Treatment Options for Management of Facial Angiofibroma Associated with Tuberous Sclerosis Complex: A Systematic Review of Evidence of Clinical Effectiveness and Cost-Effectiveness

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BACKGROUND

- Tuberous sclerosis complex (TSC) is a rare, multisystemic autosomal dominant disorder arising from the loss of function in *TSC1* and *TSC2* genes.[1] Globally, ~2 million people are estimated to have TSC.[2] In the US, one in every 6000 live birth is reported to have TSC.[2] Facial angiofibroma, one of the predominant cutaneous manifestations of TSC (reported in 83%-90% of TSC patients), is a major criterion for the diagnosis of TSC.[3]
- Physical treatments include radiofrequency ablation, cryotherapy, electrocoagulation, dermabrasion, and laser therapies.[4] However, these are associated with recurrence, adverse effects, and multiple treatment visits, causing increased healthcare utilization and costs. Pharmacological treatments include inhibitors of the mechanistic target of rapamycin (mTOR). Although systemic mTOR inhibitors have been shown to improve facial angiofibroma, questions regarding their safety remain.[5] Lack of clear and established guidelines for treating facial angiofibroma associated with TSC poses a challenge in managing the condition efficiently.
- The current systematic literature review assessed the clinical effectiveness, safety, and cost-effectiveness of physical and pharmacological treatments in patients with facial angiofibroma associated with TSC.

METHODS

SEARCH STRATEGY, SCREENING, AND STUDY INCLUSION

- PubMed, Cochrane database, health technology assessment database, trial registries, and conferences were searched for randomized controlled trials (RCTs), non-RCTs, observational and cost-effectiveness studies reporting clinical effectiveness, safety, and cost- effectiveness/cost-utility studies for facial angiofibroma associated with TSC in male and female children and adults, between 1994 to 2022.
- We included RCTs and observational studies reporting results for topical formulations of rapamycin/sirolimus, calcitriol, tacrolimus, and everolimus and physical treatments such as laser and surgery, dermabrasion, combination, and compounded therapies as the intervention for facial angiofibroma associated with TSC.
- Two reviewer panels independently reviewed and evaluated the articles at two stages: title/abstract and full-text screening. DistillerSR software removed duplicate records and managed search results and article screening.
- This systematic review was carried out per the recommendations of the Cochrane Handbook, registered with the International Prospective Register of Systematic Reviews (CRD42022315809), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

DATA SYNTHESIS AND QUALITY EVALUATION

- A random effect model using the I^2 index assessed between-study heterogeneity for quantitative outcomes where meta-analysis was possible. The between study variance was determined using the Residual Maximum Likelihood estimation method. An exploratory, pairwise meta-analysis was also performed.
- For assessing the risk of bias, quality checks were performed using the Cochrane risk of bias tool (for RCTs), ROBINS-I checklist (for non-RCTs), STROBE checklist (for cohort and cross-sectional studies), and JBI checklist (for case series and case reports).
- Data was presented in narrative form, including tables and figures, using guidance from Synthesis without Meta-Analysis (SWiM), where statistical pooling in a direct or mixed treatment was not possible for intervention studies due to heterogeneity.

OUTCOMES

- Primary and secondary outcomes included in data synthesis are presented in **Table 1**.

Table 1. Outcomes data

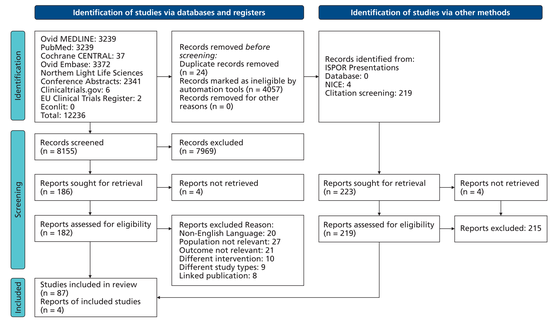
PRIMARY	
Clinical effectiveness *Subjective assessment*	• Reduction of angiofibroma in terms of number and size • Reduction in size or color assessment of erythema/papule/lesion/plaque/pigmentation/hypopigmented macule • Reduction in nodularity of angiofibroma • Removal of resistant papule • Composite improvement in angiofibroma, general appearance, assessed by the investigator or Independent Review Committee
Quantitative improvement	• Change from baseline in the Angiofibroma Grading Scale (AGS) • Response rate assessment • Score change in Facial Angiofibroma Severity Index (FASI) and modified FASI (mFASI), improvement factor assessment [a grade of erythema and the structure of facial angiofibromas: mild (≤5), moderate (6-7), and severe (≥8)]
Safety assessments	• Adverse events: Grade 3 or 4 • Treatment-Emergent-Adverse-Events (TEAEs) • Hematological tests, Plasma-drug level • Radiological • Tolerability of treatment
Cost-effectiveness	• Incremental Cost-Effectiveness Ratio (ICER) • Incremental cost per Quality-Adjusted Life Year (QALY) • Incremental cost per Disability-Adjusted Life Year (DALY)
SECONDARY	
Clinical effectiveness	• Decreased relapse/regrowth/recrudescence/recurrence of facial angiofibroma

