REVIEW ARTICLE

Safety and Efficacy of Topical Calcineurin Inhibitors in the Treatment of Facial and Genital Psoriasis: A Systematic Review

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Facial and genital psoriasis impairs quality of life and is challenging to treat because of increased percutaneous penetration and, consequently, increased risk of adverse effects. Topical calcineurin inhibitors are recognized as a valid off-label treatment for these sensitive skin areas, but data on safety and efficacy are limited. This systematic review of the literature included 24 of 3,322 studies (5 randomized controlled trials, 9 open-label studies, 2 case series and 8 case reports). All studies demonstrated positive efficacy; 11 studies found statistically significant reductions in psoriasis severity. Local stinging, burning and itching were the most common short-term adverse effects and were reported in 18 studies. Topical calcineurin inhibitors appear to have an important role in the treatment of facial and genital psoriasis. The drugs are effective and generally well-tolerated with few adverse effects.

Key words: calcineurin inhibitors; pimecrolimus; psoriasis; systematic review; tacrolimus; treatment outcome.

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SIGNIFICANCE

Among patients with psoriasis, up to 29% develop facial psoriasis and 63% develop genital psoriasis. Facial and genital psoriasis impairs quality of life and because of the sensitive nature of these skin areas, treatment is challenging. Topical calcineurin inhibitors are recognized as a valid off-label treatment. This study systematically searched the literature to investigate whether this off-label treatment is safe and effective. This systematic review confirms that topical calcineurin inhibitors are safe and effective in treating facial and genital psoriasis.

Psoriasis is a common chronic immune-mediated skin disease driven by T-lymphocytes and mediated by pro-inflammatory cytokines, which affects approximately 2–3% of the population in Western countries (1). Psoriasis lesions often present as well-demarcated, erythematous and scaly plaques (2), while genital lesions are thinner and less scaly due to increased friction in the area (3, 4). Approximately 17–29% of adult patients with psoriasis have facial lesions and 33–63% have genital lesions (3, 4), and these patients report significantly decreased quality of life compared with patients with psoriasis located elsewhere (5, 6). Adequate and efficient treatment is important to reduce the negative impact on quality of life. Treatment of these sensitive skin areas, however, is challenging because of increased percutaneous penetration (7, 8), which increases the risk of adverse effects. First-line treatment of psoriasis is topical treatment, with the most prescribed being vitamin D analogues, low-potency corticosteroids and calcineurin inhibitors (9). Although highly efficacious, topical corticosteroids are, especially in facial and genital areas, associated with adverse effects, such as skin atrophy, striae, telangiectasia, perioral dermatitis and acneiform eruptions (10, 11). The use of topical vitamin D analogues is limited in sensitive skin areas since they induce skin irritation (12, 13). In recent years, topical calcineurin inhibitors, especially tacrolimus and pimecrolimus, have been recognized as valid off-label treatments for psoriasis in sensitive skin areas. Topical calcineurin inhibitors are anti-inflammatory drugs that inhibit the activation of T-lymphocytes and the production and secretion of pro-inflammatory cytokines and are approved for the treatment of atopic dermatitis. They are well-tolerated with mild, transient and self-limiting adverse effects (14) and do not cause skin atrophy (15).

The aim of this systematic review was to assess the safety and efficacy of off-label treatment of facial and genital psoriasis with topical calcineurin inhibitors.

MATERIALS AND METHODS

Literature search

This systematic review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16). The study protocol is registered at PROSPERO (ID: CRD42022315216). The 3 databases, PubMed, Web of Science and Embase, were systematically searched from database inception until 18 February 2022. Search terms were "(tacrolimus OR protopic OR fk506 OR calcineurin inhibitor OR calcineurin inhibitors OR pimecrolimus OR elidel OR topical calcineurin inhibitor OR tci) AND (psoriasis)". The search results were uploaded to Rayyan Qatar Computing Research Institute, a web/mobile application for systematic reviews, to expedite the screening of abstracts and titles (17). The resulting titles were screened by a single author (DA) in order to exclude duplicates. Two authors (CWS and DA) independently screened all titles and abstracts for eligibility, based on the inclusion criteria described

below. Relevant full-text articles were retrieved and read. Disagreement between the reviewers was resolved through debate and the resulting outcome was agreed upon.

