Title: Topical sirolimus in dermatology: a systematic review

***Running head*:** Topical sirolimus

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Abstract

Context: Topical sirolimus is increasingly utilised off-license to manage various dermatological conditions whilst avoiding typical adverse effects associated with systemic sirolimus. However, widespread use is limited by a highly heterogeneous evidence base of mixed quality.

Objective: to evaluate the current evidence base for the indications, efficacy and safety profile for topical sirolimus in dermatology.

Data sources: A literature search was conducted from 2005 to July 4th, 2023, of English language studies, with the following databases consulted: MEDLINE, PubMed, Embase, CENTRAL and EBSCO. Key words included 'topical', 'rapamycin', 'sirolimus' and 'dermatology'.

Data extraction: Data on drug efficacy, concentration, side effects, co-interventions and follow up were extracted.

Results: The search identified 202 studies; 71 studies met the inclusion criteria. Efficacy of topical sirolimus was demonstrated in facial angiofibromas (799 patients) compared to placebo across multiple randomised controlled trials with a predominant concentration of 0.1%. Evidence was mixed for sirolimus use in port-wine stains (61 patients), with evidence of effectiveness in combined sirolimus and pulsed-dye laser. Multiple case reports demonstrated clinical improvement with topical sirolimus use in cutaneous vascular abnormalities (33 patients) at a higher concentration of 1%. Other applications of topical sirolimus were predominantly case reports demonstrating generally favourable outcomes. Topical sirolimus was generally well tolerated – most reported adverse effects were localised irritation and pruritus. Ointment-based preparations and once-daily dosing appeared to confer a better side effect profile.

Conclusion: Most high-quality data pertain to the efficacy of topical sirolimus in treating facial angiofibromas in tuberous sclerosis. Outcomes are generally promising in other indications and good tolerability, but data quality is mixed.

Introduction

Sirolimus, also known as rapamycin, is a macrolide compound typically administered orally to prevent kidney transplant rejection and coat coronary stents. Studies have shown oral sirolimus to confer a reduction in incidence of cutaneous squamous cell carcinoma in solid organ transplant patients[1], through blocking cell growth and proliferation pathways, as well as demonstrating clinical improvement in a host of other conditions such as autoimmune disease, vascular disease and genodermatoses such as Cowden's syndrome.[2] Classified as a mammalian target of rapamycin (mTOR) inhibitor, it effectively inhibits T and B cell activation. However, topical sirolimus is employed off-label due to the lack of a standardised therapeutic protocol. This systematic review aims to investigate the indications, efficacy, and safety of topical sirolimus in dermatology.

Characteristic	Description
Mechanism of action	mTOR inhibitor, inhibiting T-lymphocyte activation and proliferation
Indications for which there is evidence	Strongest evidence for facial angiofibromas, port wine stains and trichilemmoma. Multiple other indications often restricted to case reports.
Dosing	Available as ointment, cream, gel or solution. Various concentrations most commonly used are 1% and 0.5%.
Contraindications	Hypersensitivity to sirolimus or any other component
Caution	Hyperlipidaemia, immunosuppression or lymphoma. Patients should limit exposure to UV light.
Adverse effects	Generally well tolerated with limited systemic absorption. Common: Erythema, pruritus, burning sensation. Rare: allergic contact dermatitis, infection.

Table 1 Summary of topical sirolimus use in dermatology. mTOR, mammalian target of rapamycin.

Search strategy

A literature search was conducted from 2005 to July 4th, 2023, with the following databases consulted: MEDLINE, PubMed, Embase, CENTRAL and EBSCO. Keywords included 'topical', 'rapamycin', 'sirolimus' and 'dermatology' (Figure 1).

Levels of evidence were assigned as per the classification developed by the Centre for Evidence Based Medicine (CEBM)[3], see Table 2.

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

Table 2 Levels of Evidence for Therapeutic Studies adapted from the Centre for Evidence-Based Medicine[3]

