therapy, such as case series and several clinical trials, with a higher evidence level^{9–13}. However, significant variability was evident in the concentrations, dosages, and formulations tested in the literature.

In our hospital pharmacy service, we decided to optimize the conventional formulation commonly used by dermatologists in accordance with standard clinical practice: rapamycin 0.4% in vaseline. The result of galenic research and development was a more advanced and complex formula: a 0.4% liposomal formulation of rapamycin^{3,14} prepared in a biological safety cabinet. The exact composition of the liposomal formulation was rapamycin 0.4%, Transcutol® 3%, liposomal solution (Guinoxome®) 25%, cholesterol 0.1%, isopropyl myristate 10%, propylene glycol 10%, carbopol 2%, NaOH 10% q.s. pH 7.5, and water for injection q.s. 20 g. In the cosmetic and pharmaceutical fields, pre-prepared and commercially available lipid solutions are used, which can form liposomes upon incorporating an aqueous solution. Specifically, the Guinoxome® liposomal solution allows for easy and high-quality liposome formation. The remaining components of the formulation serve as humectants and stabilizers, with special attention given to transcutol. This solvent functions as an excellent absorption promoter, showing a higher solubility of rapamycin in this vehicle compared to liquid paraffin¹⁵. The

liposomes obtained were lighter, with better extensibility, and because of their characteristics, they are compatible with all skin types¹⁶. In addition, previous studies have reported a greater release of the active ingredient in liposomal vesicles than in other formulations, like gels¹⁷. This new liposomal formulation was validated based on its chemical, physical, and microbiological stability, with an encapsulation efficiency of 89% for rapamycin¹⁸. The validity period was 3 months at 3–8 °C¹⁹.

According to standard clinical practice, topical liposomal rapamycin administration can improve the appearance of FA, demonstrating the drug's effectiveness and safety following formulation optimization.

This study aims to evaluate the effectiveness and safety of liposomal topical rapamycin for the treatment of FA in rare TS disease.

Method

Study design and development

This was an observational, prospective, longitudinal, and multicenter study. The study period during which patients were recruited was between December 2021 and October 2023. The participating centers were the Doctor Peset University Hospital and University Clinical Hospital of Valencia, Spain. The clinical services involved were the Pharmacy Service of the Doctor Peset University Hospital and the Dermatology Service of both hospitals.

Description

This study was divided into 3 distinct phases: screening, treatment, and follow-up. Detailed assessments can be found in Annex 1.

Screening phase

The suitability of the participants for inclusion in the study was assessed. Informed consent was obtained, and patient demographics, medical history, and concomitant medications were collected.

Treatment phase

The treatment phase consisted of a clinical visit at baseline (V_0) and 3 subsequent clinical visits after 2, 12, and 24 weeks of treatment with the rapamycin liposomal formulation (P_1 , V_2 , and V_3). Patients were instructed how to administer the treatment: 3 times per week in the afternoon using a nitrile glove. The amount of formulation required to produce a thin confluent layer on the skin was 6 mg/cm² and was based on the size of the affected area. Its gel texture allows for excellent application and absorption onto skin conditions on the cheeks, nose, and chin. Patients completely removed the formulation after 2 or 3 h of exposure by washing with water and neutral soap. It was

recommended to keep the area well hydrated, avoid sun exposure, and use sunscreen creams with SPF 50. Patients who discontinued treatment prematurely underwent a visit (V_x) in whom effectiveness and safety (adverse events) were evaluated.

Follow-up

A follow-up visit (P_4) was performed 4 weeks after the V_3 or V_x visit.

Inclusion criteria

1. Male and female patients aged ≥ 10 years and ≤ 65 years on the day informed consent was obtained.
2. Patients diagnosed with TS and presenting visible FA.
3. FASI (facial angiofibroma severity index) score²⁰ of at least 3 and no greater than 8 (Annex 2).
4. IGA (investigator's global assessment) score¹³ of at least 2 and no greater than 4 (Annex 2).