Inclusion and exclusion criteria

All studies in languages other than Danish or English were excluded. All study designs were eligible for inclusion; however, studies had to be original and include patients with facial and/or genital psoriasis treated with topical calcineurin inhibitors. All types of psoriatic lesions in these areas and all age groups were included. Studies investigating combination therapy and studies not including facial and genital psoriasis were excluded.

Data extraction

The following data were retrieved from each publication when applicable: author information, title, publication year, study design, country, number of patients, sex, mean or median age, measure of psoriasis severity, type of psoriasis, psoriasis site, topical calcineurin inhibitor type and strength, treatment area, frequency of treatment, treatment duration, follow-up, evaluation week of response, response in relation to relevant psoriasis severity measures and adverse events.

Quality assessment

To assess the quality of the studies, this study used an adapted version of the Newcastle-Ottawa scale for randomized controlled trials and open-label studies. Each study was evaluated based on 8 items in 3 categories: study selection, comparability and ascertainment of either the exposure or outcome of interest (18). Quality assessment was performed by 2 authors (CWS and DA) and any disagreements were resolved through debate. A Newcastle-Ottawa score of ≥7 points was considered high quality (Table SI).

RESULTS

The initial literature search resulted in 3,322 non-duplicate publications. The PRISMA flow diagram in **Fig. 1** illustrates the search history. The search resulted in the inclusion of 24 publications with a total of 568 patients. The studies originated from Asia ($n=7$) (19–25), Europe ($n=9$) (26–34), the Middle East ($n=2$) (35, 36) and North America ($n=6$) (37–42). Of these 24 publications, 17 included adults aged ≥18 years (19, 21–28, 30–34, 37–40) and 6 included paediatric patients aged 6 months to 16 years (20, 29, 35, 36, 41, 42). Among the 24 publications, 16 studied tacrolimus 0.1% (19, 21–24, 28–30, 32–34, 37, 39–42), 1 studied tacrolimus 0.03% (25) and 7 studied pimecrolimus 1% (20, 26, 27, 31, 35, 36, 38). The publications consisted of 5 randomized controlled trials (25, 26, 30, 38, 40), 9 open-label studies (23, 24, 27, 28, 31, 33, 37, 39, 41), 2 case series (32, 42), and 8 case reports (19–22, 29, 34–36).

Efficacy of tacrolimus

In total, 16 studies assessed the efficacy of treatment with tacrolimus 0.1%/0.03% (**Table I**). Three randomized double-blind controlled studies assessed the efficacy of twice-daily application of tacrolimus. Liao et al. (25) found that significantly more patients with moderate facial and genital psoriasis were "clear" or "almost clear" after 6 weeks of treatment (60% of patients, $n=25$) compared with calcitriol (33% of patients, $n=24$, $p=0.04$), measured by Physician's Global Assessment. Likewise, Lebwohl et al. (40) found tacrolimus to be superior to the vehicle in moderate facial and genital psoriasis after 8 weeks of treatment. This was measured by Physician's Global Assessment, with 67% of patients in the tacrolimus group ($n=112$) being "clear" or "excellent", compared with 37% in the vehicle group ($n=55$, $p=0.002$). Kleyn et al. (30) found tacrolimus to be equally effective as a mid-potency topical corticosteroid. Tacrolimus and clobetasone butyrate both decreased the Total Affected Area after 6 weeks of treatment (22% decrease in tacrolimus group and 18% decrease in clobetasone butyrate group) with no significant treatment difference.

