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Topical tacrolimus for atopic dermatitis (Review)

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[Intervention Review]

Topical tacrolimus for atopic dermatitis

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ABSTRACT

Background

Atopic dermatitis (AD) (or atopic eczema) is a chronic inflammatory skin condition that affects children and adults and has an important impact on quality of life. Topical corticosteroids (TCS) are the first-line therapy for this condition; however, they can be associated with significant adverse effects when used chronically. Tacrolimus ointment (in its 2 manufactured strengths of 0.1% and 0.03%) might be an alternative treatment. Tacrolimus, together with pimecrolimus, are drugs called topical calcineurin inhibitors (TCIs).

Objectives

To assess the efficacy and safety of topical tacrolimus for moderate and severe atopic dermatitis compared with other active treatments.

Search methods

We searched the following databases up to 3 June 2015: the Cochrane Skin Group Specialised Register, CENTRAL in the Cochrane Library (Issue 5, 2015), MEDLINE (from 1946), EMBASE (from 1974), LILACS (from 1982), and the Global Resource of Eczema Trials (GREAT database). We searched six trials registers and checked the bibliographies of included studies for further references to relevant trials. We contacted specialists in the field for unpublished data.

A separate search for adverse effects of topical tacrolimus was undertaken in MEDLINE and EMBASE on 30 July 2013. We also scrutinised the U.S. Food and Drug Administration (FDA) websites for adverse effects information.

Selection criteria

All randomised controlled trials (RCTs) of participants with moderate to severe atopic dermatitis (both children and adults) using topical tacrolimus at any dose, course duration, and follow-up time compared with other active treatments.

Data collection and analysis

Two authors independently screened and examined the full text of selected studies for compliance with eligibility criteria, risk of bias, and data extraction. Our three prespecified primary outcomes were physician's assessment, participant's self-assessment of improvement, and adverse effects. Our secondary outcomes included assessment of improvement of the disease by validated or objective measures, such as SCORAD (SCORing Atopic Dermatitis), the EASI (Eczema Area and Severity Index), and BSA (Body Surface Area) scores.

Main results

We included 20 studies, with 5885 participants. The variability of drug doses, outcomes, and follow-up periods made it difficult to carry out meta-analyses.

A single trial showed that tacrolimus 0.1% was better than low-potency TCS by the physician's assessment (risk ratio (RR) 3.09, 95% confidence interval (CI) 2.14 to 4.45, 1 study, n = 371, moderate-quality evidence). It was also marginally better than low-potency TCS on face and neck areas and moderate-potency TCS on the trunk and extremities by the physician's assessment (RR 1.32, 95% CI 1.17 to 1.49, 1 study, n = 972, moderate level of evidence) and for some of the secondary outcomes. Compared with pimecrolimus 1%, people treated with tacrolimus were almost twice as likely to improve by the physician's assessment (RR 1.80, 95% CI 1.34 to 2.42, 2 studies, n = 506, moderate quality of evidence). Compared with the lower concentration of 0.03%, the tacrolimus 0.1% formulation reduced the risk of not having an improvement by 18% as evaluated by the physician's assessment (RR 0.82, 95% CI 0.72 to 0.92, 6 studies, n = 1640, high-quality evidence). Tacrolimus 0.1% compared with moderate-to-potent TCS showed no difference by the physician's assessment, and 2 secondary outcomes (1 study, 377 participants) and a marginal benefit favouring tacrolimus 0.1% was found by the participant's assessment (RR 1.21, 95% CI 1.13 to 1.29, 1 study, n = 974, low quality of evidence) and SCORAD.

Based on data from 2 trials, tacrolimus 0.03% was superior to mild TCS for the physician's assessment (RR 2.58, 95% CI 1.96 to 3.38, 2 studies, n = 790, moderate-quality evidence) and the participant's self-assessment (RR 1.64, 95% CI 1.41 to 1.90, 1 study, n = 416, moderate quality of evidence). One trial showed moderate benefit of tacrolimus 0.03% compared with pimecrolimus 1% on the physician's assessment (RR 1.42, 95% CI 1.02 to 1.98, 1 study, n = 139, low-quality evidence), but the effects were equivocal when evaluating BSA. In the comparison of tacrolimus 0.03% with moderate-to-potent corticosteroids, no difference was found in most of the outcomes measured (including physician's and participant's assessment and also for the secondary outcomes), but in two studies, a marginal benefit favouring the corticosteroid group was found for the EASI and BSA scores.

Burning was more frequent in those using calcineurin inhibitors than those using corticosteroid tacrolimus 0.03% (RR 2.48, 95% CI 1.96 to 3.14, 5 studies, 1883 participants, high-quality evidence), but no difference was found for skin infections. Symptoms observed were mild and transient. The comparison between the two calcineurin inhibitors (pimecrolimus and tacrolimus) showed the same overall incidence of adverse events, but with a small difference in the frequency of local effects.

Serious adverse events were rare; occurred in both the tacrolimus and corticosteroid groups; and in most cases, were considered to be unrelated to the treatment. No cases of lymphoma were noted in the included studies nor in the non-comparative studies. Cases were only noted in spontaneous reports, cohorts, and case-control studies. Systemic absorption was rarely detectable, only in low levels, and this decreased with time. Exception is made for diseases with severe barrier defects, such as Netherton's syndrome, lamellar ichthyosis, and a few others, with case reports of a higher absorption. We evaluated clinical trials; case reports; and in vivo, in vitro, and animal studies; and didn't find any evidence that topical tacrolimus could cause skin atrophy.

Authors' conclusions

Tacrolimus 0.1% was better than low-potency corticosteroids, pimecrolimus 1%, and tacrolimus 0.03%. Results were equivocal when comparing both dose formulations to moderate-to-potent corticosteroids. Tacrolimus 0.03% was superior to mild corticosteroids and pimecrolimus. Both tacrolimus formulations seemed to be safe, and no evidence was found to support the possible increased risk of malignancies or skin atrophy with their use. The reliability and strength of the evidence was limited by the lack of data; thus, findings of this review should be interpreted with caution. We did not evaluate costs.

PLAIN LANGUAGE SUMMARY

Topical tacrolimus for atopic dermatitis

Background

Atopic dermatitis (AD) (or atopic eczema) is a chronic skin condition that affects the quality of life of both adults and children. Topical corticosteroids (TCS) are the main ointments used for treatment, but there is a risk of side-effects with their use, such as skin thinning. A class of drugs called topical calcineurin inhibitors, which include topical tacrolimus (and pimecrolimus), might provide an alternative to this problem, but since tacrolimus is a newer ointment compared with corticosteroids, there are still some questions about its effectiveness and safety.

Review question

Is tacrolimus ointment an effective and safe alternative to other treatments for moderate to severe atopic dermatitis (in children and adults)?

Study characteristics

We included 20 studies, with 5885 participants, in this review. We searched for studies until June 2015. We were interested in the physicians' assessment of improvement, the participants' self-assessment, and any adverse effects. Other outcomes were by objective measures of

improvement, such as SCORAD (SCORing Atopic Dermatitis, a tool for measuring atopic dermatitis severity) and the affected body surface area.

Key results

We found tacrolimus 0.1% to be better than low-potency TCS on the face and neck areas and moderate-potency TCS on the trunk and extremities. We evaluated the physician's assessment of pimecrolimus 1% and tacrolimus 0.03% in most of the studies. When compared with moderate-to-potent corticosteroids, there was a marginal benefit favouring tacrolimus 0.1% by the participant's self-assessment and SCORAD.

Combined results of 2 studies indicated that tacrolimus 0.03% more than doubled the chance of achieving improvement by the physician's assessment compared with mild TCS. Another study found tacrolimus 0.03% to be better than pimecrolimus 1% for the same outcome, while no difference was found on the body surface area of skin affected with disease. For the comparison with moderate-to-potent corticosteroids, we found no significant difference in most of the results, but in two studies, we found a slight difference favouring the corticosteroids group.

Burning and itching were more frequent in those using tacrolimus than TCS, but we found no difference in skin infection. Symptoms were mild and temporary. The comparison between pimecrolimus and tacrolimus showed the same overall frequency of side-effects, with local side-effects being more frequent in the tacrolimus groups. Tacrolimus also showed a longer duration of the local symptoms, between 30 minutes and 12 hours, while pimecrolimus users experienced symptoms for less than 30 minutes.

Serious adverse events were rare, occurred both in tacrolimus and TCS groups, and were considered to be unrelated to treatment in most instances. No cases of lymphoma (a type of cancer of the lymph nodes) were noted in the included studies nor in the non-comparative studies. Cases were only noted retrospectively in studies and reports, with no confirmed relation to the drug.

Systemic absorption (substance entering the bloodstream) was rarely detectable, only in low levels and decreased with time. Only in diseases with severe skin barrier problems, such as Netherton's syndrome, lamellar ichthyosis (rare genetic disorders), and a few others, were there case reports of systemic absorption.

After evaluating clinical trials, case reports, human and animal studies, we found a lack of evidence associating the use of topical tacrolimus with skin thinning.

In summary, tacrolimus ointment seems to be safe and effective for moderate to severe atopic dermatitis in children and adults. It should be used with caution, though, in those having diseases with a severely damaged skin barrier. We found no risk of skin thinning with its use, even for longer periods. We did not find any evidence associating a risk of malignancies with the use of topical tacrolimus. We did not evaluate costs in this review.

Quality of the evidence

The variability of drug doses, results, and follow-up periods made it difficult to combine the results. The lack of data limited the reliability and strength of the evidence; thus, findings of this review should be interpreted with caution.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Tacrolimus 0.1% compared with corticosteroids for atopic dermatitis

Tacrolimus 0.1% compared with corticosteroids for atopic dermatitis

Patient or population: people with atopic dermatitis
Settings: outpatients, Europe and Canada

Intervention: tacrolimus 0.1%
Comparison: corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Corticosteroids	Tacrolimus 0.1%				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 3.09** (2.14 to 4.45)	371 (1 study)	⊕⊕⊕⊖ **moderate**[1]	-
	157 per 1000	**484 per 1000** (335 to 698)				
	Moderate					
	157 per 1000	**485 per 1000** (336 to 699)				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 0.95** (0.78 to 1.16)	377 (1 study)	⊕⊕⊖⊖ **low**[1, 2]	-
	516 per 1000	**490 per 1000** (403 to 599)				
	Moderate					
	516 per 1000	**490 per 1000** (402 to 599)				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short term (6 months) Follow-up: 6 months	**Study population**		**RR 1.32** (1.17 to 1.49)	972 (1 study)	⊕⊕⊖⊖ **moderate**[1]	-
	464 per 1000	**612 per 1000** (543 to 691)				

	Moderate					
	464 per 1000	**612 per 1000** (543 to 691)				
Adverse effects: burning - tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 2.91** (1.6 to 5.28)	371 (1 study)	⊕⊕⊕⊖ **moderate**[1]	-
	70 per 1000	**204 per 1000** (112 to 371)				
	Moderate					
	70 per 1000	**204 per 1000** (112 to 370)				
Adverse effects: burning - tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 4.59** (3.1 to 6.78)	377 (1 study)	⊕⊕⊕⊖ **moderate**[1]	-
	129 per 1000	**592 per 1000** (400 to 875)				
	Moderate					
	129 per 1000	**592 per 1000** (400 to 875)				
Adverse effects: burning - tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: 6 months Follow-up: 6 months	**Study population**		**RR 3.79** (2.99 to 4.81)	972 (1 study)	⊕⊕⊕⊖ **moderate**[1]	-
	138 per 1000	**524 per 1000** (413 to 664)				
	Moderate					
	138 per 1000	**524 per 1000** (413 to 664)				
Participant's self-assessment of global response of improvement Follow-up: mean 6 months	**Study population**		**RR 1.21** (1.13 to 1.29)	974 (1 study)	⊕⊕⊖⊖ **low**[1, 3]	-
	718 per 1000	**868 per 1000** (811 to 926)				
	Moderate					

	718 per 1000	**869 per 1000** (811 to 926)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Downgraded one level due to publication bias because only one study was identified and publication bias was strongly suspected.
[2]Downgraded one level due to Imprecision: sample size falls below the optimal information size; 95% CI of the estimated effect includes both no effect and appreciable benefit.
[3]Downgraded one level due to Imprecision: sample size falls below the optimal information size.

Summary of findings 2. Tacrolimus 0.1% compared with pimecrolimus 1% for atopic dermatitis

Tacrolimus 0.1% compared with pimecrolimus 1% for atopic dermatitis

Patient or population: people with atopic dermatitis
Settings: outpatients, USA
Intervention: tacrolimus 0.1%
Comparison: pimecrolimus 1%

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Pimecrolimus 1%	**Tacrolimus 0.1%**				
Physician's assessment of global response of improvement, clear or excellent - 6 weeks Follow-up: mean 6 weeks	**Study population**		**RR 1.8** (1.34 to 2.42)	506 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	-
	202 per 1000	**363 per 1000** (270 to 488)				
	Moderate					
	199 per 1000	**358 per 1000** (267 to 482)				

Adverse effects - 6 weeks Follow-up: mean 6 weeks	**Study population**		**RR 0.89** (0.47 to 1.71)	506 (2 studies)	⊕⊖⊖⊖ **very low**[1, 2, 3]	-
	229 per 1000	**204 per 1000** (108 to 392)				
	Moderate					
	227 per 1000	**202 per 1000** (107 to 388)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Downgraded one level due to publication bias because only one study was identified and publication bias was strongly suspected.
[2]Downgraded one level due to inconsistency: there is moderate level of heterogeneity between studies: I^2 value of 69%.
[3]Downgraded one level due to imprecision: 95% CI of the estimate of summary effect includes both no effect and appreciable harm.

Summary of findings 3. Tacrolimus 0.03% compared with corticosteroids for atopic dermatitis

Tacrolimus 0.03% compared with corticosteroids for atopic dermatitis

Patient or population: people with atopic dermatitis
Settings: outpatients, Europe, Tunisia, Pakistan, Morocco, Taiwan
Intervention: tacrolimus 0.03%
Comparison: corticosteroids

Outcomes	Ilustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Corticosteroids	**Tacrolimus 0.03%**				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.03% 1x/day ver-	**Study population**		**RR 2.05** (1.36 to 3.08)	411 (1 study)	⊕⊕⊕⊖ **moderate**[1]	-
	136 per 1000	**279 per 1000**				

sus hydrocortisone acetate 1% 2x/day Follow-up: mean 3 weeks		(185 to 419)				
	Moderate					
	136 per 1000	**279 per 1000** (185 to 419)				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.03% 2x/day versus hydrocortisone acetate 1% 2x/day Follow-up: mean 3 weeks	**Study population**		**RR 2.58** (1.96 to 3.38)	790 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	-
	146 per 1000	**376 per 1000** (286 to 493)				
	Moderate					
	146 per 1000	**377 per 1000** (286 to 493)				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.03% 2x/day versus corticosteroids moderate-potency 2x/day Follow-up: 3 to 4 weeks	**Study population**		**RR 0.45** (0.13 to 1.57)	409 (2 studies)	⊕⊖⊖⊖ **very low**[1, 2, 3]	-
	527 per 1000	**237 per 1000** (69 to 828)				
	Moderate					
	591 per 1000	**266 per 1000** (77 to 928)				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.03% 2x/day versus methylprednisolone 0.03% 1x/day Follow-up: mean 3 weeks	**Study population**		**RR 1** (0.85 to 1.19)	265 (1 study)	⊕⊕⊖⊖ **low**[1, 3]	-
	667 per 1000	**667 per 1000** (567 to 793)				
	Moderate					
	667 per 1000	**667 per 1000** (567 to 794)				
Adverse effects: burning - tacrolimus 0.03% versus steroids	**Study population**		**RR2.48** (1.96 to 3.14)	1883 (5 studies)	⊕⊕⊕⊕ **high**	-
	89 per 1000	**221 per 1000** (174 to 279)				
	Moderate					

	70 per 1000	**174 per 1000** (137 to 220)				
Participant's self-assessment of global response of improvement: tacrolimus 0.03% 2x/day versus hydrocortisone acetate 1% 2x/day Follow-up: 3 weeks	**Study population**		**RR 1.64** (1.41 to 1.90)	416 (1 study)	⊕⊕⊕⊖ **moderate**[1]	-
	505 per 1000	**828 per 1000** (712 to 959)				
	Moderate					
	505 per 1000	**828 per 1000** (712 to 959)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Downgraded one level due to publication bias because only very small number of studies were identified and publication bias was strongly suspected.
[2]Downgraded one level due to inconsistency: there is moderate level of heterogeneity between studies: I^2 value of 79%.
[3]Downgraded one level due to imprecision: 95% CI of estimated summary effect includes both no effect and appreciable harm.

Summary of findings 4. Tacrolimus 0.03% compared with tacrolimus 0.1% for atopic dermatitis

Tacrolimus 0.03% compared with tacrolimus 0.1% for atopic dermatitis

Patient or population: people with atopic dermatitis
Settings: outpatients, USA, Japan, China
Intervention: tacrolimus 0.03%
Comparison: tacrolimus 0.1%

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Tacrolimus 0.1%	**Tacrolimus 0.03%**				

Physician's assessment of global response of improvement, clear or excellent Follow-up: 3 to 12 weeks	**Study population**		**RR 0.82** (0.72 to 0.92)	1640 (6 studies)	⊕⊕⊕⊕ **high**	-
	430 per 1000	**353 per 1000** (310 to 396)				
	Moderate					
	445 per 1000	**365 per 1000** (320 to 409)				
Adverse effects Follow-up: mean 3 weeks	**Study population**		**RR 0.95** (0.86 to 1.06)	986 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	-
	573 per 1000	**544 per 1000** (492 to 607)				
	Moderate					
	448 per 1000	**426 per 1000** (385 to 475)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: sample size is below the optimal information size.

Summary of findings 5. Tacrolimus 0.03% versus pimecrolimus 1% for atopic dermatitis

Tacrolimus 0.03% versus pimecrolimus 1% for atopic dermatitis

Patient or population: people with atopic dermatitis
Settings: outpatients, USA
Intervention: tacrolimus 0.03% versus pimecrolimus 1%

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	Control	Tacrolimus 0.03% versus pimecrolimus 1%				
Physician's assessment of global response of improvement Follow-up: mean 6 weeks	**Study population**		**RR 1.42** (1.02 to 1.98)	139 (1 study)	⊕⊕⊖⊖ **low**[1, 2]	-
	429 per 1000	**609 per 1000** (437 to 849)				
	Moderate					
	429 per 1000	**609 per 1000** (438 to 849)				
Adverse effects - application site reaction Follow-up: mean 6 weeks	**Study population**		**RR 1.07** (0.6 to 1.91)	141 (1 study)	⊕⊕⊖⊖ **low**[2, 3]	-
	239 per 1000	**256 per 1000** (144 to 457)				
	Moderate					
	239 per 1000	**256 per 1000** (143 to 456)				
Adverse effects - burning Follow-up: mean 6 weeks	**Study population**		**RR 0.87** (0.43 to 1.75)	141 (1 study)	⊕⊕⊖⊖ **low**[2, 3]	-
	197 per 1000	**172 per 1000** (85 to 345)				
	Moderate					
	197 per 1000	**171 per 1000** (85 to 345)				
Adverse effects - itching Follow-up: mean 6 weeks	**Study population**		**RR 2.37** (0.96 to 5.81)	141 (1 study)	⊕⊕⊖⊖ **low**[2, 3]	-
	85 per 1000	**200 per 1000** (81 to 491)				
	Moderate					
	85 per 1000	**201 per 1000**				

		(82 to 494)				
Adverse effects - erythema Follow-up: mean 6 weeks	**Study population**		**RR 2.2** (0.89 to 5.46)	141 (1 study)	⊕⊕⊖⊖ **low**[2, 3]	-
	85 per 1000	**186 per 1000** (75 to 461)				
	Moderate					
	85 per 1000	**187 per 1000** (76 to 464)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: sample size is smaller than the optimal information size.
[2]Downgraded one level due to publication bias because only one study was identified and publication bias was strongly suspected.
[3]Downgraded one level due to imprecision: 95% CI of the estimate of summary effect includes both no effect and appreciable harm.