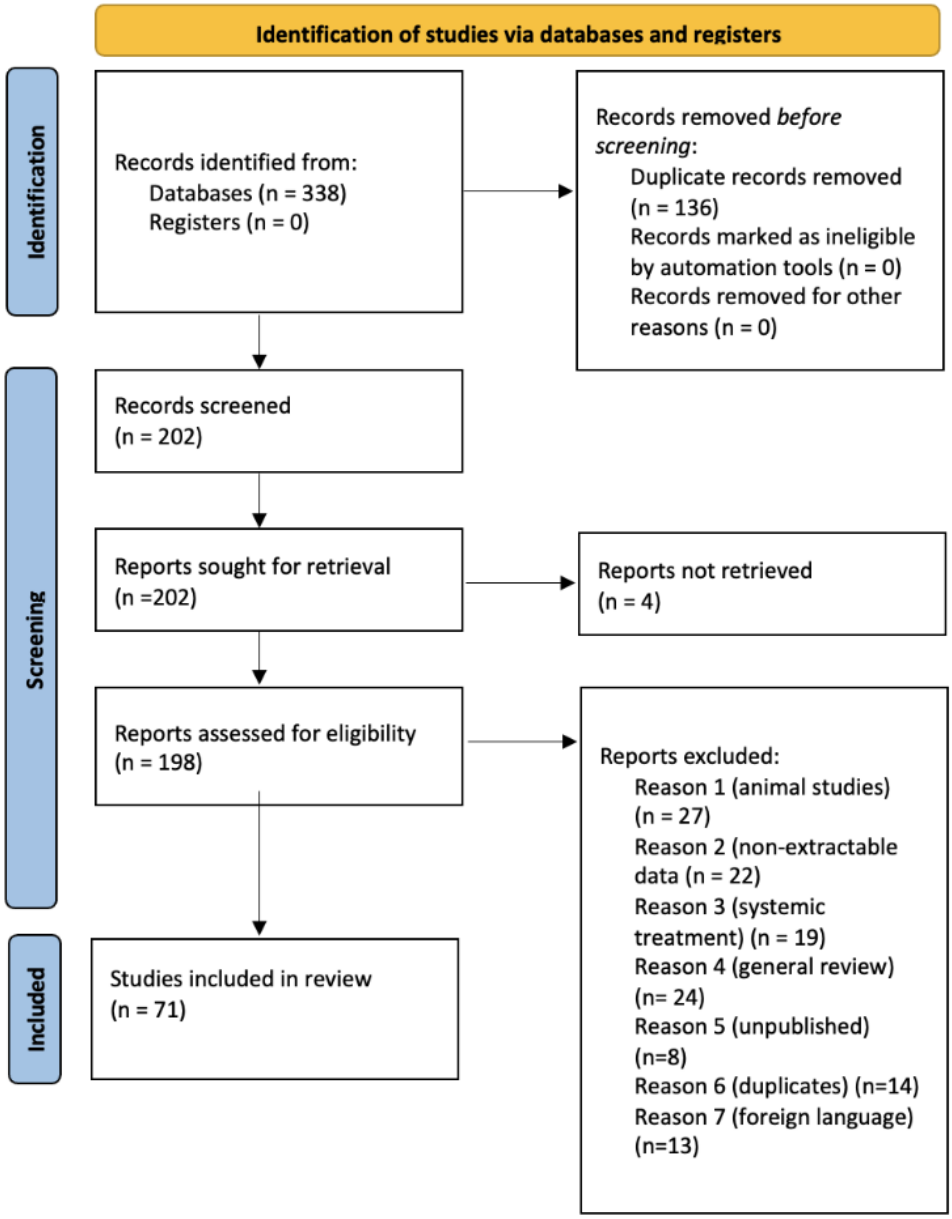

Figure 1 – Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram

Table 3 Systematic review of literature – Angiofibromas

Indication	Year	Author	Level of evidence (CEBM)	N	Sirolimus concentration	Vehicle	Study design	Other associated therapies	Posology	Duration (weeks)	Summary of results
Angiofibromas	2022	Cortell et al	1a	508	0.1%, 0.2%, multiple others	Ointment, Gel, Solution	Systematic review	Laser, electrosurgery, calcitriol			30 studies comprising 508 patients. Multiple sirolimus concentrations (0.003–1%) and formulations used. Sirolimus was effective in all studies except for 5 patients in a 1b study. Deemed safe to use in FAs.
	2020	Chen et al	1b	52	0.1%	Ointment	Sirolimus 0.1% vs sirolimus-calcitriol 0.1% vs calcitriol only	Topical calcitriol	Twice daily	24	Sirolimus-calcitriol combination and sirolimus had similar statistically significant reduction in mFASI at week 12. Sirolimus-calcitriol combination resulted in greater clinical improvement (erythema, papule size).

	2018	Koenig et al	1b	179	0.1%, 1%	NR	0.1% vs 1% vs placebo	None	NR	24	Statistically significant improvement in FAs was observed for all combinations, with most improvement occurring within the first month. Topical sirolimus was generally well-tolerated, with no measurable systemic absorption.
	2017	Wataya-Kaneda et al	1b	36	0.05%; 0.1%; 0.2%	Gel	0.05% vs 0.1% vs 0.2%vs vehicle only	None	Twice daily	16	Statistically significant improvement factor in all active treatment groups receiving 0.2% sirolimus unlike those receiving 0.1% and 0.05% sirolimus. No significant adverse effects were observed.
	2017	Ebrahimi-Fakhri et al	4	1	0.1%	Ointment	-	None	Twice daily	164	Sustained remission achieved over three years follow up.