RESULTS

STUDY CHARACTERISTICS

- Of the 12,459 articles searched, 8,155 were screened at the title/abstract level, and 4,081 were deduplicated; 91 studies (13 experimental and 78 observational) were included for final review (**Figure 1**). Of the 2,591 studies identified for cost-effectiveness, none were included as they did not meet the inclusion criteria.
  - Thirteen experimental studies were analyzed, including 6 RCTs and 7 non-RCTs. Among these, 3 were conducted in the US, 5 in Japan, and 1 each in Taiwan, Turkey, the United Kingdom, Spain, and Australia, respectively. Among the RCTs, 2 were phase III trials, 2 phase II trials, and 1 phase I trial; 1 single-blind prospective RCT and another open-label prospective RCT did not specify the trial phases, and 3 trials used left-right split-face comparison study designs.
- Ten studies (4 RCTs and 6 non-RCTs) reported different concentrations of rapamycin (henceforth referred to as topical sirolimus - 0.003%, 0.015%, 0.05%, 0.1%, 0.2%, 0.4% and 1%) for treating facial angiofibroma associated with TSC.[6-15] All observational studies reported the effect of medical treatments. Physical treatments included various laser methods and surgical processes, epithelial autografting, and dermabrasion (5 cohort studies, 10 case series, and 18 case reports).

Figure 1. PRISMA 2020 flowchart



PRISMA, preferred reporting items for systematic reviews and meta-analyses

EFFECTIVENESS OUTCOMES

- Clinical effectiveness:
  - The effects of topical sirolimus 0.1% were most frequently evaluated (3 clinical trials and 8 observational studies), followed by sirolimus 0.2% gel (3 clinical trials and observational studies each).
  - Subjective improvements were reported in all the experimental studies. Combining rapamycin in different concentrations with other pharmacological treatments effectively reduced erythema, papule clearance, and appearance.[6]
  - In a cohort study, topical sirolimus 0.2% gel reduced facial angiofibroma associated with TSC by 80%-100%.[16] Another topical sirolimus 0.1% gel study showed similar improvement (87.1%).[17]
- **Table 2** presents the details of pharmacological and physical treatments.

Table 2. Outcomes for pharmacological and physical treatments

Studies (Country, Study design)	Sample size: Treatment	Sample size: Comparator	Intervention (rapamycin/ sirolimus)*	Comparator	Outcomes
Clinical Effectiveness - Pharmacological Treatments					
Koenig et al., 2018 (United States, Australia, RCT)	122	57	1% topical application	Vehicle	**Angiofibroma Grading Scale -** 16.7-point improvement
		63	0.1% topical application	Vehicle	**Angiofibroma Grading Scale -** 11-point improvement
Wataya-Kaneda et al., 2017 (Japan, RCT)	8	12	0.05% gel	Placebo	**FASI score improvement -** 1.63 [0.95]; p=0.01
	8		0.1% gel		**FASI score improvement -** 1.06 [0.62]; p=0.06
	8		0.2% gel		**Most effective treatment** **FASI score improvement -** 1.94 [0.68]; p<0.001
Cinar et al., 2017 (Turkey, cross-over)	12	12	0.1% cream	Vaseline	**FASI** Pretreatment score - 7.58±0.90 Post-treatment score - 5.17±1.34; p=0.002
Salido et al., 2012 (Spain, non-RCT)	10	0	0.4% ointment	NR	FASI score mean decrease of 60.2% (34.3-100)
Amin et al., 2017 (United Kingdom, Cohort)	14	0	0.1% ointment	NR	FASI score improvement (1-4 points) in 12 patients post-treatments Children had better results (all improved)
Hatano et al., 2020 (Japan, Cohort)	33	0	0.2% gel	NR	Improved (change from baseline) - 23/33 (70%) Unchanged (no change from baseline) - 10 (30%)
Malissen et al., 2017 (France, Observational)	25-1	0	1% cream	NR	Pretreatment FASI scores: mild: 33%, moderate: 46%, severe - 21% At 3 months, the FASI erythema score had decreased by a median of 1 point (Range 0-2) and, by the end of treatment, by 2 points (Range 1-3)
Wang et al., 2017 (China, Cohort)	29	0	0.1% ointment	NR	FASI score: mean decrease in the FASI score at 36 weeks was 47.6±30.4% FASI score of each patient at Weeks 4, 12, and 36: (F=25.02, p<0.001) FASI scores at week 24 ≤week 12 (F=7.27, p<0.05) FASI scores at week 36 were not significantly different from those at week 24 (F=1.00, p=0.33). Hence plateau was observed.
Gajjar et al., 2018 (India, Case report)	1	0	0.1% gel + 1% gel	NR	FASI score: Pretreatment overall score - 6; Post treatment score - 5