Summary of findings 6. Tacrolimus 0.1% versus ciclosporin for atopic dermatitis

Tacrolimus 0.1% versus ciclosporin for atopic dermatitis

Patient or population: people with atopic dermatitis
Settings: outpatients, Italy
Intervention: tacrolimus 0.1% versus ciclosporin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Tacrolimus 0.1% versus ciclosporin				
Adverse effects Follow-up: mean 6 weeks	**Study population**		**RR 1** (0.31 to 3.28)	30 (1 study)	⊕⊖⊖⊖ **very low**[1, 2, 3]	-
	267 per 1000	**267 per 1000**				

		(83 to 875)
Moderate		
267 per 1000	**267 per 1000** (83 to 876)	

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Downgraded one level due to risk of bias: randomisation and allocation concealment procedures were unclear.
[2]Downgraded one level due to imprecision: sample size is smaller than optimal information size; 95% CI of the estimate of summary effect includes both no effect and appreciable benefit and harm.
[3]Downgraded one level due to publication bias because only one study was identified and publication bias was strongly suspected.

BACKGROUND

Description of the condition

Atopic dermatitis (AD) is a chronic inflammatory skin condition, with periods of inflammation and periods of relapse (McCollum 2010). It mainly affects infants and young children, but it can persist or relapse in adulthood. Symptoms can also start in adulthood (Ellis 2012). Clinically, this condition has an acute phase with red scaly patches and a chronic phase with lichenification (skin thickening). In children under two years of age, atopic dermatitis typically occurs on the face as well as the trunk and limbs. In older children and adults, it is found more often on the neck and flexor surfaces (on the inside of the joints, such as the knees and elbows). This is the typical distribution, although any part of the body can be affected (Akdis 2006; Bos 2010). Hand eczema is also a possible manifestation of atopic dermatitis, but it can have other causes, including contact dermatitis (with or without atopy, see below) or idiopathic hand eczema (where the cause is unknown) (Fitzpatrick 2008). Itch is a hallmark of the disease, and those affected also tend to have dry skin (Boguniewicz 2006).

The term 'atopy' should only refer to those with confirmed immunoglobulin E (IgE) hypersensitivity reactions, where either the finding of specific IgE antibodies in the blood or a skin prick test positive to common allergens has been made (Bath-Hextall 2008). An immunoglobulin is an antibody used by the immune system to identify and neutralise other proteins foreign to the individual (Medline Plus® a). The skin prick test to identify common allergens is a method used for the diagnosis of allergies, which tries to provoke small, controlled allergic reactions (Medline Plus® b). However, 40% of children with atopic dermatitis do not have atopy (Böhme 2001). In a recent review of allergy nomenclature, a proposal was made to replace the previously used terms 'atopic dermatitis' or 'atopic eczema' with the term 'eczema', including in this term both those with and without atopy (Bos 2010; Johansson 2004). Since this is a recently defined term and still not used by all authors, we used the term 'atopic dermatitis' in this review, even in those people without IgE hypersensitivity.

There has been an increase in the prevalence of atopic dermatitis in recent decades, and it has become a public health issue in industrialised countries, where the prevalence stays at around 10% to 20% in children and 1% to 3% in adults (Ashcroft 2005; Finch 2010; Fitzpatrick 2008). Multicentre ecological studies in many countries around the world also confirmed this high prevalence, with differences encountered between and within countries (Asher 2010; Harrop 2007; Odhiambo 2009; Williams 1999). In agricultural countries, this rate is lower, which may be due to children having more intense contact with mites and infections in early childhood, providing a protective effect against allergy development. This is an explanation put forward by the hygiene hypothesis (Fitzpatrick 2008; Strachan 1989).

The exact cause of atopic dermatitis is not entirely clear, but it is probably due to the interaction between environmental and genetic factors (Bath-Hextall 2008). What is already known is that affected individuals frequently have a damaged or defective skin barrier as well as alterations in the response of their immune system to immunological triggers (Luger 2011). The genes affecting the formation of epidermal barrier proteins, such as filaggrin, and other genes regulating the production of cytokines (inflammatory substances) that are involved in the immune response are likely to be involved (Finch 2010).

The rate of staphylococcal colonisation (bacterial growth) on the skin is around 90% compared with only 5% in people with healthy skin. So, those with atopic dermatitis are more likely to develop infections (Czarnecka-Operacz 2012; Macias 2011).

The role of diet, nutrition, and food allergy in the development, prevention, and treatment of atopic dermatitis is still controversial. In a Cochrane review on exclusion diets, with the exception "of an egg-free diet in infants with a positive specific IgE to eggs", no evidence of benefit of dietary exclusions was found (Bath-Hextall 2008). Phase one of the International Study of Asthma and Allergies in Childhood (ISAAC) (Ellwood 2001) tried to correlate the differences found in atopic dermatitis prevalence with the food intake characteristics of the participating countries. They found some negative associations, but with all the limitations of an ecological analysis. Because of all the controversial data and the methodological difficulties, caution should be taken in interpreting results and recommending dietary restrictions for children with atopic dermatitis (Finch 2010).

The mechanism that generates pruritus (itch) in atopic dermatitis is still not completely understood, as antihistamines (a class of drugs that act against many types of pruritus) are not as effective in controlling itch in this condition as they are in other pruritic dermatoses (Fitzpatrick 2008). An important part of any management of chronic atopic dermatitis is the avoidance or disruption of the scratch-itch cycle, as anything that perpetuates these symptoms inevitably worsens the damage to the skin (Bos 2010).

Impact of the disease

Atopic dermatitis has an important impact on an individual and their family. Many studies have assessed the ways in which it can affect quality of life. This disease can affect the social, emotional, and physical health of a person. Symptoms and visible lesions can cause behavioural problems, dependency, irritability, sleep loss, pain, itch, physical fatigue, shame, low self-esteem, anxiety, problems with relationships, and emotional distress (Maksimovic 2012). There is also an important economic impact due to frequent visits to physicians, frequent treatments, and days lost at work, which may lead to less opportunities (Brenninkmeijer 2009; Chamlin 2004). The severity of the disease bears a close relation to the degree of impact on a person's quality of life. The estimated annual costs of illness are high: billions of dollars in some high-income countries, such as the UK, the US, and Germany (Ashcroft 2005).

Treatment options

Emollients are the basic treatment for atopic dermatitis, and they are used in both acute and chronic phases; they do not reduce inflammation of acute lesions, but in all phases of treatment, they act by helping to hydrate the skin and restore or keep the integrity of the epidermal barrier (Eichenfield 2014). Acute flares, though, must be taken care of with additional therapeutic options (Luger 2011).

Traditionally, topical corticosteroids (TCS) are the most commonly used topical agents (Hultsch 2005). They act via a number of pathways to reduce inflammation (Luger 2011). They are an effective treatment though with potential adverse effects, most

of which are local to the site of application; however, they can occasionally cause adverse effects systemically (Ashcroft 2005; Neumann 2008).

Topical corticosteroids can cause skin thinning, telangiectasias (visible enlarged blood vessels on the skin), and striae (linear depressions of the skin with skin thinning) (Fitzpatrick 2008). Other effects include perioral dermatitis, tinea incognito, corticosteroid-induced acne, rosacea (chronic inflammation of the skin on the face), and hypertrichosis (excessive hair growth) (Antille 2004; Fujiwara 2010; Teraki 2012). Systemic absorption can cause hormonal changes, with adrenal gland suppression, higher blood glucose and blood pressure levels, and an alteration in bone density (Won 2004). People with atopic dermatitis and parents of children being treated with corticosteroids are usually worried about all of the possible adverse effects, causing a "corticosteroid phobia"; this can lead to incorrect use of the medication, with less frequent applications and shorter periods of treatment (McCollum 2010). As these side-effects are greater with prolonged use and because of corticosteroid phobia, seeking other treatment options is important, especially for those with moderate to severe atopic dermatitis (Ashcroft 2007; Luger 2011).

A corticosteroid-sparing therapy has emerged for the treatment of moderate to severe atopic dermatitis; this therapy belongs to a class of agents called the topical calcineurin inhibitors (TCI): pimecrolimus and tacrolimus (Rustin 2007). Calcineurin is a protein that can activate the immune system and the production of inflammatory substances (Patel 2007). Tacrolimus and pimecrolimus are topical immunosuppressive agents. Systemic immunosuppressive therapies are reserved only for severe recalcitrant cases, because of their potentially serious adverse effects (Ashcroft 2007; Roekevisch 2014; Simon 2014).

Description of the intervention

Topical tacrolimus is an immunomodulator; it might improve the control of acute flares and the prevention of new flares due to its immunomodulating mechanism of action (Fitzpatrick 2008). It has a more selective action when compared with corticosteroids, with possible similar efficacy but less adverse events, making it more acceptable for long-term use for this chronic condition (Ashcroft 2005; Ashcroft 2007). It is generally well tolerated, but the most common adverse effect is skin burning at the site of application; however, irritation tends to decrease or stop within a week (Breuer 2005). Topical tacrolimus is not associated with tachyphylaxis (a decrease in response to a drug after its administration); growth retardation; rebound effect (the tendency of some medications to cause a return of symptoms after sudden discontinuation) (Breuer 2005; Kang 2003); or irreversible local adverse effects, such as those that occur with TCS, making it a good corticosteroid-sparing therapy for atopic dermatitis (Bekersky 2001; FK506 Ointment Study Group 2001; Lotti 2008). It is also of great importance for the treatment of the face, eyelids, and intertriginous areas, which may be more sensitive to the adverse effects of corticosteroids (Doss 2009; Kang 2003).

The U.S. Food and Drug Administration (FDA) first approved tacrolimus in 2000 for short-term and non-continuous treatment of moderate to severe atopic dermatitis, but it has also been used for many other diseases for which it is not licensed (del Rosso 2007; Lotti 2008; Pitarch 2006; Skowron 2005). Concern has been raised about the increased risk of malignancies with tacrolimus, such as skin cancer and lymphomas. The FDA announced in 2006 that the long-term safety of tacrolimus had not been established. Since then, it has had a 'black box' warning (Berger 2006). This warning was based on the possible risks of systemic absorption (already proved to be minimal) (Harper 2005), data from solid organ transplantation using the same drug (blood concentrations were much higher than with the topical use) (Mitamura 2011), animal studies (results not directly transferable to people) (Patel 2007), and a few case reports (with no proven causative relation) (Ormerod 2005). This topic is still controversial, with no strong supporting evidence in the literature, leading to a large number of comments from different organisations against this 'black box' warning (Berger 2006; Luger 2005; Ring 2005; Segal 2013).

How the intervention might work

Topical tacrolimus acts by inhibiting calcineurin, thus, inhibiting T-cell proliferation and the production of many inflammatory cytokines, such as interleukin (IL)-2, IL-3, IL-4, IL-12, tumour necrosis factor (TNF), and interferon (IFN)-γ. Therefore, it may be effective in treating eczema, which is an immune-mediated skin disorder (Breuer 2005; Rustin 2007).

Why it is important to do this review

Nowadays, topical corticosteroids are the first-line therapy for atopic dermatitis. They have proven efficacy; however, they also have a confirmed risk of the associated development of adverse effects with chronic use. Since atopic dermatitis is a chronic disease and prolonged treatment is often necessary, the search for new treatments with less side-effects is an important issue.

Topical tacrolimus might be an excellent alternative to this problem, but since it is a newer agent compared with topical corticosteroids, there are still some questions about its efficacy and safety. Therefore, it is still a second-line therapy.

This review is of great importance in order to help establish more accurate guidance for the use of topical tacrolimus in this very prevalent skin disease, as well as assessing the risks associated with its use.

The plans for this review were published as a protocol '*Topical tacrolimus for atopic dermatitis*' Cury Martins 2012.

OBJECTIVES

To assess the efficacy and safety of topical tacrolimus for moderate and severe atopic dermatitis compared with other active treatments.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled clinical studies, both published and unpublished.

Types of participants

People with moderate to severe atopic dermatitis who a physician had diagnosed, with no restrictions on age, sex, or ethnicity.

Types of interventions

Topical tacrolimus at any dose, course duration, and follow-up time compared with other active treatments.

We only considered including a placebo (vehicle) group in more complex comparisons of combined treatment approaches, e.g., topical corticosteroids alongside tacrolimus versus either tacrolimus plus placebo or topical corticosteroids plus placebo.

Types of outcome measures

Primary outcomes

1. Physician's assessment of global response of improvement.
2. Participant's self-assessment of global response of improvement.
3. Occurence and severity of adverse effects.

Secondary outcomes

1. Improvement of disease assessed by a validated or objective measure, such as the following:
   - affected Body Surface Area (BSA);
   - Eczema Area and Severity Index (EASI);
   - relapse (over a period of up to one year); or
   - quality of life.

For validated scores and classification criteria, please see Appendix 1.

Timing of outcome assessment

We used the end point closest to three months (one to six months) for short-term benefit and the end point closest to three years (one year or longer) for longer-term benefit. We considered the longer-term data as the primary end point, since this was clinically more important for atopic dermatitis as it is a chronic inflammatory skin condition with a relapsing course. As most of the included studies reported short-term data, we analysed only the rapid onset of improvement.

Reactive treatment

This review focused on the reactive treatment of active eczema, leaving the preventive treatment aside, which is a separate topic that was recently reviewed by Schmitt et al (Schmitt 2011).

Search methods for identification of studies

We aimed to identify all relevant randomised controlled clinical trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 3 June 2015:

- the Cochrane Skin Group Specialised Register using the following terms: (dermatitis or eczema or neurodermatitis) AND (tacrolimus or protopic or "fk 506" or fk506);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2014, Issue 9) using the search strategy in Appendix 2;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3;
- EMBASE via Ovid (from 1974) using the strategy in Appendix 4; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

We searched the following database using the on-screen menus to navigate to the topic "topical immunomodulatory agents", up to 8 October 2014:

- the Global Resource of Eczema Trials. Centre of Evidenced Based Dermatology. Accessed at www.greatdatabase.org.uk.

Trials registers

We searched the following trials registers up to 14 June 2015 using the following search terms: eczema, dermatitis, atopic dermatitis, topical calcineurin inhibitors, tacrolimus, FK506 and FK 506.

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register (www.clinicaltrialsregister.eu).
- The Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

References from included studies

We checked the bibliographies of included studies for further references to relevant trials.

Unpublished literature

We contacted specialists in the field for any possibly relevant unpublished data.

Adverse effects

We searched the following databases for reports of adverse effects in non-randomised studies on 30 July 2013:

- MEDLINE via Ovid (from 1946) using the strategy in Appendix 6; and
- EMBASE via Ovid (from 1974) using the strategy in Appendix 7.

We also scrutinised the U.S. Food and Drug Administration (FDA) websites with periodic reports of manufacturer and surveillance databases for both topical corticosteroids (TCS) and tacrolimus, with the purpose of identifying possible rare side-effects, such as skin cancer and lymphomas (a cancer of the lymphocytes) that might not have been published. We did not include data from trials under scrutiny until a consensus was reached (see the Study Selection Form in Appendix 8).

Data collection and analysis

Selection of studies

After merging the search results and removing duplicate records, we examined titles and abstracts to select the relevant reports. Two authors (JCM and EMKS) independently screened the trials identified by the literature search. We retrieved and examined the full text of selected studies for compliance with eligibility criteria. We documented the reasons for exclusion of individual trials. We consulted a third author (CRM) for any disagreements in any stage of the analysis.

Data extraction and management

Two authors (JCM and EMKS) extracted data independently and collected data on a paper data extraction form. We resolved discrepancies in the results by discussion. We collected the following information: study features (design, participants, interventions) and outcomes (types of outcome measures, timing of outcomes, adverse events).

Assessment of risk of bias in included studies

In order to assess the risk of bias, we independently assessed the quality of the studies included in the review according to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the following domains, rating them as at low, unclear, or high risk of bias.

(a) Was the sequence generation adequate?
(b) Was allocation adequately concealed?
(c) Was knowledge by participants, personnel, and outcome assessors of the allocated interventions adequately prevented during the study?
(d) Were incomplete outcome data adequately addressed?
(e) Are reports of the study free of selective outcome reporting?
(f) Was the study apparently free of other problems that could put it at a high risk of bias, like baseline imbalance, deviation from the study protocol, early termination, and insensitive instruments used to measure outcomes?

We reported these assessments for each individual study in the 'Risk of bias' table located in the 'Characteristics of included studies' tables. We tried to contact the study author(s) to seek clarification in cases of uncertainty over data.

Measures of treatment effect

For dichotomous variables, we calculated risk ratios (RR) and 95% confidence intervals (CIs). For continuous outcomes that used similar scales, we calculated mean differences (MD) and 95% CIs. For continuous outcomes that used different scales, we calculated standardised mean differences (SMD) and 95% CIs. When study authors had not provided the necessary information, we inserted narratively any data from primary studies that were not parametric (e.g., effects reported as medians, quartiles, etc.) or without sufficient statistical information (e.g., standard deviations, number of participants, etc.).

Unit of analysis issues

The unit of analysis was based on the individual participant (unit to be randomised for interventions to be compared), i.e., the number of observations in the analysis should match the number of individuals randomised.

We did not find any cross-over studies that we considered adequate for inclusion in the meta-analysis. If we had included them, we would have included the data using the results of paired analyses (Elbourne 2002).

Dealing with missing data

For missing or unavailable data, we contacted the study authors for additional information. In case of non-response, irrespective of the type of data, we reported dropout rates in the 'Characteristics of included studies' tables of the review and, where possible, used intention-to-treat analysis (Higgins 2011).

If appropriate, we would have imputed the missing data with replacement values. For dichotomous outcomes, we would have assumed the missing data were treatment failures, and for continuous outcomes, we would have imputed the mean observed. We would have performed sensitivity analyses excluding the participants with missing data to assess the strength of the results.

Assessment of heterogeneity

We qualified inconsistency among the pooled estimates using the I^2 statistic: ((Q - df)/Q) x 100% test, where Q is the Chi^2 statistic and df represents the degree of freedom. This illustrates the percentage of the variability in effect estimates resulting from heterogeneity, rather than sampling error (Higgins 2011).

The following represented the thresholds for the interpretation of the I^2 statistic:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

In future updates of this review, if we include a sufficient number of studies assessing the same comparators and outcomes (at least 10), we will assess publication bias by drawing a funnel plot (trial effect versus trial size).

Data synthesis

If we identified no substantial heterogeneity, we computed pooled estimates of the treatment effect for each outcome under a fixed-effect model. Otherwise, if we identified substantial heterogeneity, we performed a random-effects analysis.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis included types of intervention and duration of follow up. We analysed combined data from both adults and children. If we found substantial heterogeneity and there were sufficient data, we investigated the possible causes by further exploring the impact of the condition on the individuals (i.e., participant characteristics, degree and duration of the intervention, adjuvant drugs) using subgroup analyses.