											No standard dose or formulation at present.
	2012	Koenig et al	1b	23	0.003%, 0.015%	Skincerity	0.003% vs 0.015% vehicle only	None	Once daily (nightly)	24	73% of subjects in the treatment arms versus 38% of subjects in the placebo arm described a subjective improvement in their FAs.

Table 4 Systematic review of literature – Port Wine Stains and Vascular Anomalies

Indication	Year	Author	Level of evidence (CEBM)	N	Sirolimus concentration	Vehicle	Study design	Other associated therapies	Posology	Duration (weeks)	Summary of results
Port wine stains	2021	Fallahi et al	1b	15	0.2%	Cream	PDL + sirolimus vs PDL + placebo	PDL	Once daily (nightly)	24	Medial and lateral sides of the treatment and placebo parts did not differ significantly as per colorimetric analysis. Other evaluations such as PGA and IGA found statistical significance in favour of sirolimus. Itching and dryness (86.7%), contact dermatitis (20%) were the most common adverse effects.
	2020	Artzi et al	2b	3	0.2%	Cream	PDL + Tixel + sirolimus vs PDL + sirolimus	Tixel device	Twice daily	4	Clinically significant differences in blanching responses favouring PWS with PDL, DDS, sirolimus compared to PDL & sirolimus alone. Side effects included: transient hyperpigmentation,

											irritation and dermatitis.
	2018	Musalem et al	4	5	0.5%, 1%	Cream	-	PDL	Once daily	Variable	Dual therapy (PDL + sirolimus) conferred significant improvement over a shorter period.
	2017	Greveling et al	1b	14	1%	Cream	PDL-only, PDL + sirolimus, PDL + Erbium YAG laser ablation	PDL, Erbium YAG laser ablation	Applied for 7 days under dressing	24	There were no statistically significant differences between treatments. Best photographic evaluation and highest patient satisfaction was achieved with PDL-only treatment. Pruritus was a common SE.
	2016	Griffin et al	4	1	0.5%	Ointment	-	None	-	-	Topical sirolimus ointment + PDL resulted in greater clinical improvement and fewer laser treatments compared to PDL alone.
	2015	Marques et al	1b	23	1%	Cream	Placebo, PDL + placebo, Sirolimus,	PDL	Once daily	18	PDL + sirolimus resulted in the lowest digital

							PDL + sirolimus				photographic image score and the lowest percentage of vessels in histologic analysis. A statistically significant improvement was found with PDL + sirolimus relative to the other interventions.
Cutaneous vascular anomalies	2020	Badia et al	4	23	1%	Not stated	-	-	Twice daily	88	Eighty-six percent of patients (n = 20) had improvement of cutaneous lesions. Lymphatic blebbing complications improved in 90% (n = 17). One patient electively stopped treatment due to pruritus and burning sensation.
	2020	Camacho et al	4	1	1%	Not stated	-	-	Twice daily	16	Reduced thickness, size and colour of lesion. Improvement in pruritus and pain. No adverse effects reported. Treatment stopped

											at 6 months, with no re-occurrence at 1 month.
	2018	Burleigh et al	4	2	1% and 0.1%	Phosphatidylcholine and propylene glycol solution for first case. White petrolatum ointment for second case.	-	-	Twice daily and once daily	16 and 64	Clinical improvement in thickness and induration. Local irritation occurred with twice-daily dosing in the first case, attributed to delivery vehicle. An ointment-based preparation at a lower concentration in the second case did not cause irritation.
	2018	Caliskan et al	4	1	1%	Solution	-	-	Twice daily	12	Almost full clearance of lesions. Local irritation after two weeks of twice-daily application.
	2017	Doh et al	1b	6	1%	Taro ammonium lactate lotion 12%	1) PDL + placebo, PDL + topical sirolimus 1 weeks after laser, and 8 weeks after laser	PDL	Once daily (nightly)	16	Only one of six patients showed clinical improvement with combined rapamycin treatment. Overall, no statistically significant

											difference in erythema and blanching rate among PDL alone and combined rapamycin regimens. No adverse effects reported.