Exclusion criteria

1. Patients who have received any mTOR inhibitor in the 3 months prior to selection by any route of administration.
2. Patients with laser or surgical therapy in the 6 months prior to selection.
3. Patients with serious skin lesions like erosions or ulcers.
4. Patients with known hypersensitivity to any component of the study product.
5. Patients with immune dysfunction or receiving any form of immunosuppression.
6. Pregnant or lactating females.

Prohibited concomitant medications

The following medications were prohibited during the study to avoid potential interference with the assessment of effectiveness and safety:

- i. Laser and surgical treatment in the targeted treatment area.
- ii. Application of steroids or other immunosuppressive agents to the designated area.
- iii. Administration of mTOR inhibitors (rapamycin, everolimus, temsirolimus, etc.) by any route of administration.
- iv. Potent inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampicin) by any route of administration.

Evaluation of effectiveness

Objective evaluation by investigator (OEI)

Primary endpoints.

- Percentage of patients with successful treatment according to a decrease of 2 or more points on FASI score after treatment.
- Percentage of patients with successful treatment according to a decrease of 1 or more points on IGA score after treatment.
- Median values of FASI score and the subcategories: erythema, size, and extension before and after treatment.
- Median values of IGA score before and after treatment.

Secondary endpoints.

- Percentage of patients with successful treatment according to a decrease of 2 or more points on FASI score after 12 weeks of treatment.
- Percentage of patients with successful treatment according to a decrease of 1 or more points on IGA score after 12 weeks of treatment.

- Time to treatment success (weeks of treatment) according to FASI and IGA scores.

Subjective evaluation by investigator (SEI)

Primary endpoints.

- Subjective improvement score (SIS): minimal, moderate, good, or excellent in photographs of FA after treatment.

Secondary endpoints.

- SIS (minimal, moderate, good, or excellent) in photographs of FA after 12 weeks of treatment.

Quality of life

Primary endpoints.

- Percentage of patients with an improvement in quality of life according to a decrease in score on the dermatology life quality index (DLQI) questionnaire after treatment (Annex 3).
- Median values of DLQI questionnaire before and after treatment.

Secondary endpoints.

- Percentage of patients with an improvement in quality of life according to a decrease in score on the DLQI questionnaire after 12 weeks of treatment.

Evaluation of safety

Adverse events (AEs)

- Notification of adverse reactions during P_1 , V_2 , V_3 , and P_4 visits.

Hematology

- Blood tests with complete blood count using flow cytometry (white blood cell, red blood cell, and platelet counts) during V_0 , V_2 , and V_3 visits. (Abbott Architect[®], Abbott Park, IL, USA).

Pharmacokinetics

- Blood rapamycin levels at V_2 and V_3 visits. A chemiluminescent microparticle immunoassay (CMIA) was utilized for the quantitative determination of rapamycin in human whole blood (Abbott Architect[®], Abbott Park, IL, USA). Prior to initiating the automated Architect sequence, a manual pretreatment step was undertaken. This involved extracting the whole blood sample (150 μ L) with a precipitation reagent (300 μ L), followed by heating (10 min at 42 °C) and centrifugation (5 min at 10,900 rpm). Subsequently, the supernatant was decanted into a Transplant Pretreatment Tube, which was then placed onto the Architect i System for further processing. The limit of detection of the Architect rapamycin assay was 0.3 ng/mL.

Statistical methods

A standard descriptive analysis was performed on all variables at baseline, continuous variables were expressed as mean and standard deviation, and qualitative variables were expressed as absolute frequencies, percentages, and proportions. The statistical analysis was conducted using the intention-to-treat (ITT) approach. All study participants were included in the analysis, regardless of their compliance with the treatment or any protocol deviations. To evaluate the normality of the data, the Shapiro–Wilk test was employed, which is