Sensitivity analysis

If there were an adequate number of studies, we would have performed sensitivity analyses based on separation of studies according to our assessment of the risk of bias of allocation

concealment (high, low, or unclear) and blinding of outcome assessment (high, low, or unclear).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Figure 1 displays the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram. Seven hundred and seventy-five records were identified through searching the Skin Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and LILACS (the Latin American and Caribbean Health Science Information database). One additional record was found in the trials registers and other sources. Of these 776 records, 7 were duplicates. We assessed a total of 769 records for eligibility. Of these, we excluded 720 after assessing the titles and abstracts. We identified one study as ongoing (NCT00475605). We obtained the remaining 48 records and read them as full text articles. We further excluded 23 records and added 1 to studies awaiting classification (Drake 2001). We included the remaining 20 studies reported in 24 papers.

Figure 1. Study flow diagram

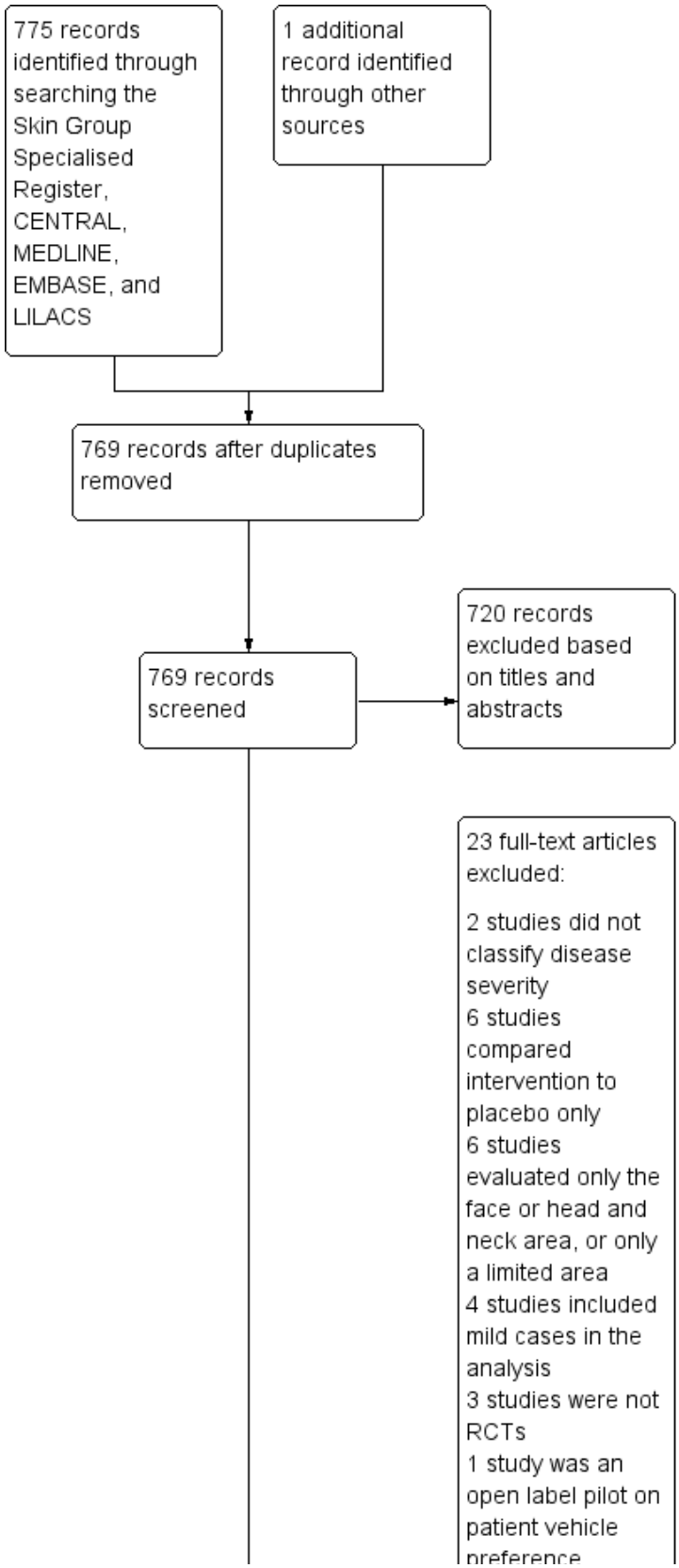
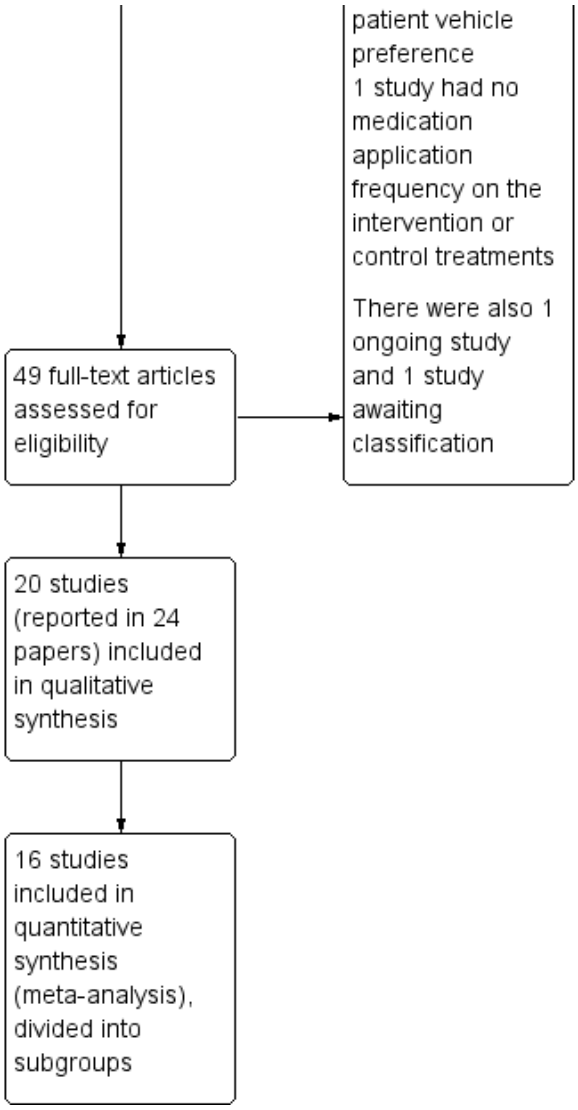


Figure 1. (Continued)



Included studies

This review included 20 studies, with a total of 5885 participants. Table 1 summarises the overall features of the different treatments and participants in the included studies.

Design

All included studies were randomised, comparative, parallel group studies.

Three of the studies were single centre (Antiga 2010; Caproni 2007; Hung 2007); the remaining represented multicentre trials.

Participants

Thirteen studies defined atopic dermatitis according to the Hanifin and Rajka criteria (Appendix 1), while in the other studies, a physician clinically diagnosed atopic dermatitis.

Seventeen of the studies included participants with moderate or severe atopic dermatitis (using the Rajka and Langeland criteria (Rajka 1989), the SCORing Atopic Dermatitis (SCORAD) classification, or the Investigators' Global Assessment (IGA) classification - view Appendix 1); one study included participants with moderate or severe atopic dermatitis (Rajka and Langeland criteria (Rajka 1989) or IGA) who showed inadequate response to topical corticosteroids (Doss 2010). One study included only participants with moderate atopic dermatitis (IGA criteria) (Kempers 2004), and another study included participants with a severe flare (IGA > 4) and prior history of moderate to severe atopic dermatitis (Bieber 2007).

We classified participants as adults or paediatric age groups according to the study authors' definitions: participants considered as adults were older than age 16 or 18 years, depending on the study; participants considered in the 'paediatric' age group were between 6 months or 2 years and 16 or 18 years old, depending on the study. Eight studies included only adult participants (> = 16 or 18 years) (Antiga 2010; Caproni 2007; Dou 2006; Draelos 2005; Fleischer 2007; Hanifin 2001; Reitamo 2002a; Reitamo 2005). Another 10 studies included only paediatric participants (6 months to 18 years) (Bieber 2007; Doss 2010; Kempers 2004; Otsuki 2003; Paller 2001; Paller 2005; Reitamo 2004; Reitamo 2002b), and of those, 2 included

only older children (7 to 16 years) (Boguniewicz 1998; Sikder 2005). Two studies included both adults and paediatric participants with ages ranging from 9 months to 45 years (Hung 2007; Pacor 2004).

Sample size

Sample sizes ranged from 16 (Caproni 2007) to 972 (Reitamo 2005).

Interventions

We searched for trials comparing tacrolimus at any dose, course duration, and follow-up time with other active treatments.

- Three studies, Antiga 2010; Caproni 2007; Reitamo 2002a, compared tacrolimus 0.1% ointment with a mid-potency topical corticosteroid (hydrocortisone butyrate 0.1%) administered twice a day (BID).
- One study, Reitamo 2005 (1 original study and 2 subanalyses), compared tacrolimus 0.1% ointment with a mid-potency topical corticosteroid (hydrocortisone butyrate 0.1% ointment) applied to the trunk and extremities and with a low-potency topical corticosteroid (hydrocortisone acetate 1% ointment) applied to the face and neck areas (BID).
- Three studies, Draelos 2005; Fleischer 2007; Paller 2005, compared tacrolimus 0.1% ointment with pimecrolimus 1% cream (BID).
- Four studies, Doss 2010; Hung 2007; Reitamo 2002a; Sikder 2005, compared tacrolimus 0.03% ointment with a mid-potency topical corticosteroid (hydrocortisone butyrate 0.1% ointment, fluticasone propionate 0.05% cream or clobetasol butyrate) (BID). One of the studies, Sikder 2005, also compared it with the combined treatment (topical corticosteroid in the morning and topical tacrolimus in the evening), and Hung 2007 also compared both treatments alone or in combination with fusidic acid 2% cream.
- Two studies, Reitamo 2002b; Reitamo 2004, compared tacrolimus 0.03% ointment with low-potency topical corticosteroids (TCS) (hydrocortisone acetate 1% ointment). The Reitamo 2002b study compared tacrolimus 0.03% ointment versus tacrolimus 0.1% ointment versus TCS all administered twice a day. The Reitamo 2004 study compared tacrolimus 0.03% once a day versus tacrolimus 0.03% twice a day versus TCS once a day.
- Bieber 2007 compared tacrolimus 0.03% ointment (BID) with a high-potency topical corticosteroid (once a day (QD)) (methylprednisolone aceponate 0.1% ointment).
- Seven studies (Boguniewicz 1998; Dou 2006; Hanifin 2001; Otsuki 2003; Paller 2001; Reitamo 2002a; Reitamo 2002b) compared tacrolimus 0.1% ointment with tacrolimus 0.03% ointment, and Boguniewicz 1998 also compared it to tacrolimus 0.3% ointment.
- Kempers 2004 compared tacrolimus 0.03% ointment with pimecrolimus 1% cream (BID).
- Pacor 2004 compared tacrolimus 0.1% ointment with oral ciclosporin at a dose of 3 mg/kg.

Duration of treatment was established as a previously determined maximum treatment time period. If complete clearance of the lesion was achieved prior to that maximum period, treatment was continued for another week and then stopped. We carried out the analysis on the maximum time period pre-established. This period varied from 1 week to 12 months: 2 weeks in 1 study, 3 weeks in 9 studies, 4 weeks in 1 study, 6 weeks in 4 studies, 3 months in 1 study, 6 months in 2 studies, and 12 months in a subanalysis of Reitamo 2005. As most of the included studies reported short-term data, we analysed only the rapid onset of improvement.

We only considered including a placebo (vehicle) group in more complex comparisons of combined treatment approaches. Six studies compared more than two treatment options.

We did not include in this review comparisons of tacrolimus only with placebo (vehicle), because of the already proven efficacy of the drug over placebo in other systematic reviews (Ashcroft 2005b; Chen 2010; El-Batawy 2009; Yan 2008).

Outcomes

The following numbers of our included studies addressed our prespecified primary outcomes.

1. Physician's assessment of global response of improvement*: 15 studies.
2. Participant's self-assessment of global response of improvement*: five studies.
3. Occurence and severity of adverse effects: 16 studies.

*Physicians and participants grade the skin improvement in a subjective manner. Though subjective, these tools are also used to assess treatment efficacy. They (the tools) evaluate skin improvement, for example, as excellent improvement (> 90% of improvement), marked improvement (75% to 89%), or moderate improvement (50% to 74%) from the participant's or physician's viewpoint.

The following numbers of our included studies addressed our prespecified secondary outcomes.

1. Improvement of disease assessed by a validated or objective measure, such as the following:
   - affected Body Surface Area (BSA): 10 studies;
   - Eczema Area and Severity Index (EASI): 5 studies;
   - modified Eczema Area and Severity Index (mEASI): 7 studies;
   - relapse: 0 studies;
   - quality of life: 2 studies; or
   - SCORing Atopic Dermatitis (SCORAD): 4 studies.

Excluded studies

We excluded 23 studies and list the reasons for exclusion in the 'Characteristics of excluded studies' tables. In brief, the reasons were as follows.

- In two studies, there was no classification of disease severity (Reitamo 2009; Torok 2003).
- Six studies compared intervention with placebo only and made no comparisons with active treatments (Chapman 2005; Granlund 2001; Ishibashi 1997; Liu 2005; Rahman 2008; Schachner 2005).
- Two studies evaluated only the face or the head and neck area (Doss 2010; Kang 2003).
- Four other studies evaluated only a limited area (Dähnhardt-Pfeiffer 2013; del Rosso 2007; Ruzicka 1997; Xhauflaire-Uhoda 2007).

- Four studies included also mild cases in their analyses (Gradman 2007; Hebert 2006; Kirsner 2010; Takeuchi 2012).
- Three studies were not randomised controlled trials (Arkwright 2006; Hjelmgren 2007; Won 2004).
- Onumah 2013 was an open-labelled pilot study on patient vehicle (ointment versus cream) preference.
- In one study, Neumann 2008, there was no established medication application frequency (once a day (QD) or twice a day (BID)) on the use of both intervention and control treatments for standardisation and comparison.

Risk of bias in included studies

Please see the 'Characteristics of included studies' tables with the 'Risk of bias' assessment for each included study. Figure 2 and Figure 3 summarise the risk of bias.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies

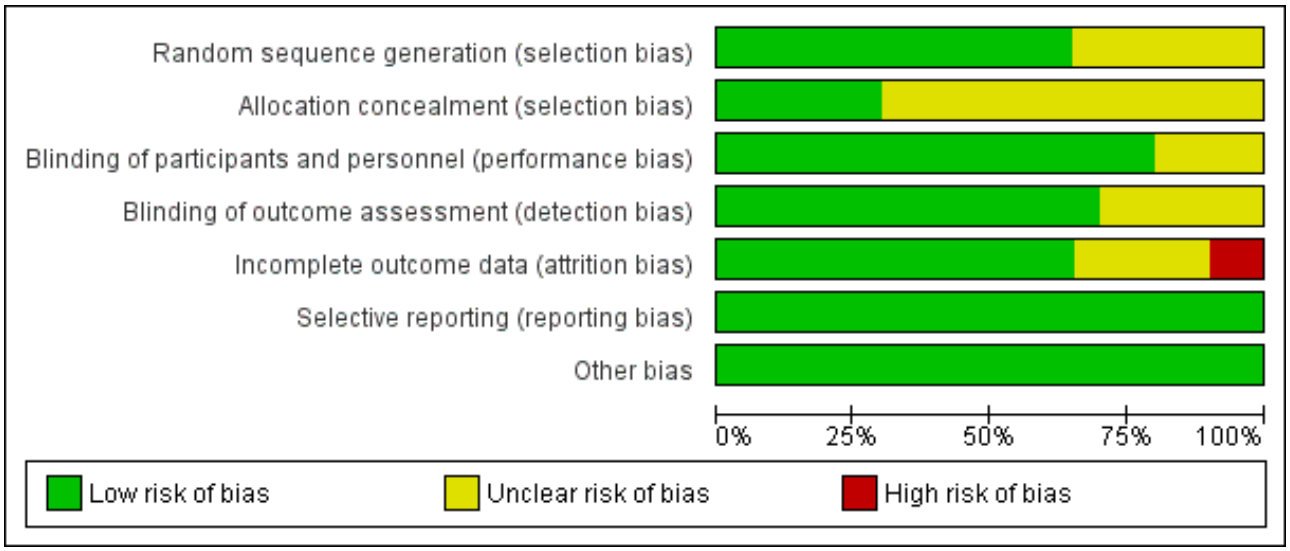


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

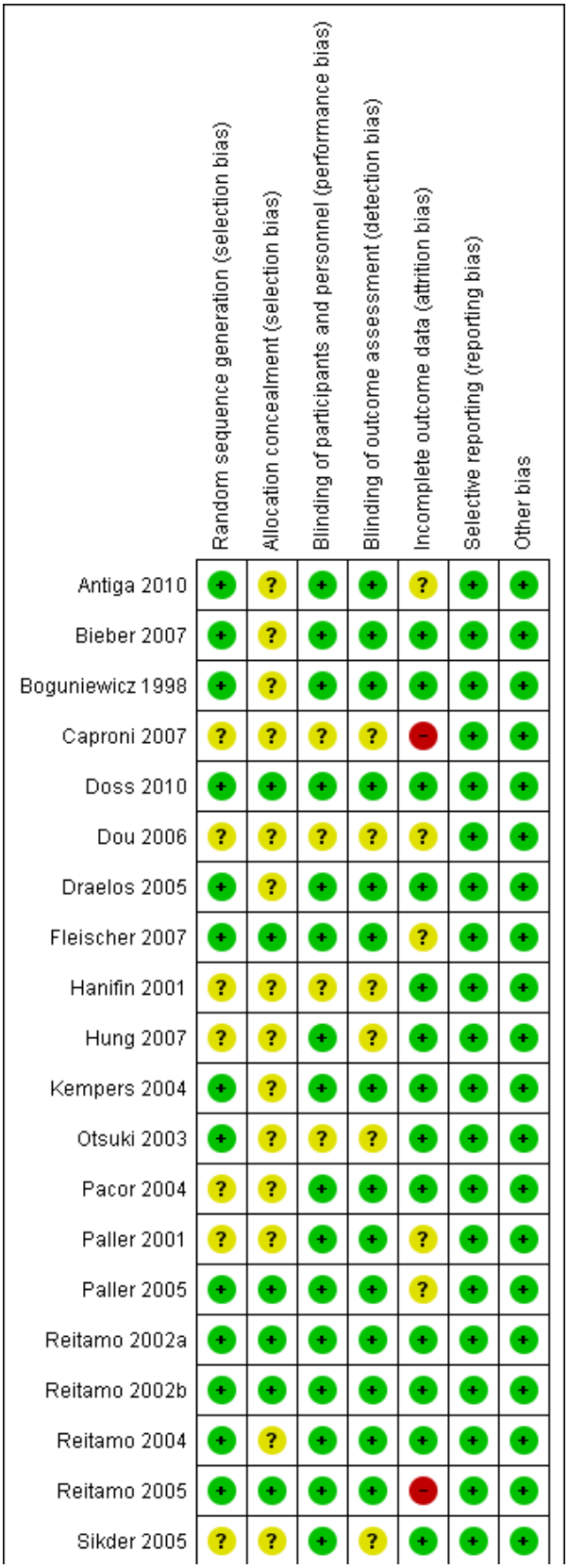
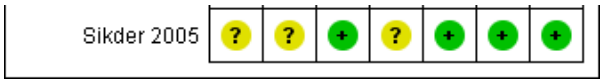


Figure 3. (Continued)



Allocation

Random sequence generation

Thirteen of the 20 included studies described an adequate method to generate the randomisation sequence (Antiga 2010; Bieber 2007; Boguniewicz 1998; Doss 2010; Draelos 2005; Fleischer 2007; Kempers 2004; Otsuki 2003; Paller 2005; Reitamo 2002a; Reitamo 2002b; Reitamo 2004; Reitamo 2005), and we classified these as at a low risk of bias. We considered the remaining studies as presenting an unclear risk of bias for random sequence generation.