Table 5 Systematic review of literature – Lichen Planus, Hair Follicle Tumours and Miscellaneous

Indication	Year	Author	Level of evidence (CEBM)	N	Sirolimus concentration	Vehicle	Study design	Other associated therapies	Posology	Duration (weeks)	Summary of results
Lichen planus	2020	Samimi et al	1b	76	1%	Solution	Sirolimus vs Betamethasone	-	Once daily	12	At 3 months, 39.4% of patients with betamethasone and 27.3% with sirolimus achieved clinical remission. Recurrence rates were similar between groups. Adverse events occurred in 43.6% of patients with sirolimus such as burning sensation, impaired taste and 27.8% with betamethasone

											such as oral candidiasis.
	2009	Soria et al	2b	7	1%	Solution	-	-	Twice daily	20	At 3 months, 4 patients had complete remission and 2 patients had partial remission. Only 1 patient had detectable serum sirolimus levels.
Benign hair follicle tumours	2023	Bhanot et al	4	1	0.2%	Gel	-	-	Once daily	72	9-month course of 0.2% topical sirolimus applied to the entire face, daily, resulted in near clearance of papules.
	2020	Shimizu et al	4	1	0.2%	Gel			Three times daily	12	0.2% topical sirolimus for a period of 3 months resulted in marked reduction in number of facial nodules.
	2019	Dreyfus et al	4	5	1%	Cream			Twice daily	20	Physicians scored a median efficacy rating of 3.5/10 at 5 months compared to

											5.5/10 scored by patients. The clinical response was characterized by a decrease in the density of the lesions. Four patients reported an improvement in the lesions whereas patient 5 did not report any improvement.
	2017	Tu et al	4	2	1%	Cream		CO2 laser ablation + sirolimus in one sibling and sirolimus alone in other sibling	Twice daily	52	Both siblings had a reduction in the growth of new lesions with no reported recurrence or side effects.
Keratosis pilaris rubra	2022	Eckburg et al	4	1	1%	Cream			Twice daily	72	Total resolution of facial erythema and burning sensation. Nil notable side effects.
Squamous cell cancer chemoprevention	2022	Chong et al	1b	18	1%	Gel	Sirolimus vs placebo		Once daily	12	At 12 weeks, number of keratotic lesions was reduced in each patient by

											31 ± 5% (from an average of 9.7 to 7.9) in the treated side, whereas it increased marginally in the placebo only group.
Acanthosis nigricans	2021	Coerdt et al	4	1	1%	Cream			Twice daily	42	Significant improvement with lightening and thinning of the plaques was observed.
Papillomatosis	2021	Kurtyka et al	4	1	1%	Cream			Twice daily	16	Marked improvement of the appearance of the plaques was seen on the central chest and neck with no associated side effects or recurrence
Benign cephalic histiocytosis	2019	Habeshian et al	4	1	1%	Ointment			Twice daily	28	A split face model was employed with significant improvement (based on physician and parental perception).

Anti-ageing	2019	Chung et al	1b	36	10 µM	Cream	Sirolimus vs placebo		Once daily	24	Statistically significant increase in Collagen VII was noted in all participants. Relative improvement in clinical appearance of skin.
Cardiofacio-cutaneous syndrome	2019	Bessis et al	4	2	1%	Cream			Twice daily	52	No substantial improvement in the redness and keratotic components of ulerythema ophryogenes was witnessed in the two patients involved.
Fibrofolliculomas	2014	Gijezen et al	1b	19	1%	Ointment	Sirolimus vs placebo		Twice daily	24	No significant difference was noted in number, size or severity of fibrofolliculomas.
Oral pemphigus vulgaris	2012	Poot et al	4	3	1%	Solution			Twice daily	3	Mucosal symptoms in all three patients worsened with an improvement only noticed when sirolimus was stopped.

Chronic plaque psoriasis	2005	Ormerod et al	1b	24	2.2% for 6 weeks, then 8% for 6 weeks.	Solution	Sirolimus vs placebo		Not stated	12	A significant reduction in the clinical score (mean score 9.1 following sirolimus vs. 11.2 in control) was achieved with topical sirolimus. Biopsies showed a significant reduction in CD4+ cells and proliferating cells in the epidermis

Tuberous sclerosis complex

One of the well-established applications of topical sirolimus is the treatment of facial angiofibromas (FA) in tuberous sclerosis. FAs cause substantial psychological distress, but invasive procedural treatments are not suitable for all patients. *Table 3* summarises all relevant papers relating to sirolimus use in treating angiofibromas.

A recent systematic review[4] encompassed 30 studies involving a total of 508 patients to examine the effectiveness and safety of topical sirolimus for treating FAs in tuberous sclerosis. This review included four randomized controlled trials (RCTs)[5–8] with 79 (15.6%) patients, 17 case series, and nine case reports. In 25 studies, topical sirolimus was employed as monotherapy. In the remaining five studies, topical sirolimus was used in conjunction with other treatments, such as calcitriol, electrosurgery, topical tacrolimus, laser therapy, and in one instance, oral sirolimus. There was a notable variability in the concentration of topical sirolimus, with 0.1% used in 41.9% of cases, 0.2% in 21.3%, and other concentrations (0.5%, 0.4%, 0.05%, 0.003%, and 0.015%) collectively used in 11.8% of cases. The predominant vehicle for topical sirolimus was an ointment, and the most common application frequency was twice daily, accounting for 46.9% of patients. Importantly, all studies, except for one,[5] demonstrated clinical effectiveness. Subjective assessments were employed in 355 patients (69.9%), with 153 patients (30.1%) utilizing the Facial Angiofibroma Severity Index score (FASI), while other unvalidated scoring systems were used in 10.4% (n=53) of cases.