Seven open-label studies found improvement in psoriasis with tacrolimus treatment (Table I). Five of these studies reported significant improvement in psoriasis after twice-daily applications of tacrolimus 0.1% compared with baseline (23, 33, 37, 39, 41). Bissonnette et al. (37) found a significant reduction in the severity of genital psoriasis after 8 weeks of treatment measured by Modified Psoriasis Area and Severity Index ($n=12$, $p<0.001$). Freeman et al. (33) found a significant reduction in Individual Symptom Score after 57 days of treatment ($n=21$, $p<0.0001$), and Ezquerra et al. reported similar results after 60 days ($n=15$, $p<0.001$). Both studies assessed severe facial and genital psoriasis. Brune

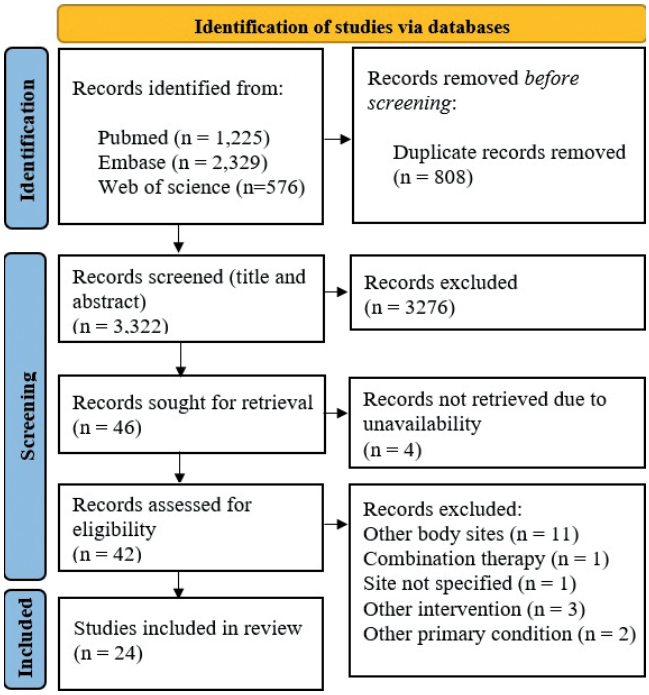

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram.

