Topical use of mammalian target of rapamycin inhibitors in dermatology: A systematic review with meta-analysis

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Background: Systemic mammalian target of rapamycin (mTOR) inhibitors are currently used in many dermatologic indications. Their topical use is recent and poorly codified.

Objective: To provide an overview of the topical use of mTOR inhibitors in dermatologic conditions and evaluate their efficacy and safety.

Methods: A literature search was performed in January 2017. Reports of all studies investigating the use of topical mTOR inhibitors in any dermatology diseases were included. The exclusion criteria were systemic use and mucosal administration.

Results: We included 40 studies with a total of 262 patients. In all, 11 dermatologic conditions were found, the most frequent being angiofibromas linked to tuberous sclerosis complex (157 patients). Topical mTOR inhibitors were significantly more efficient than placebo for angiofibromas (relative risk, 2.52; 95% confidence interval, 1.27-5.00; I^2 = 0%). The median concentration of sirolimus was 0.1%, with a median treatment duration of 12 weeks. Topical mTOR inhibitors were well tolerated, with only mild or moderate local side effects (mostly irritative) reported. Blood level of sirolimus was not detected in 90% of patients.

Limitations: High heterogeneity in most studies.

Conclusion: This systematic review supports the efficacy of topical sirolimus for angiofibromas linked to tuberous sclerosis complex, with only local side effects reported. Other indications require further research. (J Am Acad Dermatol 2019;80:735-42.)

Key words: dermatology; mTOR inhibitor; rapamycin; sirolimus; systematic review; topical.

Mammalian target of rapamycin (mTOR) inhibitors are systemic drugs used in various conditions. mTOR is a serine/threonine protein kinase that belongs to the phosphoinositide-3 kinase (PI3K)-related kinase family. It is a catalytic subunit of 2 biochemically distinct complexes called mTORC1 and mTORC2. mTORC1 controls cell autonomous growth in

Abbreviations used:

AEs:	adverse effects
mTOR:	mammalian target of rapamycin
PDL:	pulsed dye laser
PWS:	port-wine stain
RCT:	randomized controlled trial
RRs:	relative risk
TSC:	tuberous sclerosis complex

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response to nutrient availability and growth factors, whereas mTORC2 mediates cell proliferation and cell survival.[1] mTOR inhibitors include sirolimus (also called rapamycin), which was first developed in the 1990s, and rapalogs such as everolimus, temsirolimus, and deforolimus. Sirolimus is currently approved by the US Food and Drug Administration for preventing allograft rejection in renal transplantation.[2] It is also used to treat renal and brain tumors linked to tuberous sclerosis complex (TSC).[3] Rapalogs are mainly used in therapies for various cancers.[4]

Oral sirolimus is increasingly used in dermatologic conditions, especially vascular tumors and complicated vascular malformations, because of its antiproliferative and antiangiogenic and antilymphangiogenetic properties.[5,6] Topical sirolimus administration has been tested since 2010 in facial angiofibromas linked to TSC and is increasingly being tested in varied cutaneous conditions.[7-9] As topical sirolimus is not yet marketed, the modalities of its use are heterogeneous, with widespread uncontrolled use.

The aim of this systematic review was to provide an overview of the dermatologic indications for use of topical mTOR inhibitors, with a meta-analysis aggregating data from randomized trials to estimate their efficacy and safety.

CAPSULE SUMMARY

- Topical use of mammalian target of rapamycin inhibitors is recent and poorly codified.
- This meta-analysis supports the efficacy of topical sirolimus in adults and children for facial angiofibromas linked to tuberous sclerosis complex. Only local adverse effects (mostly irritative) were reported, and no significant blood level of sirolimus was found.

METHODS

Search strategy

We searched electronic databases, including MEDLINE via PubMed, CENTRAL, Latin American and Caribbean Health Sciences (LILACS), and EMBASE from inception to January 2017 by using the terms *mTOR inhibitor*, *sirolimus*, *rapamycin*, *everolimus*, and *TOR serine-threonine kinases/antagonists*, combined with the terms *topical*, *local*, *ointment*, *cream*, and *gels*.