Topical sirolimus was generally well-tolerated, with only two cases of adverse reactions reported: one case of pneumonia secondary to a seizure and one case of urosepsis—both cases resolved with basic management. The four RCTs revealed that the most common side effects included pain, dry skin, erythema, and pruritus. Sirolimus plasma levels were undetectable in 99.1% (340) of the 343 patients (67.5%) who underwent testing.

One of the cited RCTs[5] involved 23 subjects who applied topical sirolimus nightly for six months. The investigational product involved either no sirolimus, 0.003% or 0.015%. Notably, 73% of participants in the treatment arm reported subjective improvements in their FA compared to 38% in the placebo arm. Interestingly, a second RCT[6] (n=36) employing more objective measures of clinical response (volume, redness, height) found statistically significant improvements only in the group receiving a higher concentration of topical sirolimus 0.2% compared to 0.1% and 0.05% topical sirolimus or placebo. A third RCT[7] enrolled 179 subjects into three groups: 59 in the 1% sirolimus group, 63 in the 0.1% sirolimus group, and 57 in the vehicle-only group. At 6 months, the 1% sirolimus group demonstrated the most significant average improvement in Angiofibroma Grading Scale (AGS) scores completed by independent masked dermatologists, and post-treatment images corroborated these findings.

Another RCT[8] compared the effectiveness of topical sirolimus with or without calcitriol in improving FAs in a cohort of 52 patients over three 12-week periods. Statistically significant differences were found in the mean changes of mFASI at week 12 compared to baseline: -0.92 for sirolimus ($p \leq 0.001$), -0.44 for calcitriol ($p=0.039$), and -1.09 for sirolimus-calcitriol dual therapy ($p \leq 0.001$), indicating substantial improvements in all treatment groups. Notably, sirolimus-calcitriol dual therapy demonstrated superior effectiveness in reducing erythema and papule size when compared to sirolimus used as monotherapy.

Notably, our search identified only four RCTs out of a total of 28 papers, indicating a paucity of high-quality studies in this area. Furthermore, there is substantial heterogeneity in the concentration, dosing regimen, treatment duration, and measures of clinical efficacy for topical sirolimus application. Nevertheless, it can be reasonably concluded that topical sirolimus represents a safe and effective treatment for FAs in TSC. However, patient compliance is crucial, as evidence suggests a risk of recurrence when treatment is discontinued.[9]

Despite large-scale RCTs, there is no clearly established therapeutic dosage or protocol for treating angiofibromas. Although the predominant dosage that yielded effective results across most studies was 0.1% topical sirolimus, NICE nor NHS England have not produced guidance.[10] Therefore, further clinical trials are required to substantiate the clinical efficacy of topical sirolimus.

Port Wine Stain

Pulsed dye laser (PDL) is the standard treatment for port wine stains (PWS), but incomplete regression and recurrence often occur due to post-PDL revascularization. Sirolimus, an inhibitor of angiogenesis, shows promise as an adjuvant treatment, but topical application has yielded mixed results. *Table 4* summarises all relevant papers relating to sirolimus use in treating PWS'.

An RCT evaluated the safety and efficacy of topical sirolimus at a concentration of 0.2% as an adjuvant therapy alongside pulsed dye laser for PWS treatment in 15 patients.[11] While colorimetric analysis didn't reveal significant differences between treatment and placebo areas, subjective assessments, such as the Investigator Global Assessment (IGA) and Patient Global Assessment (PGA), showed significant differences favouring sirolimus. Common adverse effects included dryness and itching (86.7%) and contact dermatitis (20%).

A RCT investigated the efficacy of topical sirolimus 1% combined with PDL in the treatment of capillary vascular malformations in Sturge-Weber syndrome.[12] This study, involving 23 patients, recorded significant improvements during the 18-week treatment duration.

Contrastingly, a RCT compared four treatment approaches: PDL-only, PDL + sirolimus, PDL + Erbium YAG laser ablation of the stratum corneum + sirolimus, and sirolimus monotherapy.[13] The study involved 14 patients, and while the highest percentage clearance was observed with PDL-only treatment, no statistically significant differences were found between the treatment groups. PDL-only treatment yielded the best photographic evaluation and highest patient satisfaction, with the only statistically significant difference observed between PDL-only and sirolimus monotherapy. The study concluded that the topical application of commercially available sirolimus solution as an adjuvant to PDL did not enhance the blanching of PWS lesions.