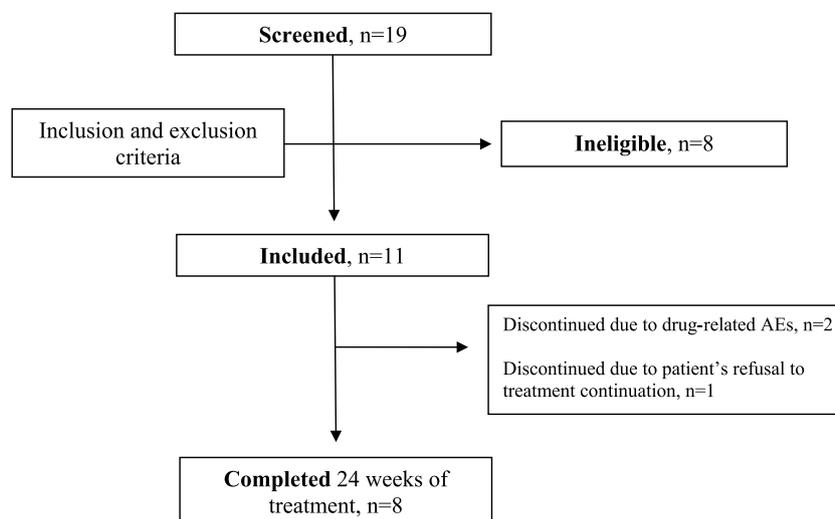


Fig. 1. Patient disposition. AEs: adverse events.

suitable for small samples ($n < 30$). The logarithmic transformation was applied due to the non-normal distribution but was not entirely effective in normalizing the data. Non-parametric tests were subsequently conducted, specifically the Wilcoxon signed-rank test for paired samples, with variables expressed as median values and interquartile ranges (IQR). Deviations were considered statistically significant when $p < .05$. Stata® 13.1 was used for the processing of statistical information.

Results

Eleven patients were screened. After exclusion of 8 ineligible patients, 11 patients were included (Fig. 1), of which 8 were women. The median age was 36 (11–64) years at screening. Most of the patients were of Caucasian ethnicity, which is predominant in Spain. Five patients additionally had hamartomas in different locations, such as the kidneys or lungs. Three patients had prior treatment with topical rapamycin, while four underwent laser or surgical pre-treatment. However, these patients always met the inclusion/exclusion criteria. Two patients also presented atopic-prone skin as a dermatological condition (Table 1). Baseline FASI and IGA scores can be seen in Table 2.

Eight patients completed 24 weeks of treatment, and 3 did not. Two due to drug-related AEs (patient 01 and patient 07) and one due to patient's refusal to treatment continuation (patient 08). Consequently, effectiveness and safety were evaluated in all patients except patient 08.

Evaluation of effectiveness

Objective evaluation by investigator (OEI)

Eight of eleven (73%) patients obtained successful treatment according to FASI and IGA scores after 24 weeks of treatment (Table 2). All

Table 1

Patient characteristics at baseline ($n = 11$).

Characteristic	Value, n (%) or mean (SD)
Gender (female)	8 (73)
Age (years)	36.5 (18.6)
Ethnicity	
Caucasian	8 (73)
Hispanic or latino	2 (18)
Not hispanic or latino	1 (9)
Unknown or not reported	0 (0)
Hamartomas in different locations	5 (45)
Pre-treated with topical rapamycin	3 (27)
Pre-treated with laser or surgery	4 (36)
Other dermatological conditions	2 (18)

patients decreased or maintained their FASI and IGA scores after treatment. The final evaluation of effectiveness for patients 01 and 07 occurred at Vx (prior to week 24 of treatment). Table 2 displays the median values and IQR for the FASI score, including its subcategories (erythema, size, and extension), as well as the IGA score before and after treatment. The Fig. 2 corresponds to the box plots showing the distribution of FASI and IGA scores before and after treatment. The central line represents the median, the box spans the IQR, and outliers are depicted as individual data points.

After 12 weeks of treatment, 6/11 patients (55%) achieved successful treatment according to the FASI score. In contrast, based on the IGA score, successful treatment was observed in 7 patients (64%) (Table 2).

The time to treatment success, measured in weeks of treatment according to the FASI score, was 12 weeks for 6 patients and 24 weeks for 2 patients. Likewise, according to the IGA score, treatment success occurred at 12 weeks for 7 patients and at 24 weeks for 1 patient (Table 2).

Subjective evaluation by investigator (SEI)

SIS of FA after treatment was minimal for 2/11 (18%) patients, good for another 2 patients and excellent for 6/11 (55%) patients (Table 2).