Inclusion and exclusion criteria

We included all original reports regardless of the language in which they were written, describing use of any topical mTOR inhibitor, alone or in association with other treatments, in any cutaneous condition in humans. Reports of systemic use and mucosal administration (oral or conjunctival) were excluded, as were reports with nonextractable data (on drug or condition).

Study selection strategy and data extraction

Two authors (S.L. and A.M.) independently selected studies on the basis of their title and abstract and then examined the full texts of articles. They independently extracted data, including the following: first author, publication year, journal, characteristics of the study and the study patients, condition, drug modalities, drug efficacy and side effects, blood level of mTOR inhibitor, cointerventions, and follow-up. Any disagreements in selection or extraction were resolved by consensus.

Quality and risk of bias assessment

Two authors (S.L. and A.M.) independently assessed the risk of bias of each randomized controlled trial (RCT) by using the Cochrane Collaboration risk of bias tool. In cases of disagreement, a methodologist (E.T.) gave the final decision.

Statistical analyses

Descriptive data were expressed with median and interquartile range (IQR) for quantitative data and number (%) for categoric data. A meta-analysis was planned if we could pool data from the RCTs. It was performed by computing relative risks (RRs) with use of random-effects modeling. RRs and 95% confidence intervals were calculated. Heterogeneity of results across RCTs was assessed by the Q and I^2 statistics, and any heterogeneity was predefined as $P < .05$ for the Q statistic or I^2 value of 50% or higher. Statistical analyses were performed with R software (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria) and SAS software (version 9.4, SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of the included reports

The 1042 reports identified included 40 reports of studies involving 262 patients (Fig 1 and Table I) that were published between 2005 and 2017; 33 were observational studies (n = 128 patients) and 7 were RCTs (n = 134 patients). The median age of the participants was 25.5 years (IQR, 12-33); 124 of 246 (50.4%) were male.