The Tixel device (Novoxel, Israel), a non-laser thermal resurfacing system, may enhance drug delivery and improve treatment outcomes. A retrospective study involved three teenage patients with large, previously treated PWS that had not shown sufficient improvement after PDL treatment.[14] Each PWS was divided into two halves (A and B), with half A receiving treatment with the Tixel drug delivery system (DDS) in addition to PDL and topical sirolimus, while half B received PDL and topical sirolimus alone. PWS halves treated with PDL + DDS + sirolimus (PTR) demonstrated better clearance and higher patient satisfaction compared to the PDL + sirolimus (PR) halves.

In a case report featuring a 56-year-old male with extensive PWS, initial PDL therapy showed marginal improvement, but the introduction of 0.5% sirolimus ointment yielded more favorable

therapeutic outcomes, requiring fewer laser treatments.[15] A similar case series of five patients showed unsatisfactory results for PWS malformations with the use of a pulse dye laser only but significant improvement in a short timeframe after the introduction of dual therapy with topical sirolimus (0.5-1%).[16]

Overall, there is a greater quantity of data accounting for 1% sirolimus as the predominant dosage that has yielded the greatest benefit.

Vascular anomalies

Systemic sirolimus has previously been shown to be effective in the treatment of complicated vascular anomalies (VA). Cutaneous manifestations of VA, such as lymphatic blebs, nodular overgrowth, skin thickening, and pruritus, are common and cause significant morbidity. Emerging data on the use of topical sirolimus for the treatment of these cutaneous manifestations of VA offer a less invasive therapeutic option. *Table 4* summarises all relevant papers relating to sirolimus use in treating VAs.

A case series evaluated topical sirolimus 1% for the treatment of cutaneous manifestations of vascular anomalies (VA) by retrospectively reviewing medical records of pediatric patients with VA treated with topical sirolimus 1%.[17] Out of 23 patients, 20 (86%) experienced clinical improvement, particularly in lymphatic blebbing complications (90%). No major side effects were reported, and sirolimus blood levels were undetectable in all patients. Patients already receiving systemic sirolimus therapy also benefited from the addition of topical sirolimus. Conversely, a prospective study investigated the combined use of 1% topical sirolimus with PDL for non-facial cutaneous capillary malformation, with only one out of six patients benefiting from the treatment.[18] No statistically significant differences in erythema and balancing rate were observed, suggesting limited effectiveness for sirolimus in non-facial capillary malformations.

Oral sirolimus has been used with success in refractory cases of tufted angioma and other complex vascular malformations in children, but the risks of systemic treatment are not always warranted in uncomplicated lesions. Topical sirolimus was used for the first time to treat tufted angiomas on the arm and neck of two children.[19] The first patient reported irritation as the sole side effect of a twice-daily dosing regimen, while the second patient tolerated the treatment well with once-daily dosing. Further case reports highlighted the successful treatment of solitary angiokeratoma[20] and microcystic lymphatic malformation[21] using topical sirolimus 1%, resulting in improved appearance and symptom relief.

The predominant dosage that yielded effective results across most studies was 1% topical sirolimus. Ointment preparations and once-daily dosing appeared to confer a greater side effect profile.

Lichen Planus

A randomized controlled trial showed a similar clinical response between topical corticosteroids and topical sirolimus in the management of oral erosive lichen planus.[22] Topical sirolimus solution 1% was compared to betamethasone dipropionate ointment 0.05% with associated blinding. The findings revealed no significant difference in clinical remission between the two groups at the end of the three-month duration, though betamethasone showed a significantly greater reduction in the Visual Analog Scale (VAS) scores compared to sirolimus (RR = 0.59). Moreover, both groups reported adverse effects, with the rapamycin group experiencing a higher frequency of burning sensations (n = 15) compared to betamethasone (n = 1). *Table 5* summarises all relevant papers relating to sirolimus use in treating lichen planus.

Another prospective study also on the use of topical sirolimus in oral erosive lichen planus involved seven women.[23] Over a three-month period, patients applied the rapamycin solution twice daily to oral erosive lesions, with some individuals having concurrent erosive vulvar lesions treated with the same solution. The results revealed promising outcomes, with four women achieving complete remission, two experiencing partial remission, and only one discontinuing treatment due to local discomfort. Blood sirolimus levels were detectable in just one patient, suggesting minimal systemic absorption and minimal side effects. Another report demonstrated pain reduction within four weeks and complete ulcer elimination after 20 weeks of topical sirolimus 1%.[24]

According to the studies evaluated, a 1% topical sirolimus concentration appears to confer the greatest clinical benefit, with limited data for other concentrations.