Table I. Efficacy of tacrolimus in the treatment of facial and genital psoriasis

Author	Study design	Patients *n*	Age, years Mean (±SD)	Sex (M/F), *n*	Psoriasis type	Psoriasis site(s)	Psoriasis severity	Intervention(s)	Outcome measure	Result
Kleyn et al. (30)	RCT	28	42	M: 11 F: 17	–	Face, flexures, genital	–	1: Tacrolimus 0.1% 2: Clobetasone butyrate 0.05%	Decrease in TAA from baseline	From 32% to 10% in tacrolimus group and from 32% to 14% in the clobetasone butyrate group at week 6
Lebwohl et al. (40)	RCT	167	1: 48.0 (±15.7) 2: 48.0 (±15.6)	M: 98 F: 69	Plaque psoriasis	Face, intertriginous	Moderate psoriasis	1: Tacrolimus 0.1% 2: Vehicle	PGA[b] of clear or excellent improvement	67% in the tacrolimus group and 37% in the vehicle group at week 8 ($p=0.002$)
Liao et al(26)	RCT	49	39.6 ±12.8)	M: 36 F: 13	Plaque psoriasis	Face, genitofemoral	Moderate psoriasis	1: Tacrolimus 0.03% 2: Calcitriol 0.0003%	PGA[a] of 4 or 5	60% in the tacrolimus group and 33% in the calcitriol group at week 6 ($p=0.04$)
Bissonnette et al. (37)	Open-label	12	42	M: 12	Plaque psoriasis	Penis, scrotum	Severe psoriasis	Tacrolimus 0.1%	Decrease in M-PASI[c] from baseline	From 15.8 at baseline to 1.2 at week 8 ($p<0.001$)
Brune et al. (41)	Open-label	11	10.5	M: 6 F: 5	–	Face, intertriginous	Mild to moderate psoriasis	Tacrolimus 0.1%	Overall severity score[f]	From 1.63 at baseline to 0.71 at day 180 ($p<0.0001$)
Ezquerra et al. (33)	Open-label	15	53	M: 8 F: 7	–	Face, intertriginous, genital	Severe psoriasis	Tacrolimus 0.1%	Individual symptom score[e]	From 6.88 at baseline to 0.37 at day 60 ($p<0.001$)
Freeman et al.(40)	Open-label	21	48	M: 15 F: 6	–	Face, intertriginous	Severe psoriasis	Tacrolimus 0.1%	Individual symptom score[e]	From 6.7 at baseline to 0.3 at day 57 ($p<0.0001$)
Rallis et al. (29)	Open-label	10	32.2	M: 9 F: 1	–	Face, glans penis, scrotum	Moderate psoriasis	Tacrolimus 0.1%	Overall severity score[d]	From 7.8 at baseline to 0 at week 3
Yamamoto et al. (23)	Open-label	21	51.1	M: 15 F: 6	Psoriasis vulgaris	Face	Moderate psoriasis	Tacrolimus 0.1%	Decrease in clinical score (erythema, infiltration, desquamation) from baseline[g]	Erythema from 1.76 to 0.62 at week 4 ($p<0.0001$), infiltration from 1.33 to 0.43 at week 4 ($p<0.0005$), and desquamation from 0.95 to 0.24 at week 4 ($p<0.001$)
Yamamoto et al. (24)	Open-label	11	49.3	M: 6 F: 5	Psoriasis vulgaris	Face	–	Tacrolimus 0.1%	Global evaluation of response	45.5% with complete response, 45.5% with partial response, and 9% resistant at week 4
Clayton et al.(32)	Case series	4	30.3	M: 1 F: 3	Plaque psoriasis	Face	–	Tacrolimus 0.1%	Resolution	75% with complete clearance, 25% with considerable improvement at 2 months
Karajovanov et al. (29)	Case report	1	11	M: 1	–	Axillae, genital, auricular	–	Tacrolimus 0.1%	Resolution	Resolution of the lesions at week 4
Kroft et al. (34)	Case report	1	51	M: 1	Plaque psoriasis	Face	–	Tacrolimus 0.1%	Resolution	Almost complete clearance at week 8
Steele et al. (43)	Case series Retrospective study	13	6.6	M: 9 F: 4	–	Penis, scrotum, buttocks, perianal, intertriginous, vulva	–	Tacrolimus 0.1%	Resolution	92% with complete clearance, 8% with no improvement at week 2
Yamamoto et al. (22)	Case report	2	39.5	M: 2	–	Face, lips	Severe psoriasis	Tacrolimus 0.1%	Physician assessment	Completely disappeared and good improvement at week 2
Yao et al. (22)	Case report	1	37	M: 1	Psoriasis vulgaris	Glans penis	–	Tacrolimus 0.1%	Resolution	Resolution of the lesion at week 3

[a]PGA: −1 = Worse than baseline, 0 = No change, 1 = 25% from baseline minimal improvement, 2 = 50% from baseline, 3 = 75% from baseline marked improvement, 4 = 90% from baseline almost clear and 5 = 100% from baseline clear. [b]PGA: 100% = clear, 90–99% = Excellent improvement, 60–89% = Good improvement, 30–59% = Fair improvement, 1–29% = Slight improvement, 0 = No change. [c]M-PASI: Scale 0–4 (none, mild, moderate, severe, very severe), (erythema + induration + desquamation) · Genital area. 0=no involvement; 1=1–9%, 2=10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–90% and 6 = 90–100% involvement. [d]Severity score: Scale 0–3 (none, mild, moderate, severe) in erythema, scaling, infiltration and lesional extent. 0=clear, 1–4 = mild, 5–8 = moderate, 9–12 = severe. [e]Individual symptom score: Scale 0–3 (absent, mild, moderate, severe) in erythema, infiltration, and desquamation. [f]Severity score: Scale 0–3 (none, mild, moderate, severe). [g]Clinical score (Erythema, desquamation, infiltration) 0 = absent, 1 = slight, 2 = moderate, 3 = striking 4 = exceptionally striking.
M-PASI: Modified Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; TAA: Total Affected Area in %; M: male; F: female; RCT: randomized controlled trial; SD: standard deviation.

et al. (41) found a significant reduction in the Overall Severity Score of mild-to-moderate psoriasis after 180 days of treatment ($n=8, p<0.0001$). Yamamoto et al. (23) found a significant reduction in all clinical parameters for moderate facial psoriasis after 4 weeks of treatment ($n=19$, erythema $p<0.0001$, infiltration $p<0.0005$, desquamation $p<0.001$).