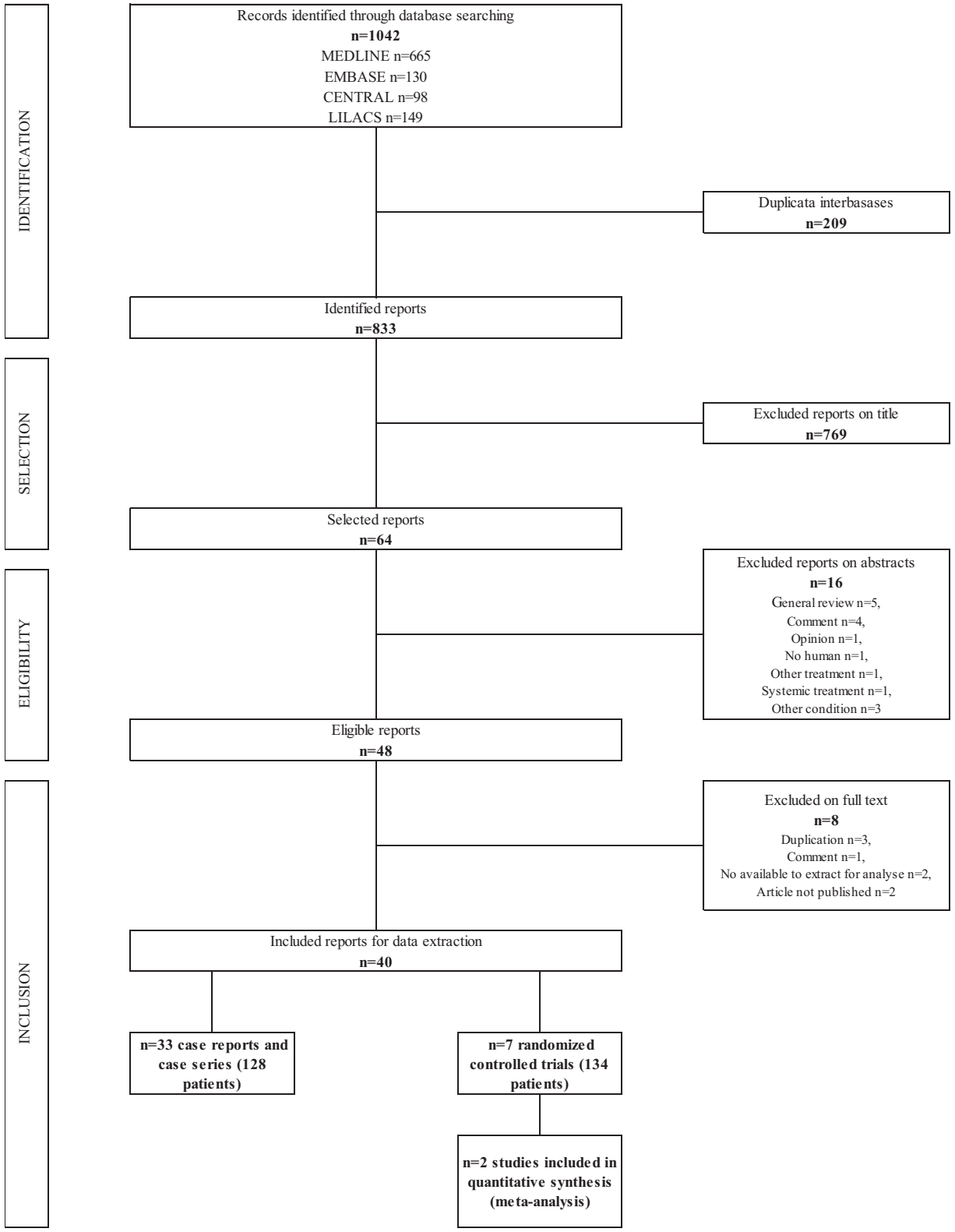

Fig 1. Flowchart of included reports.

Table I. Characteristics of reports included in the systematic review

Indications	Total no. of publications (no. of RCTs)	Total no. of patients (no. of patients included in RCTs)	Median drug concentration, % (IQR)	Median duration of treatment, wk (IQR)	Safety (no. of AEs*)
Angiofibromas in TSC					
Angiofibromas	26 (3)	157 (51)	0.1 (0.1- 0.2)	16 (12-24)	Irritation (38) Local pruritus (1)
Hypomelanotic macules and subungual fibromas linked to TSC					
Hypomelanotic macules	2 (0)	8 (0)	0.2	12	0
Subungual fibromas	1 (0)	1 (0)	0.1	24	0
Benign cutaneous tumors					
Fibrofolliculomas	1 (1)	19 (19)	0.1	24	Irritation (29) Local pruritus (3)
Trichoepitheliomas	1 (0)	2 (0)	1	38 (28-48)	0
FMDF	1 (0)	1 (0)	0.1	16	Irritation (1)
Kaposi sarcoma					
Kaposi sarcoma	1 (0)	1 (0)	0.5	16	Local pruritus (1)
Inflammatory skin diseases					
Chronic plaque psoriasis	1 (1)	24 (24)	2.2, then 8	12	Topical allergy (3)
Lichen plan	1 (0)	1 (0)	0.1	20	-
Vascular malformations					
Port-wine stain	4 (2)	47 (40)	1 (0.1-1)	11 (10-12)	Irritation (14) Local pruritus (12) Facial acne (8) Transient numbness (4) Sores (3) Topical allergy (2) Herpes infection (1)
CMLM	1 (0)	1 (0)	0.8	12	0

AEs, Adverse events; *CMLM*, cutaneous microcystic lymphatic malformation; *FMDF*, familial multiple discoid fibromas; *IQR*, interquartile range; *RCT*, randomized controlled trial; *TSC*, tuberous sclerosis complex.
*Adverse events with a possible or probable causal relationship with topical mammalian target of rapamycin inhibitors.

A total of 11 dermatologic conditions were identified; they included tumors (angiofibromas, subungual fibromas, and hypomelanotic macules linked to TSC; fibrofolliculomas; trichoepitheliomas; familial multiple discoid fibromas; and Kaposi sarcoma), inflammatory diseases (psoriasis plaques and lichen planus), and vascular malformations (port-wine stains [PWSs] and cutaneous microcystic lymphatic malformations). Of the 40 reports, 39 reported use of sirolimus and 1 reported use of everolimus.