Benign hair follicle tumours

Trichilemmomas, benign hair follicle tumours, can cause cosmetic concerns to patients and currently lack medical treatment. Topical sirolimus has been studied for trichilemmoma treatment as an alternative to more invasive treatment options. *Table 5 summarises all relevant papers relating to sirolimus use in treating* benign hair follicle tumours.

In a case series involving five patients,[25] topical sirolimus 1% effect on multiple trichoepitheliomas was assessed. Four patients experienced beneficial outcomes, with a reduction in lesion size and thickness. However, one patient did not show significant improvements during the five-month treatment period. Two patients reported slight skin irritation and headaches within the first week of treatment, despite sirolimus plasma levels remaining undetectable. These results suggested that topical sirolimus could be well-tolerated and potentially interrupt the progression of trichoepitheliomas.

Another case series presented the novel use of topical 1% sirolimus cream in two siblings with multiple facial trichoepitheliomas.[26] One sibling was treated solely with 1% sirolimus cream, while the other received a combination of CO2 laser ablation and topical sirolimus. Both patients exhibited a reduction in the growth of new lesions over the 12-month treatment period. No side effects were reported, and rapamycin plasma levels were not documented.

One case involved a female patient diagnosed with trichilemmomas secondary to Cowden syndrome treated with 0.2% topical sirolimus gel once daily for 9 months.[27] Notable improvement was demonstrated, with near clearance of multiple flesh-coloured papules. Topical 0.2% sirolimus gel was also successfully used in a case of trichoepithelioma papulosum multiplex in Japan, marking the

first such case in the country.[28] Dosing was different in this study, with the thrice daily application over 3 months showing a significant reduction in trichoepitheliomas. No adverse effects were reported in both cases, and rapamycin plasma levels were undetectable.

Overall, case series data shows equal efficacy in significantly reducing benign hair follicle tumours at 0.2% and 1% concentrations.

Miscellaneous

Topical sirolimus 1% was effective in treating acanthosis nigricans in one female patient after 13 months.[29] Significant improvements were observed after just two months, including lightening and thinning of plaques. Similarly, the successful treatment of Keratosis pilaris rubra (KPR) was achieved using topical sirolimus 1% after 12 months of treatment.[30] *Table 5* summarises all relevant papers relating to sirolimus use in treating miscellaneous conditions.

A case report (32) investigated the off-label use of topical sirolimus 1% cream for confluent and reticulated papillomatosis, with one male patient involved showing significant improvement after three months, without side effects.[31] An RCT investigating the effectiveness of topical sirolimus 1% in chemoprevention of cutaneous squamous cell carcinoma (SCC) and its precursors in organ transplant patients reported significant improvements in 18 patients after three months, concluding that switching from calcineurin inhibitors to topical sirolimus can lead to a two-fold reduction in SCC risk.[32] In the case of benign cephalic histiocytosis, a case report demonstrated the efficacy and safety of topical 1% rapamycin ointment after 7 months of treatment.[33] Results showed that the number of keratotic lesions reduced by approximately 31% at 12 weeks. An RCT by Chung et al. found topical sirolimus to reduce the expression of p16INK4A (p=0.008), which controls cell senescence, suggesting its potential for sirolimus as an anti-ageing therapy.[34] The study enrolled 36 participants, although only 17 completed the study.

Conversely, topical sirolimus 1% proved ineffective in the treatment of Cardiofaciocutanous syndrome.[35] No substantial improvement in the redness and keratotic components of ulerythema ophryogenes was witnessed in the two patients involved, with 0% benefitting from the treatment. In the case of pemphigus vulgaris of the oral cavity, a case series revealed that topical sirolimus 1% was unresponsive, with 0% of the three patients benefitting and 100% showing no improvement during the three-week treatment period.[36] Additionally, the application of topical sirolimus 1% had worse side effects, leading to an immediate cessation of further treatment. Topical 1% sirolimus ointment was not effective in the treatment of Birt-Hogg-Dube syndrome, as demonstrated in an RCT.[37] All 19 patients who applied 0.1% topical sirolimus showed no improvement during the six-month treatment period. Moreover, the patients reported side effects, such as a burning sensation and itching. An RCT evaluating topical sirolimus for psoriasis found that while it exhibited some anti-psoriatic and immunosuppressive activity, significant improvements were not consistent across all parameters.[38] Twenty-four patients with stable chronic plaque psoriasis were treated with high concentration (2.2% and 8%) topical sirolimus for a total of 12 weeks, and although there was a significant reduction in the clinical score (p=0.03), measurements of plaque thickness and erythema did not show significant improvement.