The 4 case reports and the 2 case series report favourable results of twice-daily application of tacrolimus 0.1% (Table I). All studies found complete or almost complete resolution of both facial and genital psoriasis within 2–8 weeks of treatment (21, 22, 29, 32, 34, 42).

Safety of tacrolimus

Thirteen studies assessed the safety of treatment with tacrolimus 0.1%/0.03% (Table SII). Nine of these studies reported transient stinging, burning and itching as adverse effects (23, 25, 30, 33, 37, 39–42). Kleyn et al. (30) and Brune et al. (41) both reported 1 patient withdrawal due to unbearable itching. Liao et al. (25) found that 92% of both groups had excellent tolerance and fewer patients had perilesional erythema after 6 weeks of tacrolimus treatment (16% of patients, $n=25$) compared with calcitriol treatment (58% of patients,

$n=24$, $p=0.004$). Lebwohl et al. (40) found no significant difference in burning/stinging, hyperaesthesia or itching between tacrolimus and the vehicle. One case report found deep facial dermatophytosis with tinea corporis following a 4-week treatment with tacrolimus 0.1% of facial psoriasis (19).

Efficacy of pimecrolimus

In total, 7 studies assessed the efficacy of treatment with pimecrolimus 1% (**Table II**). Two randomized double-blinded controlled studies assessed the efficacy of twice-daily application of pimecrolimus. Gribetz et al. (38) found pimecrolimus to be superior to the vehicle measured by Investigator's Global Assessment, with 71% of patients in the pimecrolimus group ($n=28$) being "clear" or "almost clear" of moderate genital psoriasis after 8 weeks of treatment compared with 21% in the vehicle group ($n=29$, $p<0.0001$). Kreuter et al. (26) did not find a significant advantage of pimecrolimus compared with the vehicle or calcipotriol 0.005% in the treatment of severe genital psoriasis measured by Modified Psoriasis Area and Severity. The study also found that betamethasone 0.1% was significantly more effective than both pimecrolimus 1% and the vehicle ($n=60$, $p<0.01$).

Two open-label studies reported improvement of moderate facial psoriasis with twice-daily application of pimecrolimus 1% (Table II) (27, 31). Jacobi et al. found a significant reduction in Total Symptom Score of moderate psoriasis after 8 weeks of treatment ($n=20$, $p<0.005$) (27).

Three case reports found complete resolution of both facial and genital psoriasis with twice-daily application of pimecrolimus 1% within 4 weeks of treatment (20, 35, 36).

Safety of pimecrolimus

Five studies assessed the safety of pimecrolimus 1% (Table SIII) and 4 reported transient stinging, burning, itching and paraesthesia as adverse effects (26, 27, 31, 38). Frigerio et al. reported that 1 of 40 patients withdrew from the study due to itching and burning (31).

DISCUSSION

This systematic review investigated the short-term safety and efficacy of topical calcineurin inhibitors in the treatment of facial and genital psoriasis in 568 patients across 24 studies. Topical tacrolimus and pimecrolimus appear to have an important role in the treatment of facial and genital psoriasis. The drugs are effective and generally well-tolerated with few local short-term adverse effects. Although 5 of the 24 studies were randomized controlled studies, it should be noted that most publications

Table II. Efficacy of pimecrolimus in the treatment of facial and genital psoriasis