Assessment of risk of bias

Figure 2[9-15] summarizes the assessment of risk of bias of the 7 RCTs, including the 2 on angiofibromas that were meta-analyzed.

Results for efficacy

Angiofibromas in TSC. Overall, 26 reports (n = 157 patients) described the use of a topical mTOR inhibitor for angiofibromas in TSC (3 RCTs and 23 observational studies).[7,10,13,15-37] Of the 141 patients, 100 (70.9%) were children and 66 (46.8%) were male. Their median age was 14.5 years (IQR, 11-38). The median concentration of mTOR inhibitor was 0.1% (IQR, 0.1-0.2), with a median of 2 applications per day. The median treatment time was 16 weeks (IQR, 12-24). The clinical criteria considering efficacy were heterogeneous, the main ones being the Facial Angiofibroma Severity Index[38] and physician assessment. Topical mTOR inhibitors were reported as efficient in 115 of 121 patients (95.0%). Follow-up data were available for 20 patients; 18 of them experienced recurrence between 2 and 12 weeks after withdrawal of the drug.[10,21,26-28]

We pooled data from 2 RCTs (n = 39 patients treated) comparing patient self-assessment of the efficacy of topical sirolimus versus placebo, which was the only common outcome (Fig 3[13,15]). Topical sirolimus use was associated with improved patient

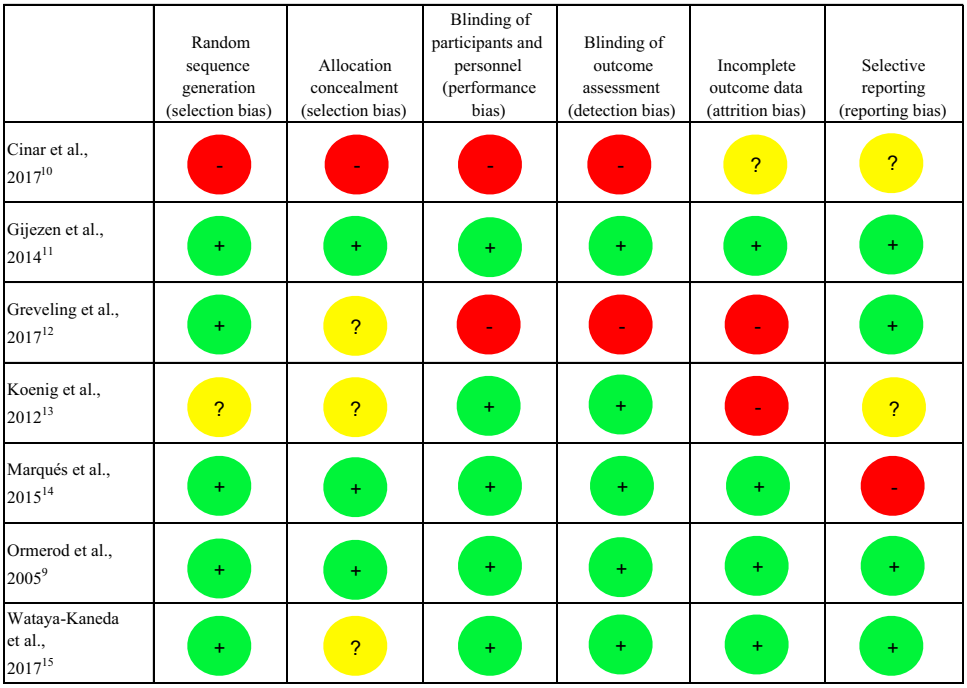

Fig 2. Risk of bias assessment of the included randomized controlled trials by the Cochrane risk of bias tool.

self-assessment (RR, 2.52; 95% confidence interval, 1.27-5.00).