Allocation sequence concealment

Fourteen studies did not describe allocation methods, so we classified these as "unclear" (Antiga 2010; Bieber 2007; Boguniewicz 1998; Caproni 2007; Dou 2006; Draelos 2005; Hanifin 2001; Hung 2007; Kempers 2004; Otsuki 2003; Pacor 2004; Paller 2001; Reitamo 2004; Sikder 2005). We classified the other six studies as at a low risk of bias.

Blinding

We judged 16 studies to be at low risk for performance bias, i.e., the participants and personnel were blinded. We judged 14 of these studies to be at low risk of bias for 'outcome assessment'. Five of the studies, which we judged to be at low risk of bias, were investigator blinded due to the different appearance of the products used (ointments or creams); participants were not allowed to discuss anything about the treatment with the investigators, and the only outcomes evaluated were based on the investigator's assessment or grading, so that the unblinded participants would not interfere with the results (Antiga 2010; Draelos 2005; Fleischer 2007; Paller 2005; Kempers 2004).

Four studies did not describe the blinding methods, so we judged these as at unclear risk of bias for both domains (Caproni 2007; Dou 2006; Hanifin 2001; Otsuki 2003).

Incomplete outcome data

Thirteen studies showed no losses or had few losses, and intention-to-treat (ITT) analyses were performed with the method described, so they were classified as at low risk of bias (Bieber 2007; Boguniewicz 1998; Doss 2010; Draelos 2005; Hanifin 2001; Hung 2007; Kempers 2004; Otsuki 2003; Pacor 2004; Reitamo 2002a; Reitamo 2002b; Reitamo 2004; Sikder 2005).

We classified 5 studies as at unclear risk of attrition bias: Antiga 2010 did not perform an ITT analysis, Dou 2006 did not mention losses, Fleischer 2007 showed high losses (22.8%), and ITT was done with last observation carried forward to analysis. Paller 2001 and Paller 2005, despite performing analysis by ITT, did not describe the method used to impute data.

We classified two studies as at a high risk of bias: Caproni 2007 did not perform ITT analysis despite losses (20%), and Reitamo 2005 had 33.7% of losses with an unclear method to perform ITT analysis.

Selective reporting

The studies described all relevant outcomes.

Other potential sources of bias

Only three studies, Caproni 2007; Hung 2007; Pacor 2004, had no financial support from the pharmaceutical industry. However, we did not use this issue to make judgments about the risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Tacrolimus 0.1% compared with corticosteroids for atopic dermatitis; **Summary of findings 2** Tacrolimus 0.1% compared with pimecrolimus 1% for atopic dermatitis; **Summary of findings 3** Tacrolimus 0.03% compared with corticosteroids for atopic dermatitis; **Summary of findings 4** Tacrolimus 0.03% compared with tacrolimus 0.1% for atopic dermatitis; **Summary of findings 5** Tacrolimus 0.03% versus pimecrolimus 1% for atopic dermatitis; **Summary of findings 6** Tacrolimus 0.1% versus ciclosporin for atopic dermatitis

The variability of drug doses, outcomes, and follow-up periods made it difficult to carry out meta-analyses. We report below the results for outcomes of this review, with subgroup analysis. Please note that our secondary outcome relapse (over a period of up to one year) was not reported in any of the included studies.

Tacrolimus 0.1% versus corticosteroids

Primary outcomes

Physician's assessment of global response of improvement

Three studies, Reitamo 2002a; Reitamo 2002b; Reitamo 2005, reported this outcome at different follow-up times (3 weeks, 6 months, and 12 months) and different corticosteroid potencies. A statistically significant difference was measured in the group receiving tacrolimus in the study comparing tacrolimus 0.1% ointment with a low-potency corticosteroid (hydrocortisone acetate 1% ointment) for 3 weeks (risk ratio (RR) 3.09, 95% confidence interval (CI) 2.14 to 4.45, 1 study (Reitamo 2002b), 371 participants). A statistically significant difference in favour of tacrolimus was also measured in the study comparing tacrolimus 0.1% with a mid-potency corticosteroid (hydrocortisone butyrate 0.1% ointment) used on the trunk and extremities and a low-potency corticosteroid (hydrocortisone acetate 1% ointment) used on the face and neck areas twice a day for 6 months (RR 1.32, 95% CI 1.17 to 1.49, 1 study (Reitamo 2005), 972 participants; Analysis 1.1).

No difference was observed in the 12-month follow-up time (RR 1.35, 95% CI 0.86 to 2.12, 1 study, 80 participants) in the Mandelin 2010 study, which was a subanalysis of Reitamo 2005. The study comparing tacrolimus 0.1% ointment and a mid-potency corticosteroid (hydrocortisone butyrate 0.1% ointment) for 3 weeks also found no significant differences between the 2 groups (RR 0.95, 95% CI 0.78 to 1.16, 1 study (Reitamo 2002a), 377 participants).

Participant's self-assessment of global response of improvement

Only one study, comparing tacrolimus 0.1% and hydrocortisone butyrate 0.1% (mid-potency corticosteroid), Reitamo 2005, reported this outcome after 6 months of treatment, with a statistically significantly higher number of participants in the tacrolimus group reporting improvement (RR 1.21, 95% CI 1.13 to 1.29, 1 study, 972 participants).

Occurence and severity of adverse effects

Four studies evaluated the sensation of burning at the application site of tacrolimus 0.1% compared with different potencies of topical corticosteroids. All four studies showed this adverse event to be statistically significantly more frequent in the tacrolimus 0.1% group compared with the topical corticosteroids, regardless of the corticosteroid potency. To list the results individually, Reitamo 2002b compared tacrolimus 0.1% to a low-potency corticosteroid (hydrocortisone acetate 1%) used for 3 weeks (RR 2.91, 95% CI 1.60 to 5.28, 1 study, 371 participants); Reitamo 2002a compared it to a mid-potency corticosteroid (hydrocortisone butyrate 0.1%) also used for 3 weeks (RR 4.59, 95% CI 3.10 to 6.78, 1 study, 377 participants); Reitamo 2005 reported 6-month and 12-month follow-up results comparing tacrolimus 0.1% with a mid-potency corticosteroid (hydrocortisone butyrate 0.1% ointment) applied to the trunk and extremities and a low-potency corticosteroid (hydrocortisone acetate 1% ointment) applied to the face and neck areas (RR 3.79, 95% CI 2.99 to 4.81, 1 study, 972 participants; RR 1.17, 95% CI 1.02 to 1.35, 1 study, 80 participants, respectively; Analysis 1.2). In the analyses, we have grouped the two interventions hydrocortisone acetate and butyrate together.

When assessing "pruritus" and "skin infection", which represent the second and third most common adverse events, we found no significant differences, even though tacrolimus was associated with more frequent reports of pruritus. The authors note the burning and pruritus adverse effects were mild to moderate and transient in all cases (Analysis 1.3; Analysis 1.4).

Secondary outcomes

Improvement of disease assessed by a validated or objective measure, such as the following: affected Body Surface Area (BSA)

Reitamo 2002a observed no differences in improvement of affected BSA between tacrolimus 0.1% and hydrocortisone butyrate 0.1% after 3 weeks. (The study report gave no data, only the images of graphs from which we could not extract data precisely. We contacted the study authors for more information, but we received no response). Reitamo 2005 reported significant improvement of affected BSA in the group receiving tacrolimus 0.1% compared with hydrocortisone butyrate 0.1% ointment used on the trunk and extremities and hydrocortisone acetate 1% ointment used on the face and neck areas after a 6-month follow-up, with a median percentage difference from baseline of -88.2% versus -80.3%, P < 0.001 (Wilcoxon test). An additional report by Mandelin of the Reitamo 2005 study, which evaluated a subgroup of 80 participants for 12 months, reported better results with tacrolimus 0.1% compared with hydrocortisone, but with no significant difference: median percentage 5.5% (1.7 to 12.0) and 12.8% (3.1 to 42.3), respectively.

Improvement of disease assessed by a validated or objective measure, such as the following: Eczema Area and Severity Index (EASI)

Three studies assessed this outcome at different follow-up times with a modified EASI score (mEASI - see Appendix 1). Reitamo 2002a compared tacrolimus 0.1% with a mid-potency corticosteroid (hydrocortisone butyrate 0.1%) for 3 weeks and observed no difference in median improvement compared with baseline between groups (63.5% versus 63.9%, Wilcoxon test). In Reitamo 2005, the comparison between tacrolimus 0.1% and a mid-potency corticosteroid (hydrocortisone butyrate 0.1% ointment) used on the trunk and extremities and a low-potency corticosteroid (hydrocortisone acetate 1% ointment) used on the face and neck areas twice a day showed a median percentage of improvement of 72.6% versus 52.3% for 3 months and a median percentage of improvement of 87.7% versus 82.5% for 6 months. This difference was significant (P < 0.001 and P < 0.008, respectively, Wilcoxon test). In the comparison with a low-potency corticosteroid, Reitamo 2002b observed 60.2% of median improvement with tacrolimus 0.1% compared with 36.0% with hydrocortisone acetate 1%, which represented a significant difference as well (P < 0.001, Wilcoxon test).

Improvement of disease assessed by a validated or objective measure, such as the following: quality of life

Only one paper, an additional report by Poole 2010 in the Reitamo 2005 study, evaluated this outcome reporting quality of life measured by the 36-Item Short Form Health Survey (SF-36) (a quality of life assessment tool, see Jenkinson 1999). In both the physical component summary (PCS) and the mental component summary (MCS), change from baseline score was statistically significantly different between the 2 groups, favouring tacrolimus 0.1% when compared with mild corticosteroid used on the trunk and extremities and a moderate-potency corticosteroid used on the face and neck areas. Evaluating the PCS, tacrolimus group participants obtained a mean of 3.3 points (standard deviation (SD) ± 7.5), and the corticosteroid group participants obtained a mean of 2.3 (SD ± 7.6), representing a relative difference in improvement of 43% (P = 0.03, t-test). The mean of improvement on MCS in the tacrolimus group was 6.0 points (SD ± 11.3) compared with 3.4 points (SD ± 10.6) in the corticosteroid group, with a relative difference of 76% (P < 0.001, t-test).

Improvement of disease assessed by a validated or objective measure, such as the following: SCORing Atopic Dermatitis (SCORAD)

Two studies used SCORAD to assess the disease outcome (Antiga 2010; Caproni 2007). After 3 weeks of treatment, there was a significant difference favouring the group that received tacrolimus 0.1% when compared with a mid-potency corticosteroid (hydrocortisone butyrate 0.1%) (mean difference (MD) -8.82, 95% CI -15.36 to -2.27, 2 studies, 37 participants; Analysis 1.5) (a decrease in SCORAD is a sign of improvement). However, these results should be viewed with caution because of the small sample size of the study.

Tacrolimus 0.1% versus pimecrolimus 1%

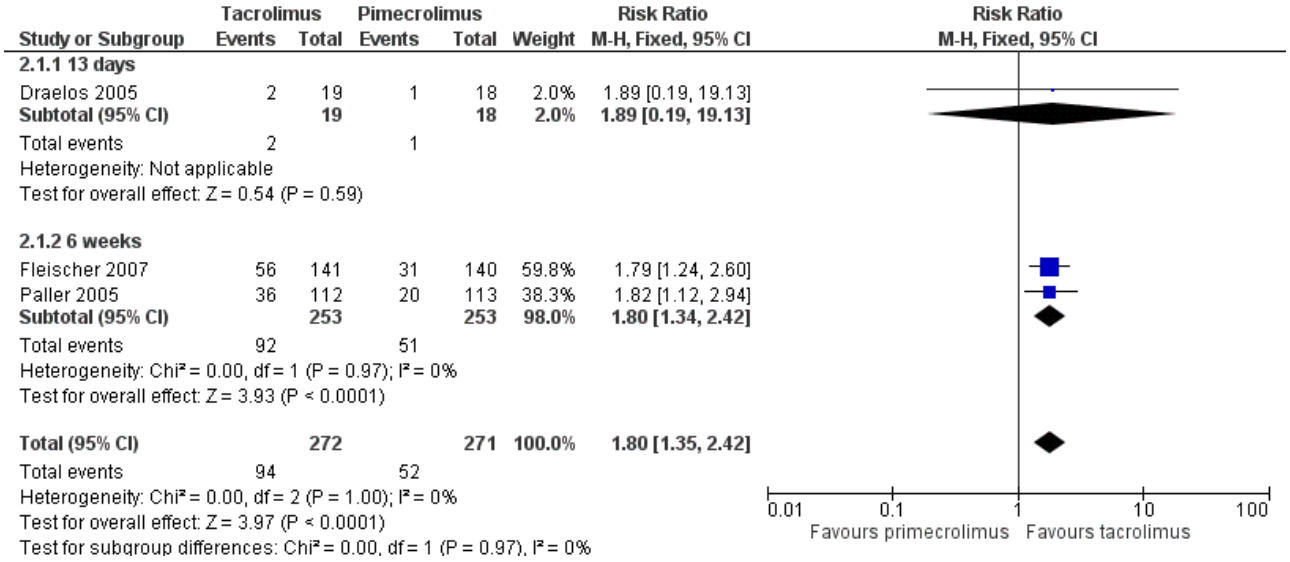
Primary outcomes

Physician's assessment of global response of improvement

Draelos 2005 reported this outcome at 13 days of treatment, and 2 studies, Fleischer 2007; Paller 2005, reported it at 6 weeks. The tacrolimus group showed significantly more improvement

compared with the pimecrolimus group (RR 1.80, 95% CI 1.35 to 2.42, 3 studies, 543 participants; Analysis 2.1; Figure 4).

Figure 4. Forest plot of comparison: 2 Tacrolimus 0.1% versus pimecrolimus 1%, outcome: 2.1 Physician's assessment of global response of improvement, clear or excellent



Participant's self-assessment of global response of improvement

This outcome was not reported in any of the studies.

Occurence and severity of adverse effects

Two included studies, Fleischer 2007; Paller 2005, after 6 weeks found no significant differences in the occurrence of adverse events between the groups (RR 0.89, 95% CI 0.47 to 1.71, 2 studies, 506 participants; Analysis 2.2). Burning and pruritus were the most frequent complaints.

Draelos 2005 analysed separately the occurrence of application site reactions after 13 days of treatment, with more frequent complaints in the tacrolimus 0.1% group (63.2% versus 27.8%, P = 0.03, Chi^2 test), and the intensity of local symptoms using a visual analogue scale, with more intense local symptoms also occurring in the tacrolimus 0.1% group (insufficient data for statistical analysis). The sample size of the study was however small (37 participants).

Secondary outcomes

Improvement of disease assessed by a validated or objective measure, such as the following: affected Body Surface Area (BSA)

Fleischer 2007 reported this outcome, and a significant difference was observed favouring the group receiving tacrolimus compared with pimecrolimus after 6 weeks of treatment, with a mean of reduction in the affected BSA of 49% and 34% (P = 0.01), respectively. In the same comparison and follow-up time, Paller 2005 also reported a significant difference favouring the tacrolimus group (mean reduction from baseline = 64.1% versus 47.5%, P < 0.001). Nevertheless, meta-analysis was not feasible due to insufficient data.

Improvement of disease assessed by a validated or objective measure, such as the following: Eczema Area and Severity Index (EASI)

Two studies comparing tacrolimus 0.1% with pimecrolimus 1% for 6 weeks reported a significant difference favouring the tacrolimus group: mean of reduction from baseline = 57% versus 39% (P = 0.0002) in Fleischer 2007 and 67.2% versus 56.4% (P < 0.001) in Paller 2005.

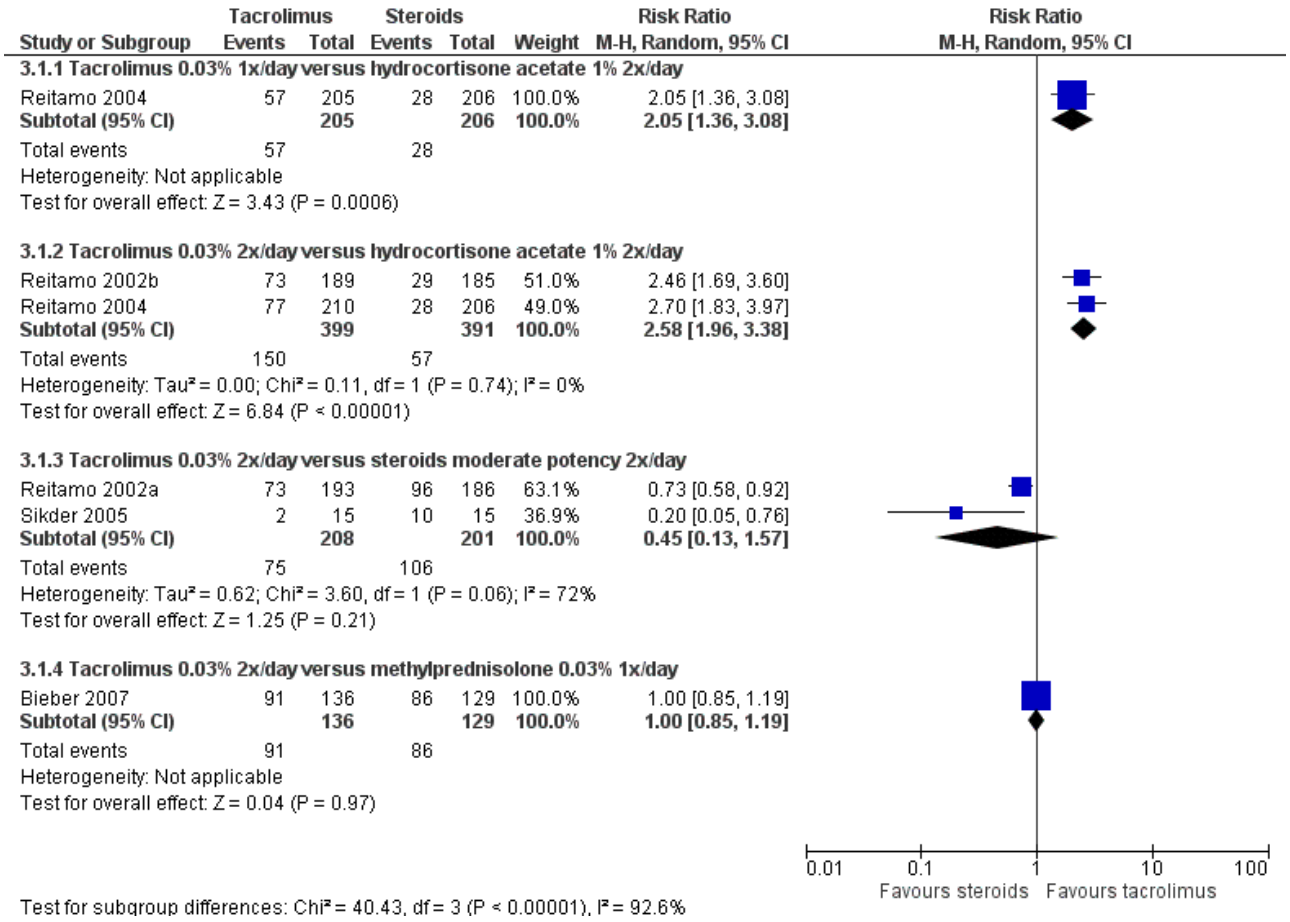
Tacrolimus 0.03% versus corticosteroids

Primary outcomes

Physician's assessment of global response of improvement

Five studies reported this outcome with varying doses of tacrolimus and types of corticosteroids with follow up of three to four weeks. One study, Reitamo 2004, showed a statistically significant improvement in the tacrolimus 0.03% (once a day) group compared with a low-potency corticosteroid twice a day (hydrocortisone acetate 1%) (RR 2.05, 95% CI 1.36 to 3.08, 1 study, 411 participants) in children. Two studies in children, Reitamo 2002b; Reitamo 2004, observed that groups receiving tacrolimus 0.03% twice a day also showed a statistically significant improvement (clear or excellent) by medical evaluation when compared with the same low-potency corticosteroid (hydrocortisone acetate 1%) (RR 2.58, 95% CI 1.96 to 3.38, 2 studies, 790 participants). Two studies, Sikder 2005; Reitamo 2002a, compared tacrolimus 0.03% ointment twice a day with mid-potency corticosteroids twice a day and found no significant differences between the groups (RR 0.45, 95% CI 0.13 to 1.57, 2 studies, 409 participants). Another study, Bieber 2007, compared tacrolimus 0.03% twice a day with methylprednisone 0.1% (once a day) and did not find any significant differences in improvement between the 2 groups (RR 1.00, 95% CI 0.85 to 1.19, 1 study, 265 participants; Analysis 3.1; Figure 5).