SIS of FA after 12 weeks of treatment was good for 8/11 (73%) patients (Table 2). Representative photographs of 2 patients are presented in Annex 4, with an excellent SIS after treatment.

Quality of life

Five of eleven (45%) patients improve their quality of life according to a decrease in score on DLQI questionnaire after treatment.

Median values and IQR for the DLQI questionnaire before and after treatment are shown in Table 2. Fig. 2 corresponds to the box plot showing the distribution of DLQI scores before and after treatment.

Four of eleven (36%) patients improve their quality of life according to a decrease in score on DLQI questionnaire after 12 weeks of treatment.

Evaluation of safety

Adverse events (AEs)

No serious adverse events were reported during the treatment or follow-up period. Five of eleven (45%) patients reported an adverse event during the treatment phase. The most common adverse reaction was mild pruritus (5/11, 45%) in the administration area that stopped in all cases after 5–10 min of exposure to the formulation. Two of eleven (18%) patients communicated dry skin and 2 other patients reported a feeling of tightness. Of note, 2 patients informed of erythema, leading

Table 2
Evaluation of effectiveness.

Patient	OEI						SEI		Quality of life		
	FASI V ₀	FASI V ₂	FASI V ₃	IGA V ₀	IGA V ₂	IGA V ₃	SIS V ₂	SIS V ₃	DLQI V ₀	DLQI V ₂	DLQI V ₃
SIRO-01	7	–	7*	4	–	4*	–	Minimal*	4	–	9*
SIRO-02	5	3	3	2	1	1	Good	Good	2	1	1
SIRO-03	7	5	4	3	2	1	Good	Excellent	1	1	5
SIRO-04	5	4	3	2	2	1	Good	Good	0	3	2
SIRO-05	8	6	5	4	3	2	Good	Excellent	5	2	0
SIRO-06	7	6	4	4	3	1	Good	Excellent	3	4	1
SIRO-07	5	–	5*	3	–	3*	–	Minimal*	0	–	2*
SIRO-08	6	–	–	3	–	–	–	–	1	–	–
SIRO-09	6	4	3	3	2	1	Good	Excellent	12	1	1
SIRO-10	6	4	3	3	2	1	Good	Excellent	0	0	0
SIRO-11	6	4	3	3	2	1	Good	Excellent	7	1	0

Wilcoxon signed-rank test for paired samples, $n = 11$. Median (interquartile range, IQR).

	V ₀	V ₃	p value
FASI	6.0 (2.0)	3.5 (2.0)	0.0063**
Erythema	2.0 (0.0)	0.5 (1.0)	0.0067**
Size	2.0 (0.0)	1.0 (1.0)	0.0143**
Extension	2.0 (1.0)	2.0 (0.0)	0.0833
IGA	3.0 (1.0)	1.0 (1.0)	0.0068**
DLQI	2.0 (5.0)	1.0 (2.0)	0.5733

OEI: objective evaluation by investigator.
 FASI: facial angiofibroma severity index.
 IGA: investigator's global assessment.
 SEI: subjective evaluation by investigator.
 SIS: subjective improvement score.
 DLQI: dermatology life quality index.
 * Assessments in Vx.
 ** Statistically significance.

to premature discontinuation of treatment before V₂. All adverse reactions disappeared when treatment was stopped, as this was confirmed during the P₄ visit.

Hematology

All hematological tests were normal for all patients. There were no significant changes in white blood cell, red blood cell, or platelet counts. All analytical values fell within the normal range.

Pharmacokinetics

All blood rapamycin levels were undetectable for all patients, being below the detection limit of the technique (<0.3 ng/mL).

Discussion

All patients who completed 24 weeks of treatment obtained successful treatment, according to FASI and IGA scores (8/11, 73%). Specifically,

FASI score to measure effectiveness is a simple, reproducible, and validated tool for assessing the severity of FA and subsequent response to rapamycin treatment. As demonstrated, this scale provides a more objective assessment, evaluating erythema, size, and extension of FA²⁰. Statistical analysis demonstrated a significant difference ($p < .05$) between FASI score, erythema, FA size, and IGA score before and after treatment with rapamycin liposomal formulation. The non-parametric tests did not show significant differences regarding the extension of FA (Table 2).