Author	Study design	Patients *n*	Age, years Mean (±SD)	Sex (M/F)	Psoriasis type	Psoriasis site(s)	Psoriasis severity	Intervention(s)	Outcome measure	Result
Gribetz et al. (38)	RCT	57	1: 47.8 (±15.17) 2: 47.8 (±14.49)	M: 29 F: 28	Inverse psoriasis Plaque psoriasis	Inguinal, gluteal cleft, inframammary, axillae	Moderate psoriasis	1: Pimecrolimus 1% 2: Vehicle	IGA[a] of almost clear or clear	71% in the pimecrolimus group and 21% in the vehicle group at week 8 ($p<0.0001$)
Kreuter et al. (27)	RCT	80	53.2 (±14.5)	M: 49 F: 31	Inverse psoriasis	Inguinal folds, gluteal cleft, genital, axillae	Severe psoriasis	1: Pimecrolimus 1% 2: Calcipotriol 0.005% 3: Betamethasone 0.1% 4: Vehicle	Decrease in M-PASI from baseline	From 19.2 to 11.5 in the pimecrolimus group ($p=0.001$) at day 28. From 25.3 to 9.7 ($p<.001$) in the calcipotriol group) at day 28. From 22.1 to 2.9 ($p<0.001$) in the betamethasone group at day 28. From 18.2 to 13.8 ($p=0.008$) in the vehicle group at day 28.
Frigerio et al. (31)	Open-label	40	48.3 ±16.5)	M: 27 F: 13	Psoriasis vulgaris	Facial	Moderate psoriasis	Pimecrolimus 1%	PGA[c] of complete resolution or excellent results.	72.5% at week 8.
Jacobi et al. (28)	Open-label	20	Mean age not stated. Range: 19–65	M: 13 F: 7	Plaque psoriasis	Facial	Moderate psoriasis	Pimecrolimus 1%	Improvement in TSS[b] from baseline	From 4.2 at baseline to 1.1 at week 8 ($p<0.005$)
Amichai (36)	Case report	1	10	M: 1	–	Glans penis	–	Pimecrolimus 1%	Resolution	Resolution at week 3.
Canpolat et al. (20)	Case report	1	6 months	F: 1	Plaque psoriasis	Anogenital, scalp, trunk, extremities	–	Pimecrolimus 1%	Resolution	Resolution after 1 month.
Mansouri et al. (36)	Case report	1	10	F: 1	Plaque psoriasis	Face, anogenital	–	Pimecrolimus 1%	Resolution	Resolution of the lesion at day 20.

[a]IGA: 5-point scale. 0 (clear) = no signs of inverse psoriasis except for residual discoloration, 1 (almost clear) = perceptible erythema, no induration, no scaling, 2 (mild disease) = mild erythema, no induration, mild or no scaling, 3 (moderate disease) = moderate erythema, mild induration, mild or no scaling, and 4 (severe disease) = severe erythema, moderate/severe induration and scaling. [b]TSS: Sum score of erythema and induration, 5-point scale (0–4) 0 = normal skin, 4 = severe erythema, and induration. [c]PGA: Not explained. > 75% = excellent results.

IGA: Investigator's Global Assessment; M-PASI: Modified Psoriasis Area and Severity Index; PGA: Physician's Global Assessment of change; TSS: Total Symptom Score.

consisted of small open-label studies, case reports and case series.

Topical corticosteroids are first-line treatment for most patients with localized psoriasis, but their use in the treatment of facial and genital psoriasis is limited due to the increased susceptibility to adverse effects, such as skin atrophy, striae, telangiectasia and acneiform eruptions. The risk of these adverse effects increases with potency, duration, frequency, and application site (11). Several studies have found variation in percutaneous absorption of topical corticosteroids, depending on application site, and 2 studies have found that percutaneous absorption of hydrocortisone on the forehead, scrotum and vulva is greater than on the forearm (7, 43). In this systematic review, 2 of the included studies compared topical corticosteroids with topical calcineurin inhibitors, and found that topical corticosteroids are equally or more effective than topical calcineurin inhibitors and have fewer adverse effects (26, 30). However, treatment durations were short, with a maximum of 6 weeks, which limits the exposure and thereby decreases the risk of adverse effects from topical corticosteroids. The common adverse effects reported, relating to treatment with topical calcineurin inhibitors for facial and genital psoriasis, are transient and mild and often decrease with ongoing use, which is consistent with data from clinical trials in patients with atopic dermatitis (14).