Figure 5. Forest plot of comparison: 3 Tacrolimus 0.03% versus corticosteroids, outcome: 3.1 Physician's assessment of global response of improvement, clear or excellent



Doss 2010 reported an improvement in the outcome 'Physician's global assessment' of 93.6% in the tacrolimus group and 92.4% in the mid-potency corticosteroid group (fluticasone 0.005%) (P = 0.05).

Participant's self-assessment of global response of improvement

Two studies reported participant's self-assessment of global response of improvement after three weeks of treatment (Doss 2010; Reitamo 2004). In the comparison of tacrolimus 0.03% once or twice a day and hydrocortisone acetate 1%, more participants in the tacrolimus group, in both the once or twice daily application groups, reported better or much better improvement (RR 1.33, 95% CI 1.13 to 1.57, 1 study, 411 participants; RR 1.64, 95% CI 1.41 to 1.90, 1 study, 416 participants, respectively). The comparison of tacrolimus 0.03% and fluticasone 0.005% found no differences between the groups (RR 0.98, 95% CI 0.92 to 1.05, 1 study, 473 participants; Analysis 3.2).

Occurence and severity of adverse effects

Five studies reported local adverse events, Doss 2010; Reitamo 2002a; Reitamo 2002b; Reitamo 2004; Sikder 2005, and there was a significantly higher incidence of burning and pruritus in the tacrolimus groups compared with the corticosteroid groups for burning (RR 2.48, 95% CI 1.96 to 3.14, 5 studies, 1883 participants; Analysis 3.3) and for pruritus (RR 1.51, 95% CI 1.17 to 1.95, 5 studies, 1883 participants; Analysis 3.4). When assessing skin infection, there was no significant difference between the groups (RR 1.07, 95% CI 0.69 to 1.66, 4 studies, 1643 participants; Analysis 3.5). The authors reported that adverse effects were transitory and not a reason for withdrawal from treatment.

Bieber 2007 reported drug-related adverse events in 6 out of 136 participants (4.4%) in the tacrolimus 0.03% twice a day group (pruritus, burning, and hot flushes) and none in the methylprednisolone aceponate 0.1% (once a day) group (n = 129) in a 3-week follow-up time.

Secondary outcomes

Improvement of disease assessed by a validated or objective measure, such as the following: affected Body Surface Area (BSA)

Two studies found less improvement of the affected BSA in the tacrolimus 0.03% group compared with mid- to high-potency corticosteroids: Reitamo 2002a (data in graphs, comparison with hydrocortisone butyrate 0.1%, 3 weeks) and Sikder 2005 (comparison with clobetasone, 4 weeks, t-test, MD 26.7, 95% CI 8.1 to 45.3, P = 0.007). Moreover, Bieber 2007, in a study comparing tacrolimus 0.03% twice a day and methylprednisolone once a day (potent corticosteroid), observed no significant difference between the 2 groups. Hung 2007 compared tacrolimus 0.03% with fluticasone 0.05%, with or without the addition of fusidic acid, and

also found no significant difference in affected BSA improvement between groups after 8 weeks of treatment. We were not able to extract any data because the original paper presented these in graphs.

Improvement of disease assessed by a validated or objective measure, such as the following: Eczema Area and Severity Index (EASI)

This outcome was reported in six studies; however, we did not perform meta-analysis because of insufficient data. Reitamo 2002a observed a significant difference, with less improvement in the group receiving tacrolimus 0.03% when compared with the group receiving hydrocortisone butyrate 0.1% (moderate-potency corticosteroid) (data in graphs). Another study comparing tacrolimus 0.03% with a mid-potency corticosteroid (clobetasone butyrate), Sikder 2005, found the same results with less improvement in the group receiving tacrolimus 0.03% compared with the clobetasone group (MD 12.5, 95% CI 2.4 to 22.7, P = 0.018). In the comparison between tacrolimus 0.03% twice a day and methylprednisolone (once a day) (high-potency corticosteroid), Bieber 2007 found no significant difference in mean change from baseline for mEASI between groups. Similarly, Doss 2010 also found no difference between the group receiving tacrolimus 0.03% and fluticasone twice a day (mid-potency). Compared with a low-potency corticosteroid (hydrocortisone acetate 1%), Reitamo 2002b showed that, averaged over the 3-week course of treatment, participants had a median improvement of mEASI of 55.2% with tacrolimus 0.03%, significantly more effective than the mean 36.0% with hydrocortisone acetate 1% ointment (P < 0.001, Wilcoxon test). Also, in Reitamo 2004, the comparison of tacrolimus 0.03%, once a day and twice a day, with the same low-potency corticosteroid showed a significantly greater decrease of the median percentage in mEASI for the tacrolimus groups (66.7%, 76.7%, and 47.6%, respectively; P < 0.001, Wilcoxon test).

Improvement of disease assessed by a validated or objective measure, such as the following: SCORing Atopic Dermatitis (SCORAD)

Hung 2007, who compared tacrolimus 0.03% with fluticasone 0.05%, with or without the addition of fusidic acid, found no significant improvement in SCORAD between the groups after 8 weeks of treatment (data shown in graphs).

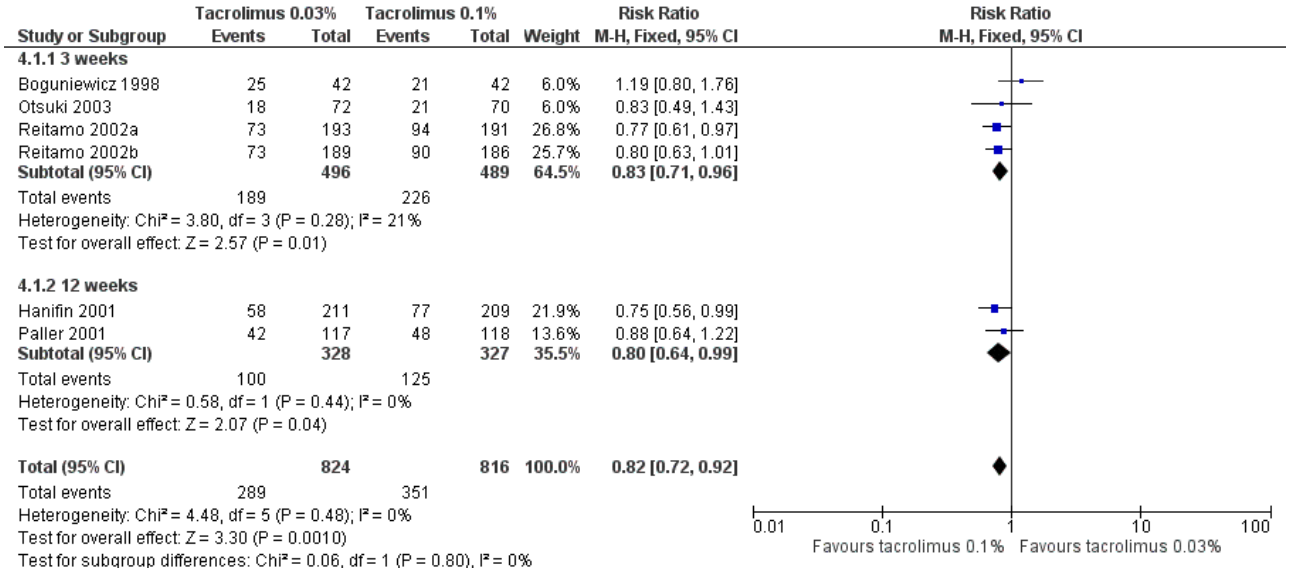
Tacrolimus 0.03% versus tacrolimus 0.1%

Primary outcomes

Physician's assessment of global response of improvement

In the 6 studies comparing these 2 formulations of tacrolimus in 3 weeks, Boguniewicz 1998; Otsuki 2003; Reitamo 2002a; Reitamo 2002b, and 12 weeks, Hanifin 2001; Paller 2001, there was a statistically significant difference in the physician's assessment of global response (clear or excellent) favouring tacrolimus 0.1% (RR 0.82, 95% CI 0.72 to 0.92, 6 studies, 1640 participants; Analysis 4.1; Figure 6).

Figure 6. Forest plot of comparison: 4 Tacrolimus 0.03% versus tacrolimus 0.1%, outcome: 4.1 Physician's assessment of global response of improvement, clear or excellent



Participant's self-assessment of global response of improvement

Only one study, Boguniewicz 1998, reported this outcome in the comparison of the 2 tacrolimus formulations, 0.03% versus 0.1%, and no differences were found between the 2 groups: 76% (32 out of 42) versus 91% (38 out of 42) (P = 0.08, Chi² test).

Occurence and severity of adverse effects

Four 3-week studies, Boguniewicz 1998; Otsuki 2003; Reitamo 2002a; Reitamo 2002b, did not find any significant differences in the incidence of adverse events (RR 0.95, 95% CI 0.86 to 1.06, 4 studies, 986 participants; Analysis 4.2). Another 12-week study, Paller 2001, also failed to find any significant difference between the groups, adjusted incidence of 42.7% versus 33.7% for burning and 41.2% versus 32.2% for pruritus (235 participants, Kaplan-Meier analyses).

Secondary outcomes

Improvement of disease assessed by a validated or objective measure, such as the following: Eczema Area and Severity Index (EASI)

Reitamo 2002b observed a median improvement of 55.2% in the mEASI with tacrolimus 0.03% and 60.2% with tacrolimus 0.1%,

which represented a significant difference (P = 0.006, Wilcoxon test) in children. In Reitamo 2002a, there was also less improvement in the tacrolimus 0.03% group when used in adults (53.0% versus 63.5% median improvement, P < 0.001, Wilcoxon test). Boguniewicz 1998 reported a mean per cent improvement of 72% with tacrolimus 0.03% and 77% with tacrolimus 0.1%, without providing the necessary data for statistical analysis. Also, Hanifin 2001 and Paller 2001 found similar results, but the study report only presented data as graphs (no numbers were given).

Improvement of disease assessed by a validated or objective measure, such as the following: quality of life

Dou 2006 evaluated the quality of life and presented narrative results referring to significant improvement in the group receiving tacrolimus 0.1% compared with tacrolimus 0.03%.

Tacrolimus 0.03% versus pimecrolimus 1%

Primary outcomes

Physician's assessment of global response of improvement

One study, Kempers 2004, compared tacrolimus 0.03% with pimecrolimus 1% for 6 weeks, with a significant difference favouring tacrolimus in the physician's global assessment of "clear" or "almost clear" response (RR 1.42, 95% CI 1.02 to 1.98,1 study, 139 participants; Analysis 5.1).

Participant's self-assessment of global response of improvement

This outcome was not reported in any of the studies.

Occurence and severity of adverse effects

Kempers 2004 compared tacrolimus 0.03% with pimecrolimus 1% used for 6 weeks (141 participants), with no significant difference at day 4 for application site reaction, burning, itching, or erythema between groups (Analysis 5.2).

Secondary outcomes

Improvement of disease assessed by a validated or objective measure, such as the following: affected Body Surface Area (BSA)

Kempers 2004 compared tacrolimus 0.03% with pimecrolimus 1% and found no significant differences in the change from baseline of the affected BSA after 6 weeks between groups (44.5% versus 43.4%, Mantel-Haenszel test, controlling for centre).

Tacrolimus 0.1% versus ciclosporin

Primary outcomes

Physician's assessment of global response of improvement

This outcome was not reported in any of the studies.

Participant's self-assessment of global response of improvement

This outcome was not reported in any of the studies.

Occurence and severity of adverse effects

Pacor 2004 was the only study that compared topical tacrolimus 0.1% twice a day to a systemic medication (oral ciclosporin 3 mg/kg/day). The number of participants reporting adverse events in the follow-up period was equal in the 2 groups (4 out of 15 in the ciclosporin group and 4 out of 15 in the tacrolimus group) (Analysis 6.1). In the tacrolimus group, the adverse effects were mild and local (burning), and in the ciclosporin group, they were mild and systemic (gastric intolerance and headache).

Secondary outcomes

Improvement of disease assessed by a validated or objective measure, such as the following: SCORing Atopic Dermatitis (SCORAD)

Pacor 2004 reported the outcome of the comparison between tacrolimus 0.1% ointment twice a day and ciclosporin tablets 3 mg/kg/day in a follow-up period of 6 weeks. After 2 weeks, SCORAD decreased in both groups. Participants in the tacrolimus group reported though a significantly lower SCORAD (that means, more improvement) when compared to those treated with oral ciclosporin. The mean difference in SCORAD in the tacrolimus group compared with SCORAD in the ciclosporin group was MD −12.6 (95% CI −18.7 to −6.5) after 14 days, MD −11.6 (95% CI −17.7 to −5.5) after 21 days, MD −18.7 (95% CI −24.8 to −12.6) after 28 days, and MD −10.1 (95% CI −16.2 to −4.0) after 35 days. After 42 days, however, the mean of SCORAD was not significantly different: MD −1.3 (95% CI−7.4 to 4.8; Analysis 6.2). Overall SCORAD, as assessed by the area under the curve between days 0 to 42 (AUC^{0} to ^{42}) (AUC = area under the curve) that represents the cumulative measurement of drug effect on this period (in the case of SCORAD, the lower the better), was significantly lower in the tacrolimus ointment group when compared with oral ciclosporin (P < 0.001, unpaired Student's test).

Safety of topical tacrolimus

Other reported adverse events and serious adverse events

Other reported local adverse events were folliculitis, erythema, maculopapular rash, and alcohol intolerance (local erythema after alcohol ingestion); the last symptom was only in the calcineurin inhibitors groups. All groups reported systemic symptoms that included flu-like symptoms, headache, and fever.

There were rare reports of serious adverse events. The two tacrolimus-dose groups and the vehicle group in the study by Otsuki 2003 reported laboratory-study abnormalities, and the study authors considered them to be unrelated to the study medication. Reitamo 2002a reported increased liver enzymes in 2 participants in the corticosteroid group and 1 participant in the tacrolimus 0.03% group. Also, this group reported one case of a mild and transient decrease in white blood cell count. Reitamo 2002b described 1 case of increased liver enzymes in the tacrolimus 0.03% group and 1 case of increased serum creatinine in the corticosteroid group. Reitamo 2004 showed 1 case of leukopenia, 1 case of failure to thrive (considered as being unrelated to treatment), and 1 case of Kaposi's varicelliform eruption with bacterial infection in the tacrolimus 0.03% twice-a-day group. The tacrolimus 0.03% (once-a-day) group reported 1 case of a decreased white blood cell count. The corticosteroid group reported one case of abdominal pain and one case of leg pain (osteoarticular infection). One participant presented with an important erythema on the forehead, with complete resolution after treatment with antihistamines in Paller 2001. (The participant completed the study.) Finally, Reitamo 2005 reported one case of lymphoma-like reaction and one case of skin carcinoma in the corticosteroid group.

Adverse events in any type of study design

Looking at other sources, we screened more than 3800 abstracts and analysed all the data on tacrolimus safety in atopic dermatitis,

independently of study design. Common and non-serious adverse events were similar to those found in the included studies. We will discuss in detail more controversial risks, especially those that lead to U.S. Food and Drug Administration (FDA) black-box warnings. We did not include in this review reports of the use of tacrolimus for other diseases, mainly because the diseases themselves carry sometimes intrinsic risks, such as development of malignancy in lichen sclerosus et atrophicus.

Risk of malignancies

Table 2, 'Spontaneous reported malignancies in association with topical tacrolimus use', lists FDA-reported malignancies (Ormerod 2005). The Spanish Pharmacovigilance System (paediatric adverse event reports from 2004 to 2009) reported another case of lymphoma in a 20-month-old participant with a T-cell lymphoma. He had used tacrolimus (the report did not specify if it was topical or systemic) and methylprednisolone (Aldea 2012).

Table 3 and Table 4 summarise cohort and case-control studies analysing lymphoma and skin cancer risks related to atopic dermatitis or treatments, respectively. None of the studies found an increased risk of skin cancers other than lymphoma. Regarding the risks of lymphoma, Arellano 2007 and Arellano 2009 showed an apparent risk related to atopic dermatitis (and its severity); other authors, Soderberg 2004, also suggested a disease-related risk. Callen 2007 described 7 studies analysing this subject, and results showed odds ratios of both > 1 and < 1, with no final conclusion. There are two possible explanations for this increased risk: either there is indeed a real increased risk of lymphomas developing in people with atopic dermatitis, or there are cases that were misdiagnosed as atopic dermatitis and were already cases of cutaneous lymphoma to start with. Many cases of skin lymphomas may start with a clinical presentation resembling chronic dermatitis, several years before they are finally diagnosed as cutaneous lymphomas. Arellano 2009 also found an increased risk of lymphomas in systemic corticosteroid users, but found insufficient data to make conclusions about users of topical calcineurin inhibitors (TCI). Schneeweiss 2009 noted an increased risk in users of TCI and topical corticosteroids when compared with the general population, but with similar risks between the treatment groups. This might have occurred because of the comparison with non-atopic dermatitis participants. We noticed similar findings in Hui 2009, with a report of an increased risk in the TCI-exposed group when compared with non-exposed individuals. Again, the proportion of participants with the diagnosis of atopic dermatitis was twice as high in the exposed group. It is questionable if the increased risk was due to exposure or due to possible intrinsic risks of lymphoma related to atopic dermatitis as discussed above. The observational studies reported no cases of lymphoma and sparse and probably unrelated cases of skin cancers (see Table 5; Margolis 2007; Naylor 2005).

The suggested potential mechanisms responsible for malignancies associated with the use of topical tacrolimus are as follows.