Ongoing research is exploring the application of topical sirolimus in addressing neglected rare diseases, including microcystic lymphatic malformations and pachyonychia congenita, as well as the prevention of basal cell carcinoma in Gorlin syndrome.[39–41]

Discussion

The quality of evidence across studies and conditions for topical sirolimus vary significantly. For tuberous sclerosis and FAs, the evidence includes a mixture of RCTs, case series, and case reports, indicating a relatively robust interest and investigation into this application. However, the RCTs, while indicating effectiveness, are limited in number and varied in methodology, concentration, and application frequency.

For other dermatological conditions, such as port wine stains, vascular anomalies, and benign hair follicle tumours, the evidence is less extensive and primarily consists of smaller RCTs, case series and individual case reports with significant methodological differences. This indicates a need for larger, well-designed RCTs to establish clearer protocols and an impression of efficacy.

Gaps in the current literature include a lack of standardisation in sirolimus concentration and formulation, dosing regimens, and inconsistent or non-validated outcome measures. Data specifically on long-term safety and efficacy in the form of delayed relapse is sparse, particularly for conditions other than tuberous sclerosis.

Future research should focus on:

1. Conducting larger-scale, high-quality RCTs across various dermatological conditions to establish standardised dosing regimens and application protocols.
2. Investigating the long-term safety and efficacy of topical sirolimus, particularly with regards to recurrence rates after discontinuation.
3. Exploring the potential of combination therapies with topical sirolimus and other treatment modalities.
4. Examining patient compliance factors and developing strategies to enhance concordance with treatment regimens.

Safety of Topical Rapamycin

The safety of topical rapamycin, as reported in several studies across various dermatological conditions, generally indicates a favourable profile. Adverse effects were primarily mild and included symptoms such as skin irritation[14,19,21,25], dryness, and itching.[13] In rare cases, transient side effects like erythema [14,42], crusting, or transient hyperpigmentation[14] were reported but resolved with discontinuation. Rare case reports of allergic contact dermatitis have also been reported.[43] Importantly, haematological tests were mostly within normal ranges, and sirolimus plasma levels were often undetectable or minimal, suggesting limited systemic absorption.[27,28,30,32,36,42] While the specific side effects varied depending on the condition being treated, the overall consensus from the studies reviewed is that topical rapamycin appears to be well-tolerated and safe for dermatological applications. However, it's essential for dermatologists to consider individual patient factors and closely monitor for any adverse reactions during treatment.

Conclusion

The literature reveals significant heterogeneity in the quality of studies and the efficacy of topical sirolimus in dermatology. Most studies relate to the application of topical sirolimus in treating FAs in tuberous sclerosis where there is clear evidence of efficacy. However, further longitudinal studies are required to develop a therapeutic protocol. With respect to other dermatological conditions, there is a limited evidence base to suggest any immediate translation to current clinical practice.

Learning points

- Topical sirolimus can be regarded as a safe and effective treatment for FAs in TSC however, patients must be counselled on the importance of compliance to prevent recurrence
- There is clear subjective improvement in PWSs after PDL + topical rapamycin application; however, there is limited objective improvement in terms of colorimetric improvement.
- There is insufficient evidence on the efficacy of topical sirolimus in treating oral mucosal conditions.
- 0.2% topical sirolimus has been found, in case reports, to be effective in treating trichilemmomas.
- Topical sirolimus has some anti-psoriatic and immunosuppressive activity. An RCT has found significant improvement in the clinical score of psoriasis patients treated with topical sirolimus.

Questions

1. In which of the following syndromes has topical sirolimus found to be a useful adjuvant treatment?
    a. Prader Willi
    b. Noonan
    c. Turner
    d. CHARGE
    e. Sturge Weber*
2. An Erbium YAG laser used to ablate PWS acts on which layer of the skin?
    a. Stratum lucideum
    b. Stratum spinosum
    c. Stratum corneum*
    d. Stratum granulosum
    e. Stratum basale
3. Which of the following topical ointments has been found to be efficacious in treating facial angiofibromas when combined with topical sirolimus?
    a. Calcitriol*
    b. Retinoids
    c. CE Ferulic acid
    d. Colloidal oatmeal
    e. Hyaluronic acid
4. Case reports have shown which of the following vascular anomalies demonstrate clinical improvement when treated with topical sirolimus?
    a. Microcystic lymphatic malformation*
    b. Spindle cell sarcoma
    c. Hereditary haemorrhagic telangiectasia
    d. Blue rubber bleb nevus syndrome
    e. Proteus syndrome
5. In which of the following inflammatory skin conditions has topical sirolimus found to have some utility in treating?

a. Seborrhoeic dermatitis
b. Acne vulgaris
c. Atopic dermatitis
d. Psoriasis*
e. Folliculitis

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