Study reference	Intervention	Sample size (Intervention)	Outcomes
Physical Treatments			
Ali et al., 2016 (United Kingdom)	UltraPulse CO_2 laser	9	Effective, safe, and tolerable
Boixeda et al., 1994 (Spain)	CO_2 laser	7	Decrease of erythema and flattening of the angiofibroma - all Palate and gum lesions were reduced in 1 patient treated with the carbon dioxide laser. Fibromatous plaques in the forehead were treated with the CO_2 laser when present.
	Argon laser	2	Excellent - 2/2 Hyperpigmentary changes observed in 1 patient treated with an argon laser.
Papadavid et al., 2002 (United Kingdom)	Pulsed dye lasers	1	Excellent - 1/1
	Superpulsed CO_2 lasers	12	Excellent - 9, Moderate - 2, Poor - 1
	FLPDL lasers	9	Excellent - 8, Moderate - 1; early treatment shows better efficacy
	CO_2 lasers + FLPDL lasers	4	Excellent - 3, Poor - 1
	FLPDL + electrosurgery	3	Excellent - 3
	CO_2 lasers + electrosurgery	1	Excellent - 1
Weinberger et al., 2009 (United States)	PDL	6	All patients had decreased erythema and lesion size, and two demonstrated decreased counts.

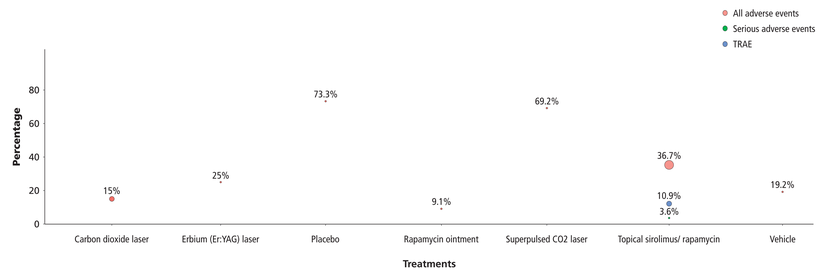
**rapamycin and sirolimus have been used interchangeably in the articles. CO_2, carbon dioxide; FASI, facial angiofibroma severity index; FLPDL, flashlamp pumped pulsed dye laser; NR, not reported; PDL, pulsed dye laser; RCT, randomized controlled trial*

- Recurrence was observed after treatment discontinuation using sirolimus (0.1%, 0.2%, 1%), everolimus (0.4%), and timolol (0.5%); following treatment resumption, recurrence was resolved in 4 studies.[14,18-25]

SAFETY OUTCOMES

- In total, 3.6% of patients treated with topical sirolimus experienced a serious adverse event (SAE), and 10.9% reported treatment-related adverse events (TRAE).
- AEs were observed in 36.7% of patients treated with topical sirolimus **(Figure 2)**.
- In a phase II RCT, post-treatment grade 3/4 AE was reported in 1.6% of patients with topical 0.1% rapamycin and 1.7% with topical 1% rapamycin.[7]

Figure 2. Bubble plot for the studies reporting adverse events

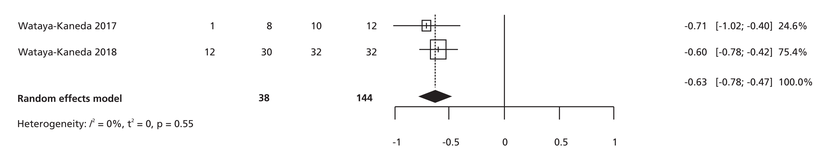


The size of the bubble indicates the total number of studies
CO_2, carbon dioxide; Er:YAG, Erbium: Yttrium-Aluminium-Garnet; TRAE, treatment-related adverse event

META-ANALYSIS

- In the meta-analysis, patients treated with sirolimus 0.2% gel experienced lower risk, with the pooled risk difference from the two studies being -0.63 (95% CI: -0.78, -0.47, I^2=0%, τ^2=0, p=0.55) - **Figure 3**.

Figure 3. Meta-analysis forest plot for risk difference



RD, risk difference; CI, confidence interval

RISK OF BIAS ASSESSMENT

- Risk of bias for RCTs (N=6; Cochrane assessment) generally showed low risk; non-RCTs (N=5; ROBIN'S checklist) showed moderate to serious risk.
- For observational studies (N=14; STROBE assessment), majority of the studies showed low to moderate risk with only 3 showing high risk. Most case series and reports had >5 in the JBI checklists demonstrating moderate risk.

CONCLUSIONS

- Topical sirolimus effectively managed facial angiofibroma associated with TSC. A 0.2% topical sirolimus concentration was most effective in treating facial angiofibroma related to TSC, demonstrating the drug's favorable efficacy and safety profile.
- In addition to pharmacological treatment, combining topical sirolimus with physical therapies was also effective.

LIMITATIONS

- Even with an exhaustive search across multiple databases, websites, and conference abstracts, we could identify and include limited trials with mTOR inhibitors. The outcome measurements across studies were non-uniform; hence, the results' consistency could not be established. Additionally, the lack of uniformity in efficacy evaluation across trials prevented conducting network meta-analysis. No studies met the inclusion criteria for cost-effectiveness analysis.

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