Hypomelanotic macules and subungual fibromas linked to TSC. Two reports described the benefit of topical sirolimus 0.2% applied for 12 weeks in 7 of 8 patients with hypomelanotic macules linked to TSC.[39,40] One report described the complete regression of subungual fibromas after 6 months of daily application of topical sirolimus 0.1%.[41]

Skin tumors. One double-blind, facial left-right controlled trial evaluated 0.1% sirolimus solution applied for 6 months for facial fibromas in 19 patients with Birt-Hogg-Dubé syndrome and showed no significant improvement with sirolimus.[11] Sirolimus 1% was also tested in 2 children with multiple familial trichoepithelioma syndrome; it led to reduced growth of new lesions after 24 and 48 weeks.[42] Also, 1 case report described efficacy of 0.1% sirolimus for familial multiple discoid fibromas,[43] and another described a 73-year-old man with Kaposi sarcoma that healed after 16 weeks of treatment with 0.5% sirolimus ointment.[44]

Inflammatory skin diseases. One vehicle-controlled, split-body RCT included 24 patients with chronic plaque psoriasis; 2.2% topical sirolimus was applied for 6 weeks and 8% topical sirolimus for 6 additional weeks.[9] The trial showed a slight improvement with treatment versus vehicle at 12 weeks. One case report of a 79-year-old male with plantar erosive lichen planus treated with 0.1% sirolimus solution for 20 weeks[45] showed a significant reduction in pain after 4 weeks and healing of the lesions after 20 weeks.

Vascular malformations. Four reports (2 RCTs and 2 observational studies) involving 47 patients described the efficacy of topical sirolimus for PWS; it was used as adjunct therapy to pulsed dye laser (PDL) treatment in all the studies.[12,14,46,47] All the patients were at least 17 years old (median age, 33 years; IQR, 29-33). The most frequent regimen was 1% sirolimus applied once daily for 11 weeks. The efficacy outcomes were heterogeneous and did not allow aggregation of the data. In the observational studies, sirolimus as an add-on to PDL treatment seemed efficient in 2 out of 7 patients.[46,47] In the RCTs, when the outcome was assessed with colorimetric tools,[12] percentage clearance did not differ between PDL treatment plus topical sirolimus versus PDL treatment plus placebo; when the outcome was based on evaluation of photographs, PDL treatment plus topical sirolimus was more efficient than PDL treatment plus placebo.[14] In 1 case report of a man in his 20s, lymphangiectasias of the genitals that was treated with 0.8% sirolimus petrolatum showed nearly complete regression after 12 weeks.[8]

Results for safety

AEs. Safety data were reported in 37 of 40 reports (n = 212 patients): 120 adverse effects (AEs) involving 50 patients (23.6%) were reported. All the

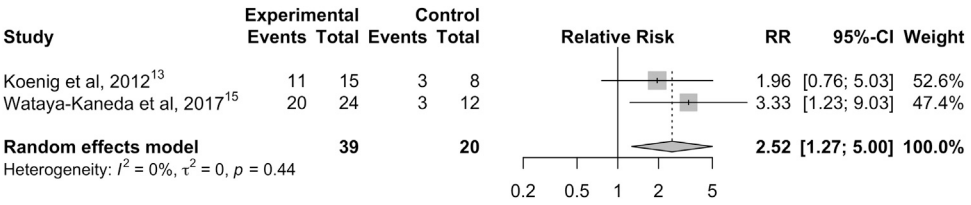

Fig 3. Forest plot showing the effect of topical sirolimus in facial angiofibromas linked to tuberous sclerosis complex. *CI*, Confidence interval; *RR*, relative risk.

AEs were local, mainly irritation (Table I). No related general or biologic AEs were reported.