- Mutagenesis or genotoxicity: evidence from pre-clinical development in bacteria and mammalian cells do not support this hypothesis (US Food and Drug Administration).
- Local effects inhibiting immunosurveillance: this effect can be responsible for skin tumours on local application sites, though no evidence from trials support this hypothesis (no increased risk of skin tumours, both melanoma and non-melanoma skin cancers when compared with the general population in the reported studies). It is important to note that atopic dermatitis itself is associated with immune dysregulation and barrier defects, regardless of the treatment used.
- Drug absorption leading to systemic immunosuppression: several different facts speak against this hypothesis, as discussed below.
  - After topical application of tacrolimus, serum concentrations of the drug are usually low or undetectable, and rates of absorption decrease with improvement of the skin barrier integrity (Fonacier 2005; Harper 2005; Hultsch 2005; US Food and Drug Administration). On the other hand, topical corticosteroids may cause thinning of the skin and even increase the absorption of topically applied drugs over time. An exception to this general rule is seen in conditions that show permanent severe barrier dysfunction, such as Netherton's syndrome, lamellar ichthyosis, and others, where higher systemic levels of tacrolimus were found, and their use in these diseases is therefore not recommended. This fact is mentioned on the labelling change, which was put in effect by the FDA in 2011 (Allen 2001; Allen 2002).
  - Studies analysing possible systemic immunosuppression after the use of topical tacrolimus, measured either by childhood immunisation responses (evaluating B cell immunity) (Stiehm 2005) or a recall antigen test to evaluate delayed-type hypersensitivity (T cell) (Hultsch 2005; Reitamo 2000) did not show any degree of decreased immunity compared with the baseline.
  - Oral tacrolimus used in transplant recipient participants does carry an increased risk of both lymphoma and non-lymphoma skin tumour development. Also, murine protocols with topical application of tacrolimus reported a higher risk of lymphoma development. However, the doses used were 26 to 47 times higher than the maximum recommended human doses and much higher than the maximum serum levels detected in people after topical use of this drug. Both examples related to systemic immunosuppression. It is important to note that in this setting of immunosuppression, we find different features characterising the lymphomas, such as occurrence in unusual sites, polymorphous or pleomorphic large cell or Hodgkin's-like morphology, Epstein-Barr virus (EBV)-related lymphomas, B-cell lymphomas, and lymphomas spontaneously regressing after interruption of immunosuppressive therapy in a significant percentage of cases (Callen 2007; Fonacier 2005; Hultsch 2005; Knowles 1999). The cases identified by the spontaneous reporting systems described none of these features, and as elicited above, there was no evidence of systemic suppression with topical use in humans. While data from animal studies should not be ignored, they often do not accurately reflect the situation of topical treatment of skin diseases and should be evaluated with caution.
- Protective effect: an in vitro study showed an inhibitory effect of tacrolimus against human liver cancer cells, and another one demonstrated that it can also inhibit 12-O-tetradecanoylphorbol-13-acetate-induced promotion of skin papilloma formation in CD-1 mice (Weischer 2007). Another study, Tran 2005, showed that pretreatment with either pimecrolimus or tacrolimus inhibited UV-mediated thymine dimer formation compared with control mice, demonstrating

a possible protective effect for UV-mediated damage, also reported in other safety reviews (Patel 2007; Rustin 2007).

For all of the reasons presented, the possibility of the majority of lymphomas reported being due to tacrolimus was low, and some of the cases could even have been misdiagnosed as atopic dermatitis, while they represented cases of cutaneous lymphomas from the start. Summarising, there was no evidence of an increased risk of malignancy with TCI. Spontaneous cases have been reported, but they are few in number and seem to be within the expected occurrence rate for the general population. Longer follow-up periods of more than 10 years might be necessary for a definitive position on this matter.

We should also keep in mind that other available treatments for atopic dermatitis, such as oral corticosteroids, oral ciclosporin, and psoralen plus ultraviolet light, are all proven to show increased risk of the development of malignancy associated with their use (Karagas 2001; Momtaz 1998; Sorensen 2004; Stern 2001; Zonneveld 1996). The risk of the development of malignancy associated with topical corticosteroids is yet to be determined.

Skin atrophy

We found no cases of skin atrophy due to topical tacrolimus use in our search. Nineteen of the included studies did not mention skin atrophy in the reported adverse events. Two papers reported no cases of skin atrophy in any of the groups (tacrolimus 0.03%, tacrolimus 0.1%, and vehicle) (Hanifin 2001 - in the additional report by Soter 2001; Paller 2001). Reitamo 2005 reported 2 cases of skin atrophy in the corticosteroid group (2 out of 485) and no cases in the tacrolimus 0.1% ointment group (0 out of 487).

Most of the papers affirmed that tacrolimus did not cause atrophy based on the paper by Reitamo 1998. In this randomised trial, 14 atopic dermatitis participants and 12 healthy volunteers used tacrolimus 0.03%, tacrolimus 0.1%, betamethasone-valerate, and vehicle on non-symptomatic abdominal skin for 7 days under occlusion. The trial measured propeptides of procollagen I and III (radioimmunoassays) and skin thickness (ultrasound), and bethametasone was the only one with a decrease by the three analysed parameters. Kyllönen 2004 analysed the same parameters in 56 atopic dermatitis participants treated with tacrolimus 0.1% ointment for 1 year compared with 36 atopic dermatitis participants treated with topical corticosteroid therapy (mostly of moderate potency) and 27 healthy controls. The tacrolimus group, which had lower levels of propeptides of procollagen than the controls at baseline, showed an increase in collagen synthesis and skin thickness. In three participants with visible skin atrophy due to prior treatments with topical corticosteroids, the condition improved after tacrolimus treatment. In the corticosteroid group, collagen synthesis was not significantly affected, but a significant reduction in skin thickness was shown. Another long-term study evaluating the use of tacrolimus ointment for more than 1 year (568 participants) reported no cases of skin atrophy (FK506 Ointment Study Group 2001). Reitamo 2000, in an open-label non-comparative study, followed 316 adults with moderate to severe atopic dermatitis using tacrolimus 0.1% twice a day for 6 to 12 months and also found no cases of skin atrophy. Also in this study, one of the participants with skin atrophy due to prior treatment with topical corticosteroids had the condition (atrophy) ameliorated after six months of tacrolimus treatment.

Studies in vitiligo (a disease that causes loss of pigmentation of areas of skin) also did not show skin thinning after tacrolimus use. In a randomised controlled trial (RCT), Lepe 2003 compared a 2-month treatment with clobetasol propionate 0.05% versus tacrolimus 0.1% (in symmetrical lesions) in 20 children with vitiligo. Clobetasol-treated lesions showed atrophy in 3 out of 20 participants and in none of the tacrolimus-treated lesions. Lotti 2008 analysed 458 vitiligo participants for 6 months using 11 types of therapy, including tacrolimus 0.1% and betamethasone dipropionate 0.05% with or without 311 nm narrow-band phototherapy. From the 11 treatment groups, only those using bethametasone showed skin atrophy.

Animal studies also found no evidence of skin atrophy with topical tacrolimus use. Bekersky 2001 cites 2 studies: 1 in mice, which noted a reduction in ear thickness with topical corticosteroid regimens (alclometasone dipropionate 0.1% and betamethasone valerate 0.12%), but not with any of the tacrolimus concentrations tested (0.3%, 0.1%, and 1%), and 1 in rats, evaluating skin weight, thickness, and histopathology, which showed no alterations compared with controls in the group using tacrolimus 0.03% ointment for 3 weeks. Animals using moderate to potent topical corticosteroids showed, in contrast, skin thinning, decreased subcutaneous tissue, and suppressed proliferation of epidermal cells.

In summary, current evidence supports the fact that tacrolimus ointment does not cause skin atrophy.

Conditions with increased risk of systemic absorption

Netherton syndrome is a rare autosomal recessive disease with congenital erythroderma that is sometimes mistaken for atopic dermatitis. Affected infants are at risk of dehydration probably due to the increase in water loss through the severe defective skin barrier. Allen 2001 reported 3 children (3, 5, and 14 years old) with this syndrome with large areas of the skin treated with topical tacrolimus 0.1% with significant systemic absorption of the drug (serum levels above the therapeutic range). Similarly, Bens 2003 reported a case of a 17-year-old girl treated with tacrolimus 0.03% with increased systemic absorption by the treated area. When limited to small areas, no significant levels were detected. In contrast, Saif 2007 reported on 4 affected siblings (a 40-day-old and a 3-, 6-, and 12-year-old), the 3 older children being treated with tacrolimus 0.1% for 2 years, with blood levels checked every 3 to 4 months and being mostly undetectable, and when detectable (occasionally), it was below the therapeutic range of transplant participants.

Lamellar ichthyosis is another rare autosomal recessive congenital erythrodermic disease, also with severe barrier defect and great transepidermal water loss. In a report (Allen 2002), a 28-month-old child was treated with tacrolimus 0.1% applied to the whole body surface area twice a day for 7 weeks. Pitarch 2006 reported a case of a 54-year-old man with extensive ulcers due to pyoderma gangrenosum (a neutrophilic dermatosis with ulcerations on the skin, frequently associated with other systemic diseases), who was treated with tacrolimus 0.1% once daily for 4 weeks in combination with systemic infliximab, and Skowron 2005 reported a case of a 54-year-old woman with extensive vulgar pemphigus (an autoimmune bullous disease) treated with tacrolimus 0.1% after refractory treatment with systemic corticosteroids and immunoglobulin. All of the three cases showed marked improvement but with

significant systemic absorption although with serum levels within the therapeutic range for transplant participants. Beyeler 2006 reported a case of an erythrodermic patient with significant systemic absorption of tacrolimus 0.1% after a 5-day course of use in an extensive area under occlusion with "Unna's" paste.

Other possible adverse effects

Rosacea-like dermatitis or perioral dermatitis (PD) is a known adverse effect of the chronic use of topical corticosteroid on the face. A few cases have been reported with the use of tacrolimus as well (Antille 2004; Fujiwara 2010; Teraki 2012). On the other hand, we can also find reports of the same condition being successfully treated (off-label) with tacrolimus (Goldman 2001; Schwarz 2008), making this a controversial issue that still needs clarification.

With regard to alcohol intolerance, some of the studies and a few case reports described flushing on the face of a few users of tacrolimus ointment after alcohol ingestion, and even in some children receiving ethanol-containing medications (Calza 2005; Knight 2005; Milingou 2004). The manufacturers reported that this adverse event occurs in approximately 6% of people using the medication. The symptoms resolve after discontinuation of ointment. In some reports, the use of aspirin might also inhibit these symptoms (Ehst 2004); however, the mechanism of action for this is still not clear.

The use of tacrolimus in infants (< 2 years) is not recommended since at the time the FDA approved tacrolimus ointment, no efficacy or safety studies had been conducted in this particular population. The issue is still controversial due to the lack of trials involving this age group. Patel 2003 evaluated 12 infants (younger than 2 years of age) with atopic dermatitis and found no increased levels of the medication in their blood levels after 30 days of their usual treatment and no reports of any significant adverse events either.

More recently, another study on infants aged 3 to 24 months and using tacrolimus 0.03% has been conducted. Results showed that there was minimal systemic absorption; however, this was highly variable between participants. The majority of the blood samples (97%) had tacrolimus levels below 1 ng/mL (Reitamo 2006; Rustin 2007). More studies are needed on this age group.

In the world literature, there are also reports of tacrolimus-induced lentiginosis (Castelo-Soccio 2012; Hickey 2004; Zattra 2010), benign neoplasms, development of Kaposi's sarcoma lesions on the tacrolimus-treated areas (in HIV patients) (Cho 2004; Schmutz 2006), tacrolimus allergic contact dermatitis (Shaw 2004), and one anecdotal report of a relapse of schizophrenia (Lin 2007).

Reports of cutaneous infections in tacrolimus ointment users (molluscum, viral warts, tinea incognito, herpes, eczema herpeticum, etc.) with the suggestion of a possible higher risk will not be discussed again, since those studies with better designs have already proven that there is no increased risk.

DISCUSSION

Summary of main results

An extensive literature search resulted in the inclusion of 20 studies (from 24 papers), with a total of 5885 participants. Sample sizes varied from 16 to 972 participants. Two concentrations of topical tacrolimus (0.03% and 0.1%) were compared with each other, as well as with pimecrolimus 1%, with low- and mid-potency topical corticosteroids, and with oral ciclosporin. The variability of drug doses, outcomes, and follow-up periods made it difficult to carry out meta-analyses.

Results of several individual trials showed a moderate benefit of tacrolimus 0.1% over low-potency corticosteroids (physician's assessment, modified Eczema Area and Severity Index (mEASI)), low-potency corticosteroids used on the face and neck areas, moderate-potency corticosteroids on the trunk and extremities (quality of life, physician's assessment, Body Surface Area (BSA), mEASI), and pimecrolimus 1% (physician's assessment, BSA, Eczema Area and Severity Index (EASI)). When compared with moderate to potent corticosteroids, we found no significant difference in three of the outcomes analysed (physician's assessment, BSA, mEASI). The participant's assessment and SCORing Atopic Dermatitis (SCORAD) found a statistically significant, but marginal difference, favouring tacrolimus 0.1%. Based on results of a couple of trials, we found tacrolimus 0.03% to be superior to mild topical corticosteroids (physician's and participant's assessment, mEASI). One study compared tacrolimus 0.03% with pimecrolimus 1% with a significant difference favouring tacrolimus by the physician's assessment and with a non-significant difference when comparing BSA. In the comparison with moderate-to-potent corticosteroids, we found no significant difference in most of the outcomes (physician's and participant's assessment, BSA, EASI, mEASI, SCORAD), but in two studies, we observed a slight difference favouring the corticosteroid group (EASI, BSA). The clinical significance of that difference is unlikely to be important. The comparison between both tacrolimus formulations significantly favoured tacrolimus 0.1% in all studies (physician's assessment, mEASI, quality of life), except for one study that found no significant difference in the participant's global assessment. Only one study compared tacrolimus 0.1% with oral ciclosporin, and in the SCORAD evaluation, we found tacrolimus 0.1% to be superior to this systemic drug. Quality of life showed better improvement in the tacrolimus 0.1% group when compared with tacrolimus 0.03% and when compared with topical corticosteroids (low-potency used on the head and neck areas and mid- to high-potency when used on the trunk and extremities).

Adverse effects

When evaluating the adverse events (one of the most controversial and important issues of this review), we carried out two different analyses. First, we analysed the data on adverse events in the included studies and carried out a meta-analysis whenever it was possible. Second, we looked for all the case reports, observational and cohort studies (see Table 5) (Gontijo 2008; Koo 2005; Mandelin 2012; Reitamo 2000; Reitamo 2007; Reitamo 2008; Remitz 2007; Saple 2003; Won 2004; Wong 2003), safety letters, industry and U.S. Food and Drug Administration (FDA) warnings, expert opinions, and so on, to do a narrative analyses of current evidence (Aldea 2012; Antille 2004; Breuer 2005; Callen 2007; Calza 2005; Castelo-Soccio 2012; Cho 2004; Czarnecka-Operacz 2012; Ehst 2004; Fonacier 2005; Fujiwara 2010; Hickey 2004; Hui 2009; Hultsch 2005; Knight 2005; Lin 2007; Milingou 2004; Naylor 2005; Ormerod 2005; Patel 2003; Patel 2007; Rustin 2007; Schmutz 2006; Shaw 2004; Siegfried 2013; Tennis 2011; Teraki 2012; US Food and Drug Administration; Weischer 2007; Zattra 2010).

The three most frequently reported adverse events in the included studies were local side-effects: burning, pruritus, and skin infection.

The comparison between tacrolimus and pimecrolimus, as well as between the two formulations of tacrolimus, showed no significant differences regarding the occurrence of adverse events. In all included studies, burning was significantly more frequent in the tacrolimus group (both formulations) than in the corticosteroid (all potencies) groups. When evaluating pruritus at the application sites, those in the tacrolimus 0.03% twice-a-day group made more complaints than those in the topical corticosteroid group, but when comparing corticosteroids with tacrolimus 0.1% (twice a day) and tacrolimus 0.03% (once a day), no difference was found. None of the studies found a significant difference in the occurrence of skin infection (viral, bacterial, or fungal) in the tacrolimus group when compared with the corticosteroid group (any potency). Symptoms of burning and pruritus were mild to moderate in the first few days of treatment and subsequently declined; they were short-lived (minutes to a few hours) and generally did not lead to discontinuation of treatment. Other reported application site adverse events were folliculitis, erythema, maculopapular rash, and ingested alcohol intolerance (local erythema after alcohol ingestion). The latter was reported only with the use of the topical calcineurin inhibitors. Systemic symptoms included flu-like symptoms, headache, and fever and were reported in all treatment groups. As detailed in the adverse events section, more serious adverse events were rare and occurred within the tacrolimus, corticosteroid, and vehicle groups and most of the time were considered not to be related to the treatment. None of the trials noted cases of lymphoma. In Reitamo 2005, the corticosteroid group reported one case of lymphoma-like reaction and one skin carcinoma, which were also considered as probably unrelated to the treatment drug.

Attention should be made to the comparison of adverse events between tacrolimus (both formulations) and pimecrolimus. We found no differences in the occurrence of all adverse events (Draelos 2005; Fleischer 2007; Kempers 2004; Paller 2005). However, Draelos 2005 (the smallest study with 37 participants: tacrolimus 0.1% versus pimecrolimus 1%), when analysing the application site reactions and the intensity of local symptoms, found them to be more frequent and more intense in the tacrolimus 0.1% group. Kempers 2004 (in the comparison between tacrolimus 0.03% and pimecrolimus 1%) also found application site reactions to be a little bit more frequent in tacrolimus participants. Also, the duration of symptoms in this study were longer in tacrolimus participants, with the majority experiencing symptoms between 30 minutes to 12 hours, while none of the pimecrolimus participants had symptoms for more than 30 minutes. Larger studies evaluating this matter might be necessary.

After analysing all of the data from animal, observational, cohort, and case-control studies, and so on, presented in detail in the section Effects of interventions, we conclude that the possibility of the majority of lymphomas reported being due to tacrolimus is low, and some of the cases could even have been misdiagnosed as atopic dermatitis, while they were actually cases of cutaneous lymphomas from the start. In summary, there is no evidence of an increased risk of malignancy with topical calcineurin inhibitors (TCI). Spontaneous cases have been reported, but they are few in number and seem to be within the expected occurrence rate for the general population. Longer follow-up periods of more than 10 years might be necessary for a definitive position on this matter.

Many safety reviews and expert opinion records have tried to analyse in detail the possible risks of topical tacrolimus and malignancies, and all of them have found insufficient evidence to support the FDA warnings. They all stated their position against it. This includes such important groups as the American Academy of Dermatology (AAD) (Berger 2006), the Canadian Dermatology Association (CDA) (Maddin 2005), the Canadian Society of Allergy and Clinical Immunology (CSACI) (Segal 2013), the German Society of Dermatology (Deutschen Dermatologischen Gesellschaft - DDG) (Luger 2005), and the European Dermatology Forum (EDF) (Ring 2005).

We should also keep in mind that other available treatments for atopic dermatitis, such as oral corticosteroids, oral ciclosporin, and psoralen plus ultraviolet light, are all proven to show increased risk of the development of malignancy associated with their use (Karagas 2001; Momtaz 1998; Sorensen 2004; Stern 2001; Zonneveld 1996). The risk of the development of malignancy associated with topical corticosteroids is yet to be determined.