Patients who completed 24 weeks of treatment considerably improved the appearance of their FA in subjective evaluation. Particularly, 6/11 (55%) patients obtained excellent improvement of their injuries. Regarding Annex 4, FA in both patients decreased in erythema, size, and extension, achieving considerable flattening of the lesions.

Patient satisfaction also represented a relevant aspect in our study, with an improvement in quality of life in 5/11 (45%) patients after treatment. Nevertheless, significant differences regarding the DLQI scores

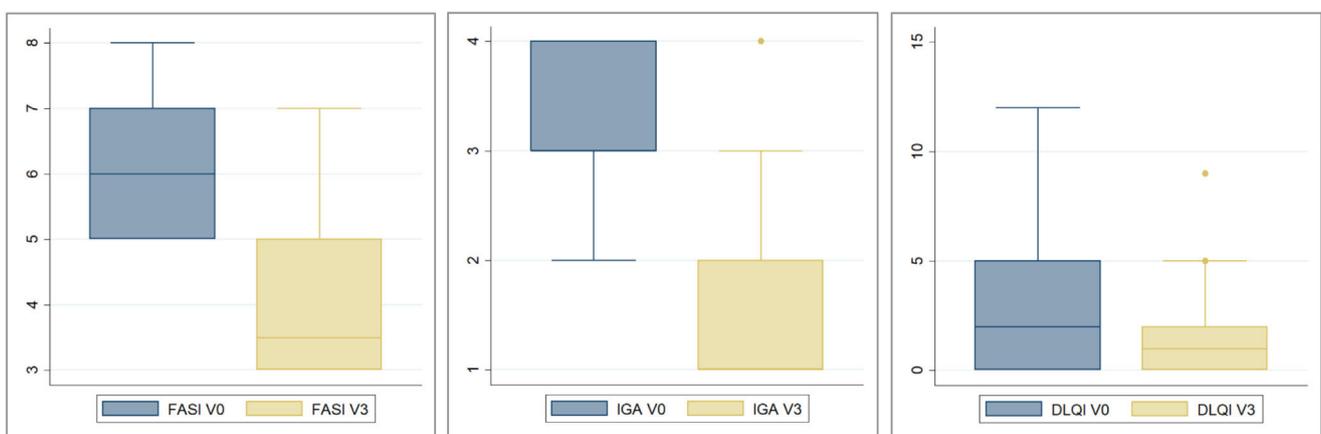


Fig. 2. Box plots of FASI, IGA, and DLQI scores before and after treatment, $n = 11$. FASI: facial angiofibroma severity index. IGA: investigator's global assessment. DLQI: dermatology life quality index.

were not observed in the non-parametric tests (Table 2). FA appeared between 2 and 5 years of age and grow in number and size, stabilizing in adolescence²¹. The visual impact of facial injuries implies a self-image issue^{4,5} especially in young patients, and sometimes dermatological treatment is not prioritized because there are other more serious complications associated with this rare disease. It has been observed that there is a greater angiogenic component at very early ages, while in elderly patients, fibromatous lesions tend to predominate. The exclusion criteria related to age are based on these observations and align with the criteria established by other similar clinical studies, including randomized clinical trials.

Overall, the new formulation was well tolerated, with mild adverse events reported that resolved upon completion of treatment. Two patients experienced moderate erythema, prompting early treatment discontinuation. Notably, both patients had a history of atopic-prone skin. Hematological and pharmacokinetic tests confirmed the lack of systemic absorption of rapamycin after topical administration, further enhancing the drug's safety profile.

Comparing our findings with existing studies proves difficult due to substantial variability in assessing effectiveness. Evaluation methods range from validated scales to subjective researcher opinions. Of the 5 randomized clinical trials found in the literature, only 2 studies evaluate effectiveness according to standardized objective scales.^{12,13} All patients treated with rapamycin showed significant improvement according to FASI and IGA scores compared to placebo. In our study, all patients who completed the 24-week treatment period achieved favorable effectiveness outcomes and the results align with previously published studies. Adverse reactions were consistent with literature and prior experiences, with no reported serious adverse events.