Systemic passage of sirolimus. Detection of the blood level of sirolimus was described in 22 reports (n = 170 patients). Overall, 17 patients (10.0%) were positive for blood sirolimus concentration, but in all cases, blood levels were below the level required for immunosuppression (4 ng/mL).[2,6] The highest blood sirolimus concentration was 3.39 ng/mL after 6 weeks of treatment with 0.1% sirolimus on a facial PWS that was previously treated with a PDL.[14]

DISCUSSION

Main results

Our systematic review included 40 reports involving 262 patients who received topical application of mTOR inhibitors, mostly sirolimus, for 11 dermatologic conditions. The most frequent was facial angiofibroma linked to TSC, for which the treatment seemed efficient. The most frequent regimen was 0.1% sirolimus, with 1 or 2 applications per day for 12 weeks. Local AEs were frequent (120 AEs in 212 patients), mainly consisting of local irritation, and they seemed related to the formulation rather than to sirolimus concentration. Sirolimus was detected in the blood of 10.0% of patients analyzed, and in all cases the concentrations were below the level required for immunosuppression.

Comments

Topical sirolimus is mainly used in facial angiofibromas in TSC, for which it seems efficient. Indeed, TSC results from mutations in the tuberous sclerosis 1 gene (*TSC1*) and tuberous sclerosis 2 gene (*TSC2*), leading to overactivation of the mTOR signaling pathway, which controls cell growth, proliferation, and survival.[1] Several reports have suggested that for this indication, topical sirolimus was more effective in young patients than in old patients, but there was no evidence of this in our review. The underlying hypothesis is that sirolimus would be efficient in proliferative tumors with less fibrosis. The second most frequent indication is PWS, for which topical sirolimus is usually given as an adjunct to PDL treatment to minimize postlaser revascularization. Indeed, sirolimus has antiangiogenic properties by downregulation of hypoxia-inducible factor 1α, a transcriptional factor that regulates vascular endothelial growth factor expression.[48] Besides its use for these 2 main indications, use of topical sirolimus has been anecdotally reported in other dermatologic conditions and seems promising for subungual fibromas and lymphangiectasias.

This review has shown heterogeneity of the treatment regimen in terms of concentration, number of applications per day, and duration. This high heterogeneity is linked to lack of a marketed drug. Topical sirolimus is produced with sirolimus in tablets, solution, and powder form combined with ointment, cream, or gel to obtain a topical preparation. Bouguéon et al. developed a 0.1% sirolimus cream formulation with solubilized sirolimus in a solvent (Transcutol, Gattefossé, Lyon, France), which is an excellent permeation agent that enhances drug diffusion through the skin.[49]

Topical sirolimus was generally well tolerated; the symptom most reported by patients was mild-to-moderate irritation limited to the site of application. We found no systemic AEs related to the treatment. Indeed, in this systematic review, we found a positive blood sirolimus concentration in only 10.0% of patients with the dosage, both in children and adults, with different concentrations, frequencies of application per day, and formulations. In all cases, blood levels were below the level required for immunosuppression. Sirolimus has a high molecular weight, 914.17 Da,[30] which allows for diffusion limited to the skin. However, absorption could be enhanced by additional physical treatment, PDL treatment for instance, or with wide surface application. The surface area of application was never indicated in any studies.

Sirolimus was the mTOR inhibitor used in all patients, except 1 who used everolimus.[20] This high use is probably due to sirolimus being the oldest mTOR inhibitor, with a well-known safety profile.

However, Dill et al. chose everolimus because of presumed advantages (better water solubility because of its additional hydroxy group and shorter half-life).

Finally, long-term maintenance therapy might be necessary, but in our reports, the data on recurrence after treatment were too few to assess the frequency and time to recurrence.

Study limitations

The first limitation is that most RCT data could not be pooled for meta-analysis. The criteria for assessing efficacy were heterogeneous: only a few studies used objective scoring systems (eg, the Facial Angiofibroma Severity Index); most used subjective criteria. Second, the systematic review showed 95.0% efficacy of a topical mTOR inhibitor for facial angiofibromas in TSC, which might be overestimated. Indeed, the reports that are usually published are those showing treatments as effective, not negative reports (publication bias). Third, the formulations of topical sirolimus, concentrations, duration, and monitoring were heterogeneous, so comparisons were difficult.

CONCLUSIONS

This systematic review and meta-analysis supports the efficacy of topical sirolimus in adults and children for facial angiofibromas linked to TSC. The treatment appears to be safe and noninvasive but often irritative locally, especially when solutions are used. Other indications require further research.

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