Facial involvement in psoriasis is typically a marker of severe disease with a longer disease duration (44). Severe facial and genital psoriasis are increasingly treated with systemic treatments because of the negative impact on quality of life. In agreement, a new classification of psoriasis severity from the International Psoriasis Council suggests separating patients with psoriasis into patients eligible for topical treatment and patients in need of systemic treatment including those with facial or genital psoriasis (45). Patients with mild facial and genital psoriasis may benefit from topical calcineurin inhibitors, or alternatively it may be used as a maintenance treatment. Patients with facial and genital psoriasis have limited options for topical treatments, since other commonly prescribed treatments, such as topical keratolytics, vitamin D analogues and coal-tar preparations either are not cosmetically acceptable in these areas or can induce severe skin irritation. These factors can affect medication adherence, which is important for adequate treatment results (46).

The efficacy and safety of pimecrolimus in the treatment of facial and genital psoriasis have been evaluated in fewer studies than tacrolimus. Pimecrolimus permeates slower through the skin than tacrolimus, thus having a later onset of action (47), and studies in patients with atopic dermatitis have found topical tacrolimus more effective than pimecrolimus (48). Although pimecrolimus appears to be effective, there is insufficient data to fully determine its role in the treatment of facial and genital psoriasis. Pimecrolimus is more lipophilic than tacrolimus and therefore has greater retention within the skin, reducing the risk of systemic adverse effects (49). These safety advantages and positive results of pimecrolimus warrant studies assessing treatment in facial and genital psoriasis and comparative studies with tacrolimus.

Paediatric studies reported a decrease in clinical severity and a few cases of common adverse effects, such as burning and itching, which is consistent with data from studies in paediatric patients with atopic dermatitis (50). Tacrolimus and pimecrolimus are extensively tested in both adult and paediatric patients with atopic dermatitis. Several randomized controlled trials have shown long-term safety and low systemic absorption of the drugs when applied topically (51–53). Patients with atopic dermatitis have an impaired skin barrier and, consequently, increased percutaneous absorption (54). The proven long-term safety of topical calcineurin inhibitors in paediatric patients with atopic dermatitis and the results from this systematic review support the safety of topical calcineurin inhibitors in the treatment of paediatric facial and genital psoriasis.

The current study has some limitations. Most of the included studies do not differentiate between inverse psoriasis and genital psoriasis, thus varying the descriptions and characterizations of genital psoriasis. Different measures of psoriasis severity are used to assess the treatment efficacy, which complicates comparison of the included studies. Safety assessment varies and few of the included studies do not report adverse effects. Most of the study durations do not exceed 8 weeks and therefore only report short-term adverse effects. The reported adverse effects only include local and not systemic effects. The increased percutaneous absorption through facial and genital skin can lead to a higher systemic concentration; however, none of the included studies measured serum concentration of tacrolimus or pimecrolimus. The systemic concentration may be negligible, but important in order to define safety.

Although there is an increasing number of studies that have assessed the safety and efficacy of topical calcineurin inhibitors in treatment of facial and genital psoriasis, long-term randomized controlled trials or clinical trials with larger sample sizes are warranted. Ten studies were case reports or case series, and therefore a substantial risk of publication bias is present. Case reports of improved facial and genital psoriasis after treatment with topical calcineurin inhibitors are more likely to be published than cases with treatment failure.

Furthermore, a consistent scoring system for the severity of facial and genital psoriasis will ease the comparison of studies and consequently aid in the determination of the most efficient treatment options for these patients.

In conclusion, topical calcineurin inhibitors appear to be effective and safe treatment options for facial and genital psoriasis with few local adverse effects. The

drugs should be considered a plausible treatment for facial and genital psoriasis, or, alternatively, used in combination with topical corticosteroids or as a maintenance treatment.

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