Greater long-term follow-up of liposomal rapamycin treatment would be appropriate to ensure effectiveness and safety. However, it should be noted that patients are not treated continuously, but rest during the summer months, to minimize or prevent the adverse events derived from rapamycin phototoxicity.

In any case, liposomes provide several advantages that allow a substantial improvement in the treatment of FA. This innovative formula exhibits superior organoleptic characteristics, appearance, and extensibility. Moreover, the sensation after application is more comfortable compared to vaseline^{16,18}. Additionally, it can be more easily removed with water and neutral soap than other formulations due to its lightweight nature, thus preventing the patient from irritating the facial skin during the washing process. All these benefits contribute to enhancing treatment compliance and patient satisfaction with topical therapy.

On the other hand, liposomes have been demonstrated to serve as carriers for molecules in chemotherapy and immunosuppressive treatments^{22,23}. Specifically, liposome-encapsulated rapamycin can reach the drug's site of action more quickly with a better release profile, providing an increased bioavailability of rapamycin and improving the penetration of the active substance¹⁷. These results underscore the importance of focusing on the optimization of formulations and the incorporation of new drug delivery systems in magistral formulation within hospital pharmacy services. Our work is an example of this approach. Drug development in hospital pharmacy services is often the only pharmacological alternative available to treat the symptoms of rare diseases, when treatment options are limited or inadequate.

In these rare diseases, pharmacy services are key elements in the pharmacotherapeutic process. In collaboration with dermatologists, hospital pharmacists can conduct a clinical follow-up of patients, contributing to improve effectiveness and minimize adverse reactions³. Pharmaceutical care demonstrates special relevance in the processes of formulation, dispensing, administration, and follow-up, promoting the correct supervision of these patients and greater integration of hospital pharmacists into the multidisciplinary team.

After galenic improvements and clinical evaluations, the rapamycin liposomal formulation proved to be effective and safe for the treatment

of FA in rare TS disease. This innovative formulation was included as a magistral formula in the Pharmacy Service of the Doctor Peset University Hospital, now accessible for prescribing by dermatologists.

The limited number of participants in this observational study could impact the reliability and applicability of the study's results. The initial sample size was not calculated due to it being a rare disease, and patient recruitment proceeded through casual or incidental sampling, as cases occurred and were referred by dermatologists. The methodology used and the statistical tests applied have taken into consideration the sample size ($n < 30$). However, it should be noted that TS is a rare disease that affects a minority of the population (fewer than 1 in 2000 people) and therefore recruiting patients is a more arduous and difficult task.

Impact statements

- This observational study proves the effectiveness and safety of a new rapamycin liposomal formulation for the treatment of facial angiofibromas in rare tuberous sclerosis disease.
- This innovative formula allows a substantial benefit for patients. Its organoleptic characteristics contribute to improve treatment compliance and patient satisfaction with topical rapamycin.
- Liposome-encapsulated rapamycin can reach the drug's site of action more quickly with a better release profile, improving the penetration of the active substance.
- This research provides new clinical data allowing support in therapeutic decisions for other authors, pharmacists, and dermatologists.

Ethics approval

This study was evaluated and approved by the Clinical Research Ethics Committee of Doctor Peset University Hospital (Registration number: 16.102 on 6 May 2021, in Valencia, Spain).

All tests and procedures of the study were performed in accordance with the Declaration of Helsinki for medical research involving human subjects, including research on identifiable human material and data (Helsinki, 1964).

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CRediT authorship contribution statement

Clara Cortell Fuster: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **María Amparo Martínez Gómez:** Validation, Supervision, Investigation. **Ana Cristina Cercós Lletí:** Validation, Supervision, Methodology, Conceptualization. **Mónica Climente Martí:** Validation, Supervision, Resources, Methodology, Conceptualization. **Tania Díaz Corpas:** Validation, Supervision, Resources, Investigation. **Almudena Mateu Puchades:** Validation, Supervision, Resources, Methodology, Investigation, Conceptualization. **Ángeles Revert Fernández:** Validation, Supervision, Resources, Investigation.

Availability of data and material

The data generated during and/or analyzed for this article are available from the corresponding author on a reasonable request.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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Appendix. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.farma.2024.04.023>.

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