In November 2011, the FDA approved a labelling change for topical tacrolimus regarding the risk of systemic absorption in some conditions with severe skin barrier defects, such as Netherton's syndrome, lamellar ichthyosis, generalised erythroderma, or cutaneous Graft Versus Host Disease. This change was due to some reports in the literature. Those reports highlighted the importance of careful use of the drug in such skin conditions, but also showed its great efficacy, even in refractory cases. Treatment of a limited area of skin with close monitoring of serum levels might be an alternative in such cases.

We found no cases of skin atrophy due to topical tacrolimus use in our search. We also evaluated clinical trials; case reports; and in vivo, in vitro, and animal studies, but did not find any evidence that topical tacrolimus could cause skin atrophy.

Other possible effects, presented as case reports, include perioral dermatitis, alcohol intolerance, tacrolimus-induced lentiginosis (Castelo-Soccio 2012; Hickey 2004; Zattra 2010), benign neoplasms, development of Kaposi's sarcoma lesions in the tacrolimus-treated areas (in HIV patients) (Cho 2004; Schmutz 2006), tacrolimus allergic contact dermatitis (Shaw 2004), and others.

The use of tacrolimus in infants (< 2 years) is not recommended since at the time the FDA approved tacrolimus ointment, no efficacy or safety studies had been conducted in this particular population. The issue is still controversial because of the lack of trials involving this age group. More studies are needed in this age group.

Evidence on corticosteroid safety

Topical corticosteroids are the first-line therapy for atopic dermatitis; however, they are also not indicated for long-term treatment (> 4 weeks), and only a few are approved in children younger than 2 years. They also have a skin-thinning potential and possible rebound and tachyphylaxis effects, none of which are seen in tacrolimus-treated skin. There are no pre-clinical carcinogenetic studies with topical corticosteroids (TCS), and the risk of malignancy in this group is still to be determined (Siegfried 2013). It should be noted that because corticosteroids have been prescribed for so many years, physicians may not feel compelled to report adverse events that may develop with their use. By contrast, the opposite may occur with calcineurin inhibitors, even more so

after the FDA warnings, which placed the safety of this relatively new class of drug at the forefront. Also, because topical tacrolimus is a second-line therapy, indicated for more severe cases, there is a risk that any adverse effects associated with it may have more severe consequences because of the intrinsic risk associated with more severe disease.

That being said, in addition to the proven efficacy of tacrolimus showed in this review and given the fact that current evidence does not support significant risks with the use of topical tacrolimus, it should definitely be considered a safe option for the treatment of moderate to severe atopic dermatitis.

Overall completeness and applicability of evidence

Although most of the included studies reported the primary outcomes of interest, it was difficult to pool any data due to the variability of drug doses and potencies, the different outcomes and scores used to evaluate the efficacy of treatment, and the different follow-up periods. Thus, the lack of data limited our confidence in any findings of this review. The lack of data on many of the secondary outcomes that we intended to evaluate further limits the completeness of evidence. For instance, quality of life and relapse are important issues in this chronic and relapsing disorder, but we found little data on the subject. Future reviews should also try to address the costs of the treatments, since one of the great disadvantages of TCI is that they are much more expensive than TCS. The relatively short follow-up duration of the included studies further limits the external validity of the review. Most of the studies were short-term studies (3 months or less) with only a minority reporting data for longer periods (maximum follow-up time of 12 months); therefore, the safety data especially should be carefully interpreted. Despite that, this review brings some tranquility for prescribers, since we found no evidence to support the most feared risk of possible development of malignancies, neither did we find any evidence of increased risk of skin atrophy, a great advantage over topical corticosteroids, especially in more sensitive areas of the body.

Quality of the evidence

We included 20 studies (from 24 papers), with a total of 5885 participants, and sample sizes varied from 16 to 972 participants. When using Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Guyatt 2008) to evaluate the studies, quality of the evidence varied from high to very low in some comparisons, as indicated in the 'Summary of findings' (SoF) tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6).

The main reasons for downgrading the quality of the studies were incomplete or unclear information on randomisation or allocation concealment; for inconsistency of results, we downgraded studies when there was a moderate level of heterogeneity between studies; for imprecision, we considered downgrading when either sample size was smaller than optimal information size or 95% confidence interval (CI) of the estimate of summary effect included both no effect and appreciable benefit and harm, or both; we also downgraded studies when we only identified one study and strongly suspected publication bias.

Despite this, we evaluated some studies with a good number of participants and found statistically significant results in most of the variables, with the exception of the comparison of tacrolimus 0.1% and oral ciclosporin and the comparison of tacrolimus 0.03% and pimecrolimus, which only had 1 small study each (30 and 139 participants, respectively). Though the different doses, outcomes, and follow-ups made it difficult to use meta-analysis to summarise all the data, the results of the different subgroups comparing a similar intervention pointed in the same direction, with no major discrepancies. This variability was also the major difficulty when creating the 'Sof' tables, but we tried to summarise the most important data in the tables.

Potential biases in the review process

A comprehensive search from a wide range of databases was conducted with no language restrictions. To reduce the risk of bias, two independent authors screened the trials identified by the literature search and examined the full text of selected studies for compliance with eligibility criteria. Both authors assessed the risk of bias of included studies and extracted the data. With regard to the age groups, as discussed above, we analysed the combined data from adults and children. When we encountered incomplete information, we contacted the study authors. Some replied and were able to provide the necessary information, while others either did not reply or no longer had access to the data requested, and we considered the information as unclear. We also contacted pharmaceutical companies supporting the trials, who could not provide the requested data.

The review authors had no conflicts of interest regarding any of the treatments or drugs analysed in this review.

Agreements and disagreements with other studies or reviews

We focused the analysis of the review on people with moderate to severe atopic dermatitis, so that the mild cases, which usually show better and easier response to treatment, would not interfere with the results. We also excluded studies comparing tacrolimus with placebo, since several studies had already proven the drug efficacy in this scenario. Still, this review included the largest number of studies when compared with the others found in the literature (Ashcroft 2005b; Chen 2010; El-Batawy 2009; Svensson 2011; Yan 2008; Yin 2012).

The results found are in accordance with the results from the other published reviews in terms of efficacy and safety. The review by Yan 2008 found the only discrepancy; it reported no differences between either 1 of the 2 tacrolimus concentrations (0.03% and 0.1%), while our analysis showed superior efficacy in the 0.1% formulation. This might have happened because Yan 2008 included only 3 studies, with a total of 702 participants, where physician's global assessment was made, while our review on this subject included 6 studies, with a total of 1640 participants, and analysed both physician's and participant's global assessment. With regard to the reporting of safety and adverse events, the results were similar to those in the other reviews that analysed comparative controlled trials, as well as with the results from observational and cohort studies. A few studies, which analysed the paediatric and adult populations separately, reported more complaints of burning in the adult population and more cases of infection in the paediatric

population. In this review, we analysed the combined data of both age groups.

AUTHORS' CONCLUSIONS

Implications for practice

Tacrolimus ointment seems to be safe and effective for the treatment of moderate to severe atopic dermatitis in both children and adults. Systemic absorption of tacrolimus may be high in those who have skin diseases that present with permanent severe impairment in the integrity of the skin barrier. Within the context of this review, there is a lack of evidence to support the U.S. Food and Drug Administration's warning of increased risk of malignancies associated with the use of topical tacrolimus.

Implications for research

It was not the objective of this review to evaluate only specific areas of treatment, such as the face and neck region, but this might be an important subject for a future review, since these sensitive areas might be more prone to adverse events of local treatments.

Standardisation of outcomes and interventions in trials analysing the same topic should be developed, so that a comparison and combination of results can be better achieved. This review found a good number of well-designed studies, but as stated earlier, the variability of drug doses, outcomes, and follow-up periods made it difficult to carry out an adequate meta-analysis. More studies looking at the population of infants with atopic dermatitis are needed.

In terms of safety, in spite of the fact that longer duration trials are lacking, the data available from observational and cohort studies, despite the lower methodological quality, should also be taken into account, since other study designs hardly demonstrate rare events, such as lymphomas. A promising 10-year prospective registry (planned N = 8000) was created to assess the risk of malignancies in children associated with topical tacrolimus ointment use ('A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety (APPLES) of tacrolimus ointment for the treatment of atopic dermatitis' (NCT00475605)). APPLES includes participants no older than 16 years of age and was initiated in 2005. The results of this promising study will most definitely contribute to significant and valuable data on this subject.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Antiga 2010

Methods	RCT
Participants	Adults with moderate to severe AD
Interventions	Tacrolimus ointment 0.1% (12 participants) compared with 17-butyrate-hydrocortisone ointment 0.1% (12 participants) (BID) for 3 weeks
Outcomes	• SCORAD
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were given a run-in number on enrolment; the randomisation list was created using Random Allocation Software
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded, but there was no interference with the results, as the participant's assessment was not evaluated. In the same way, physicians who gave the drug were not blinded, but they were not the people evaluating the outcomes, thus, also not interfering with the results. (We received this information after contacting the study author)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physician that evaluated SCORAD was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 3 losses out of 24 (12.5%) participants; there was no ITT analysis
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Bieber 2007

Methods	RCT (randomised, double-blind, multicentre, comparative study)
Participants	Paediatric patients (2 to 15 years) with history of moderate to severe AD and a severe flare (IGA > = 4)
Interventions	Tacrolimus ointment 0.03% BID (136 participants) compared with methylprednisolone aceponate 0.1% in the evening and no active treatment ointment in the morning (129 participants) for 3 weeks
Outcomes	• IGA • BSA • EASI • mEASI • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done in blocks to achieve balanced randomisation overall and within each centre
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial used identical tubes (morning and evening)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was investigator blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 8 losses out of 265 (3%) participants. ITT analysis was done, and the 'last observation carried forward' principle was applied to impute missing values
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Boguniewicz 1998

Methods	RCT (double-blind, randomised, multicentre trial)
Participants	Paediatric patients with moderate to severe AD
Interventions	Tacrolimus ointment 0.03% (43 participants) compared with tacrolimus ointment 0.1% (49 participants) versus tacrolimus ointment 0.3% (44 participants) compared with vehicle (44 participants) (BID) for 3 weeks
Outcomes	• mEASI

Boguniewicz 1998 *(Continued)*

- Physician's global assessment
- Patient's global assessment
- Adverse events

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was generated within each centre by using permuted blocks of size 8 by means of a centralised computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The interventions were identical in their appearance (identical coded tubes)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The interventions were identical in their appearance (identical coded tubes) (blinded to all investigators, participants, and the sponsor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 11 out of 180 (6.1%) losses. ITT analysis was done with no reference to the method for imputing missing data
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Caproni 2007

Methods	RCT
Participants	Adults with moderate to severe AD
Interventions	Tacrolimus ointment 0.1% (10 participants) compared with hydrocortisone butyrate 0.1% ointment (10 participants) (BID) for 3 weeks
Outcomes	• SCORAD • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned

Caproni 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 4 losses out of 20 (20%) participants in both groups. There was no ITT analysis
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Doss 2010

Methods	RCT (double-blind, randomised, non-inferiority, multicentre trial)
Participants	Paediatric patients (2 to 15 years) with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989)) and insufficient response to topical corticosteroids
Interventions	Tacrolimus ointment 0.03% (240 participants) compared with fluticasone 0.005% ointment (239 participants) (BID) for 3 weeks
Outcomes	• mEASI • Physician's global assessment • Patient's global assessment • Adverse events • Pruritus • Quality of sleep
Notes	Moderate-potency corticosteroids (fluticasone 0.005% ointment)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1: the Data Operations Department, Astellas Pharma, generated the list. Randomisation occurred in the order that the participants passed selection criteria
Allocation concealment (selection bias)	Low risk	Each participant received a unique treatment number, which was printed on sealed boxes containing the ointment tubes
Blinding of participants and personnel (performance bias)	Low risk	All interventions had the same appearance

Doss 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was investigator blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 41 losses out of 479 (8.6%) participants. ITT analysis was done with the last observation carried forward (LOCF) rule
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Dou 2006

Methods	RCT (randomised, multicentre, double-blind clinical trial)
Participants	Adults with moderate to severe AD
Interventions	Tacrolimus 0.03% ointment (67 participants) compared with tacrolimus 0.1% ointment (68 participants) compared with vehicle ointment (67 participants) (BID) for 3 weeks
Outcomes	• DLQI
Notes	Children were also evaluated, but the comparison was tacrolimus 0.03% ointment only with placebo (with no active treatment); therefore, we did not include them in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was randomised using aleatory distribution
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was double-blind, with no description of the method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was double-blind, with no description of the method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Incomplete outcome data were not described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described

Dou 2006 *(Continued)*

Other bias	Low risk	This trial was free of other bias

Draelos 2005

Methods	RCT (randomised, investigator-blind, parallel group, multicentre trial)
Participants	Adults with moderate to severe AD
Interventions	Tacrolimus 0.1% ointment (19 participants) compared with pimecrolimus 1% cream (18 participants) (BID) for 13 days
Outcomes	• IGADA (investigator's global assessment) • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drug assignment was computer-generated. (We obtained this information after contacting the author)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded because the intervention was an ointment and the control was a cream, but there was no interference with the results, as the participant's assessment was not evaluated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study lost no participants
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Fleischer 2007

Methods	RCT (prospective, randomised, investigator-blinded, multicentre, comparative trial)
Participants	Adults (> = 16 years) with moderate to severe AD
Interventions	Tacrolimus 0.1% ointment (141 participants) compared with pimecrolimus 1% cream (140 participants) (BID) for 6 weeks

Fleischer 2007 *(Continued)*

Outcomes	• IGADA • BSA • EASI • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A specialised company conducted centralised randomisation
Allocation concealment (selection bias)	Low risk	Allocation was by phone
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded because the intervention was an ointment and the control was a cream, but there was no interference with the results, as the participant's assessment was not evaluated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome investigator was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 64 losses out of 281 (22.8%) participants. ITT analysis was done with last observation carried forward analysis
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Hanifin 2001

Methods	RCT (2 randomised, double-blind, multicentre studies)
Participants	Adults (> = 16 years) with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))
Interventions	Tacrolimus 0.03% ointment (211 participants) compared with tacrolimus 0.1% ointment (209 participants) compared with vehicle (ointment base) (212 participants) (BID) for 12 weeks
Outcomes	• Physician's global assessment • BSA • EASI • Pruritus
Notes	Adverse events were reported in an additional paper (Soter 2001)

Risk of bias

Bias	Authors' judgement	Support for judgement

Hanifin 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The study was randomised 1:1:1 within each centre; the method was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was double blind (but there was no description of the blinding methods)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was double blind (but there was no description of the blinding methods)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was 1 loss out of 632 (0.16%) participants
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Hung 2007

Methods	RCT (randomised, parallel, open-label, single centre study)
Participants	9-month-old to 33-year-old participants with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))
Interventions	Tacrolimus 0.03% ointment alone compared with tacrolimus 0.03% ointment and fusidic acid 2% cream compared with fluticasone propionate 0.05% cream alone compared with fluticasone propionate 0.05% cream and fusidic acid 2% cream (15 participants randomised in each group) (BID) for 8 weeks
Outcomes	• BSA • SCORAD
Notes	Moderate-potency glucocorticoid (fluticasone propionate 0.05% cream)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the method was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded because of the different treatment appearance, but there was no interference with the results, as the participant's assessment was not evaluated

Hung 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Kempers 2004

Methods	RCT (multicentre, randomised, investigator-blind, parallel group study)
Participants	Paediatric patients (2 to 17 years) with moderate AD (IGA)
Interventions	Tacrolimus 0.03% ointment (70 participants) compared with pimecrolimus 1% cream (71 participants) (BID) for 6 weeks
Outcomes	• IGA • BSA • Pruritus • Adverse events
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial was randomised using a validated telephone system that automates the random assignment of treatment groups to randomisation numbers. A block size of 4 was used
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded because the intervention was an ointment and the control was a cream, but there was no interference with the results, as the participant's assessment was not evaluated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 16 losses out of 141 (11.3%) participants. ITT analysis was done with last observation carried forward analysis
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described

Kempers 2004 *(Continued)*

Other bias	Low risk	This trial was free of other bias

Otsuki 2003

Methods	RCT (randomised, double-blind, multicentre study)
Participants	Paediatric patients (2 to 15 years) with moderate to severe AD (Rajka and Langeland (Rajka 1989))
Interventions	Tacrolimus 0.03% ointment (72 participants) compared with tacrolimus 0.1% ointment (70 participants) compared with vehicle ointment (71 participants) (BID) for 3 weeks
Outcomes	• Investigator's global assessment • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was done through random assignment with a keycode
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was double blind, but there was no description of the blinding methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was double blind, but there was no description of the blinding methods
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 8 losses out of 221 (3.6%) participants. ITT analysis was done with no reference to the method for imputing missing data
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Pacor 2004

Methods	RCT (single centre, randomised, double-blind, double-dummy, placebo-controlled, parallel group study)
Participants	13-year-old to 45-year-old patients with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))

Pacor 2004 *(Continued)*

Interventions	Tacrolimus 0.1% ointment BID and placebo tablets (15 participants) compared with ciclosporin 3 mg/kg daily and placebo ointment (15 participants) for 6 weeks
Outcomes	• SCORAD • Adverse events • Itch • Interference with sleep
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but there was no description of the method
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both groups received tablets and ointment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatments were administered by a person who was unaware of who was participating in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Paller 2001

Methods	RCT (randomised, double-blind, multicentre trial)
Participants	Children (2 to 15 years) with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))
Interventions	Tacrolimus 0.03% ointment (117 participants) compared with tacrolimus 0.1% ointment (118 participants) compared with vehicle (ointment base) (116 participants) (BID) for 12 weeks
Outcomes	• Physician's and patient's global assessment • Adverse events • BSA • EASI • Pruritus
Notes	-

Paller 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were stratified by age and randomised 1:1:1 within each centre. The method was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigator, participants, guardian, and study co-ordinator were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator, participants, guardian, and study co-ordinator were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 40 losses out of 235 (17.0%) participants. ITT analysis was done, but the method was not described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Paller 2005

Methods	RCT (multicentre, randomised, investigator-blinded study)
Participants	Paediatric patients (2 to 15 years) with moderate to severe AD (IGADA)
Interventions	Tacrolimus 0.1% ointment (112 participants) compared with pimecrolimus 1% cream (113 participants) (BID) for 6 weeks
Outcomes	• IGADA • BSA • EASI
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was 1:1; numbers were assigned sequentially and stratified by age. A controlled randomisation system at the EMMES Corporation (Rockville, Md) conducted randomisation and stratification
Allocation concealment (selection bias)	Low risk	A study co-ordinator, independently of the examining physician, placed a call to a centralised randomisation centre to obtain the next sequential participant number and drug assignment

Paller 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded because the intervention was an ointment and the control was a cream, but there was no interference with the results, as the participant's assessment was not evaluated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was investigator blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 274 losses out of 1065 (25.7%) participants. ITT analysis was done, but the method was not described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Reitamo 2002a

Methods	RCT (multicentre, randomised, double-blind, parallel group study)
Participants	Adults (16 to 70 years) with moderate to severe AD
Interventions	Tacrolimus 0.03% ointment (193 participants) compared with tacrolimus 0.1% ointment (191 participants) compared with hydrocortisone butyrate 0.1% ointment (186 participants) (BID) for 3 weeks
Outcomes	• BSA per cent • mEASI • Physician's global assessment • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred in the order that the participants passed the selection criteria (parallel groups: 1:1:1). The sponsor supplied each centre a unique block of sequentially ordered participant numbers from a randomisation list
Allocation concealment (selection bias)	Low risk	For treatment allocation, an ointment supply box bearing a unique participant number was dispensed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical tubes were used with no information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical tubes were used with no information

Reitamo 2002a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 61 losses out of 570 (10.7%) participants. ITT analysis was done, but the method was not described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Reitamo 2002b

Methods	RCT (multicentre, randomised, double-blind, parallel group study)
Participants	Paediatric patients (2 to 15 years) with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))
Interventions	Tacrolimus 0.03% ointment (189 participants) compared with tacrolimus 0.1% ointment (186 participants) compared with hydrocortisone acetate 1% ointment (185 participants) (BID) for 3 weeks
Outcomes	• mEASI • Physician's global assessment • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred in the order that the participants passed the selection criteria (parallel groups: 1:1:1), stratified by centre and age. The sponsor supplied each centre with a unique block of sequentially ordered participant numbers from a randomisation list
Allocation concealment (selection bias)	Low risk	For treatment allocation, an ointment supply box bearing a unique participant number was dispensed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical tubes were used with no information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was investigator blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 54 losses out of 560 (9.6%) participants. ITT analysis was done, but the method was not described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Reitamo 2004

Methods	RCT (randomised, double-blind, multicentre, comparative study)
Participants	Paediatric patients (2 to 15 years) with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))
Interventions	Tacrolimus ointment 0.03% once daily (207 participants) compared with tacrolimus ointment 0.03% BID (210 participants) compared with hydrocortisone acetate ointment 1% BID (207 participants) for 3 weeks
Outcomes	• Physician's global assessment • Patient's global assessment • EASI • mEASI • Itch • Quality of sleep
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial had 1:1:1 stratification by centre and age. The sponsor supplied each centre with a unique block of sequentially ordered participant numbers from a randomisation list. Randomisation occurred in the order that the participants passed the selection criteria
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	2 sets of identical tubes (morning and evening) were used for all of the groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was investigator blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 88 losses out of 624 (14.1%) participants. ITT analysis was done, but the method was not described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Reitamo 2005

Methods	RCT (double-blind, randomised, comparative, phase III study)

Reitamo 2005 *(Continued)*

Participants	Adults with moderate to severe AD
Interventions	Tacrolimus ointment 0.1% (487 participants) compared with hydrocortisone butyrate ointment 0.1% on the trunk and extremities and hydrocortisone acetate ointment 1% on the face and neck (485 participants) (BID) for 6 months
Outcomes	• BSA • mEASI • EASI • Physician's global assessment • Patient's global assessment • Adverse events
Notes	In an additional paper (Mandelin 2010), a subgroup of 80 participants were analysed Poole 2010 reported others outcomes of the study, quality of life, and health-related utility analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study sponsor generated the list, and participants were allocated by an investigator, using 1:1 stratification by centre, in the order that participants passed the selection criteria
Allocation concealment (selection bias)	Low risk	Participants were allocated by the investigator, using 1:1, stratified by centre, in the order that the participants passed the selection criteria
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial used identical tubes: 5 tubes for the trunk and extremities and 2 tubes for the head and neck for both groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial used identical tubes: 5 tubes for the trunk and extremities and 2 tubes for the head and neck for both groups
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 328 losses out of 972 participants. ITT analysis was done, but the method was not described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

Sikder 2005

Methods	RCT (comparative, multicentre, open, randomised, parallel group study)
Participants	Older children (7 to 15 years) with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))
Interventions	Tacrolimus 0.03% ointment BID (15 participants) compared with clobetasone butyrate 0.05% cream BID (15 participants) compared with clobetasone butyrate 0.05% cream in the morning and tacrolimus 0.03% ointment in the evening (15 participants) for 4 weeks

Sikder 2005 *(Continued)*

Outcomes	• BSA • mEASI • Physician's global assessment • Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were stratified by age and disease severity and randomised in parallel groups (1:1:1)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blind because the intervention was an ointment and the control was a cream, but there was no interference with the results, as the participant's assessment was not evaluated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding was unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no participant losses
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	This trial was free of other bias

AD: atopic dermatitis.
BID: twice a day.
BSA: Body Surface Area.
DLQI: Dermatology Life Quality Index.
EASI: Eczema Area and Severity Index.
IGA: Investigators' Global Assessment.
IGADA: Investigator's Global Atopic Dermatitis Assessment.
ITT: intention-to-treat.
LOCF: last observation carried forward.
mEASI: modified Eczema Area and Severity Index.
RCT: randomised controlled trial.
SCORAD: SCORing Atopic Dermatitis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arkwright 2006	This was not randomised

Study	Reason for exclusion
Chapman 2005	This study compared the intervention only with placebo. (There was no comparison with other active treatments)
del Rosso 2007	Participants in the study were treated and assessed only on a selected area of skin; whereas, this review sought studies where the whole person was treated and evaluated
Doss 2009	This study evaluated only facial eczema
Dähnhardt-Pfeiffer 2013	This study analysed only a selected area for treatment (only lesions on the forearms); whereas, this review sought studies where the whole person was treated and evaluated
Gradman 2007	The study did not divide the different severity groups and analyse the global data; participants included mild cases, which were not of interest to this review
Granlund 2001	This study compared the intervention only with placebo. (There was no comparison with other active treatments)
Hebert 2006	The study did not divide the different severity groups and analyse the global data, including the mild cases
Hjelmgren 2007	The study was not a RCT. It was based on a RCT's data and used surveys after the treatment period to compare both groups
Ishibashi 1997	The study compared tacrolimus in the different formulations only to placebo. No comparison between the different formulations was made
Kang 2003	The study evaluated only the head and neck area
Kirsner 2010	The study did not divide the different severity groups and analyse the global data, including the mild cases
Liu 2005	The study compared the intervention only to placebo (no comparison with other active treatments)
Neumann 2008	We excluded this study because of an ineligible intervention
Onumah 2013	This was an open-labelled pilot study on patient vehicle (ointment versus cream) preference
Rahman 2008	The study compared the intervention only to placebo. (There was no comparison with other active treatments)
Reitamo 2009	The study classified atopic dermatitis based only on body surface area and not on severity scores. We could not make classification as mild, moderate, or severe
Ruzicka 1997	The study analysed only a selected area for treatment (200 to 1000 cm^2)
Schachner 2005	The study compared the intervention only with placebo. (There was no comparison with other active treatments)
Takeuchi 2012	This study used 'maintenance therapy', which was not of interest to this review. This review only investigated studies with active treatment
Torok 2003	This study did not classify disease severity
Won 2004	This was a non-comparative study

Study	Reason for exclusion
Xhauflaire-Uhoda 2007	Participants in this study were treated and assessed only on a selected area of skin; whereas, this review sought studies where the whole person was treated and evaluated

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Drake 2001

Methods	RCT (3 randomised, double-blind, multicentre studies)
Participants	Adults and children with moderate to severe AD (Rajka and Langeland criteria (Rajka 1989))
Interventions	Tacrolimus 0.03% ointment versus tacrolimus 0.1% ointment versus vehicle (ointment base) (BID)
Outcomes	• DLQI • CDLQI • Modified CDLQI (quality of life)
Notes	We contacted the author to identify the 3 original trials

AD: atopic dermatitis.
BID: twice a day.
DLQI: Dermatology Life Quality Index.
CDLQI: Children's Dermatology Life Quality Index.
RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

NCT00475605

Trial name or title	APPLES: A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis
Methods	Observational, prospective, cohort study
Participants	People who first used tacrolimus 0.03% or 0.1% before they were 16 years of age and were treated for at least 6 weeks for the treatment of atopic dermatitis
Interventions	Topical tacrolimus 0.03% or 0.1%
Outcomes	• The endpoint is the occurrence of serious adverse events, including the observation of systemic and cutaneous malignancies (time-frame: at 6-month intervals for 10 years)
Starting date	May 2005
Contact information	-
Notes	Each participant will be followed for 10 years in this study. ClinicalTrials.gov identifier: NCT00475605

DATA AND ANALYSES

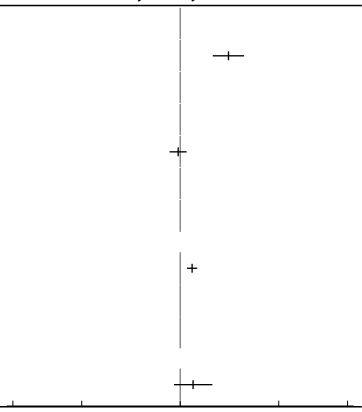
Comparison 1. Tacrolimus 0.1% versus steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement, clear or excellent	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: long-term (12 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse effects: burning	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: long-term (12 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse effects: pruritus	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Adverse effects: skin infection	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 SCORAD: 3 weeks	2	37	Mean Difference (IV, Fixed, 95% CI)	-8.82 [-15.36, -2.27]

Analysis 1.1. Comparison 1 Tacrolimus 0.1% versus steroids, Outcome 1 Physician's assessment of global response of improvement, clear or excellent.

Study or subgroup	Tacrolimus n/N	Steroid n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks				
Reitamo 2002b	90/186	29/185		3.09[2.14,4.45]
1.1.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks				
Reitamo 2002a	94/191	96/186		0.95[0.78,1.16]
1.1.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)				
Reitamo 2005	298/487	225/485		1.32[1.17,1.49]
1.1.4 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: long-term (12 months)				
Reitamo 2005	23/40	17/40		1.35[0.86,2.12]

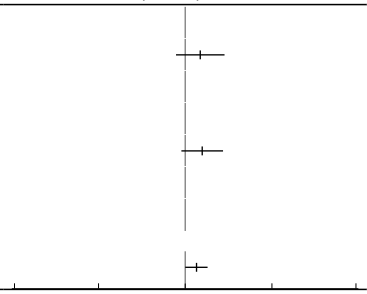


Analysis 1.2. Comparison 1 Tacrolimus 0.1% versus steroids, Outcome 2 Adverse effects: burning.

Study or subgroup	Tacrolimus n/N	Coricosteroid n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks				
Reitamo 2002b	38/186	13/185		2.91[1.6,5.28]
1.2.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks				
Reitamo 2002a	113/191	24/186		4.59[3.1,6.78]
1.2.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)				
Reitamo 2005	255/487	67/485		3.79[2.99,4.81]
1.2.4 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: long-term (12 months)				
Reitamo 2005	40/40	34/40		1.17[1.02,1.35]

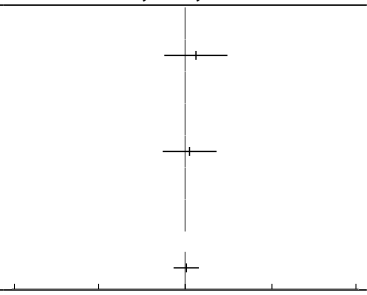
Analysis 1.3. Comparison 1 Tacrolimus 0.1% versus steroids, Outcome 3 Adverse effects: pruritus.

Study or subgroup	Tacrolimus n/N	Corticosteroid n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks				
Reitamo 2002b	21/186	14/185		1.49[0.78,2.84]
1.3.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks				
Reitamo 2002a	29/191	18/186		1.57[0.9,2.73]
1.3.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)				
Reitamo 2005	88/487	65/485		1.35[1,1.81]



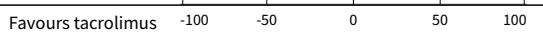
Analysis 1.4. Comparison 1 Tacrolimus 0.1% versus steroids, Outcome 4 Adverse effects: skin infection.

Study or subgroup	Tacrolimus 0.1% n/N	Steroid n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks				
Reitamo 2002b	12/186	9/185		1.33[0.57,3.07]
1.4.2 Tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks				
Reitamo 2002a	15/191	13/186		1.12[0.55,2.3]
1.4.3 Tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short-term (6 months)				
Reitamo 2005	60/487	58/485		1.03[0.73,1.44]



Analysis 1.5. Comparison 1 Tacrolimus 0.1% versus steroids, Outcome 5 SCORAD: 3 weeks.

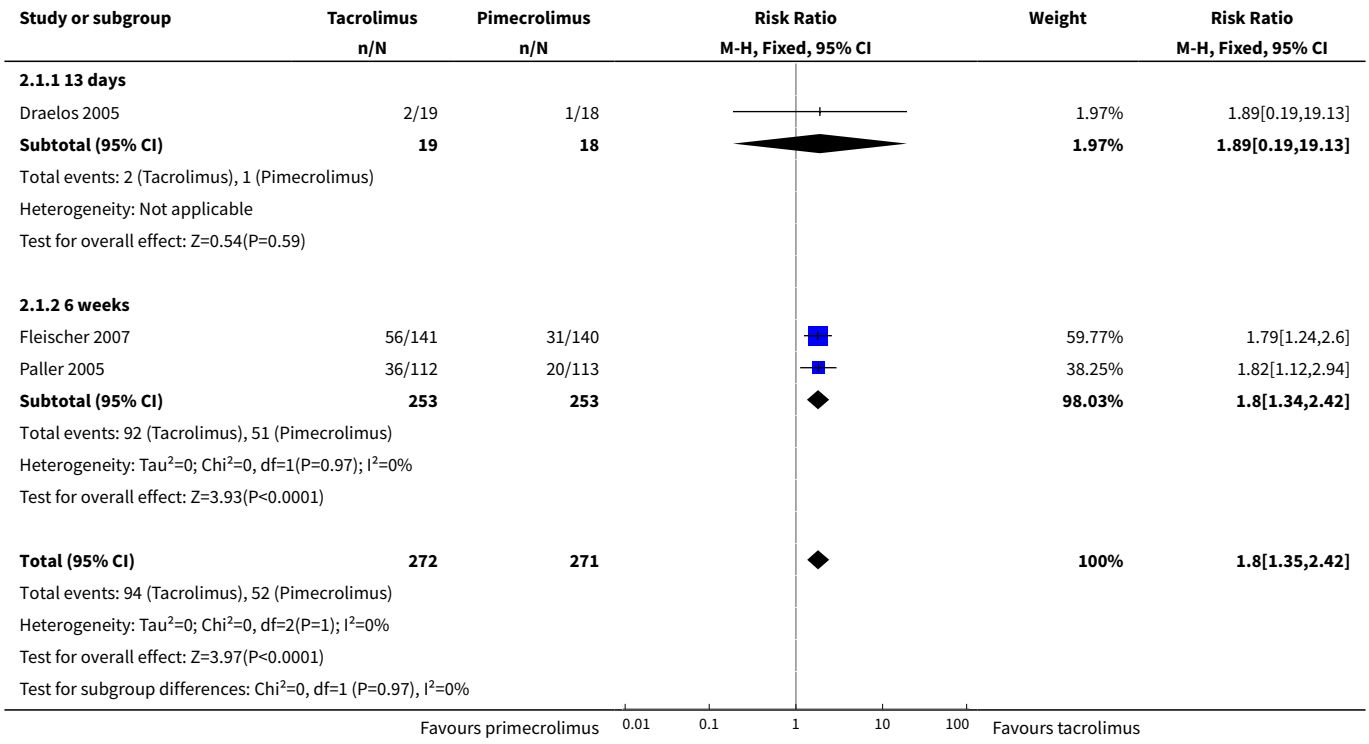
Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Steroid N	Steroid Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Antiga 2010	11	3.8 (10)	10	10.2 (10)		58.35%	-6.4[-14.96,2.16]
Caproni 2007	9	11.4 (8.4)	7	23.6 (11.5)		41.65%	-12.2[-22.34,-2.06]
Total ***	**20**		**17**			**100%**	**-8.82[-15.36,-2.27]**
Heterogeneity: Tau^2=0; Chi^2=0.73, df=1(P=0.39); I^2=0%							
Test for overall effect: Z=2.64(P=0.01)							



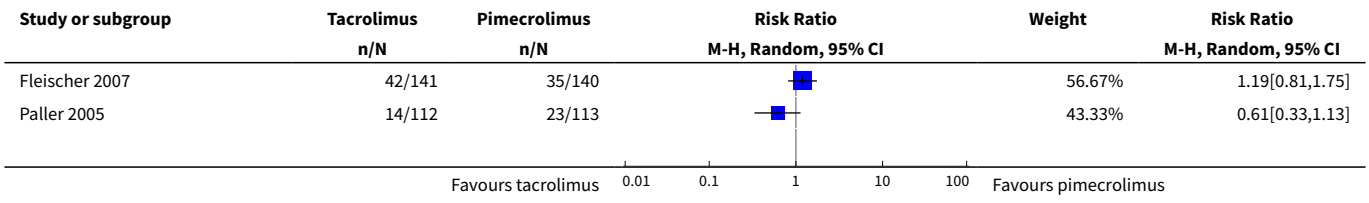
Comparison 2. Tacrolimus 0.1% versus pimecrolimus 1%

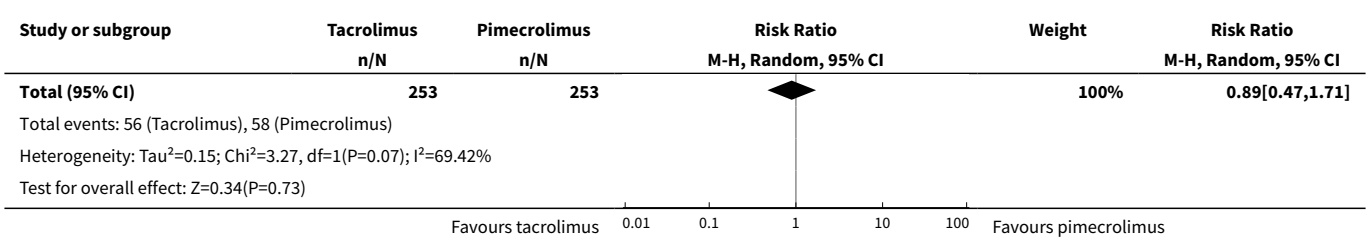
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement, clear or excellent	3	543	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.35, 2.42]
1.1 13 days	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.19, 19.13]
1.2 6 weeks	2	506	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.34, 2.42]
2 Adverse effects - 6 weeks	2	506	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.47, 1.71]

Analysis 2.1. Comparison 2 Tacrolimus 0.1% versus pimecrolimus 1%, Outcome 1 Physician's assessment of global response of improvement, clear or excellent.



Analysis 2.2. Comparison 2 Tacrolimus 0.1% versus pimecrolimus 1%, Outcome 2 Adverse effects - 6 weeks.





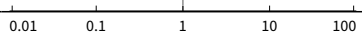
Comparison 3. Tacrolimus 0.03% versus steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement, clear or excellent	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Tacrolimus 0.03% 1x/day versus hydrocortisone acetate 1% 2x/day	1	411	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.36, 3.08]
1.2 Tacrolimus 0.03% 2x/day versus hydrocortisone acetate 1% 2x/day	2	790	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.96, 3.38]
1.3 Tacrolimus 0.03% 2x/day versus steroids moderate potency 2x/day	2	409	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.13, 1.57]
1.4 Tacrolimus 0.03% 2x/day versus methylprednisolone 0.03% 1x/day	1	265	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.19]
2 Participants's assessment of global response of improvement better or much better	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Tacrolimus 0.03 1x/day versus hydrocortisone acetate 1% 2x/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Tacrolimus 0.03% 2x/day versus hydrocortisone acetate 1% 2x/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Tacrolimus 0.03% 2x/day versus fluticasone 0.005% 2x/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse effects: burning	5	1883	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.96, 3.14]
3.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%	2	998	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.36, 2.57]
3.2 Tacrolimus 0.03% versus steroids moderate potency	3	885	Risk Ratio (M-H, Fixed, 95% CI)	3.52 [2.45, 5.06]
4 Adverse effects: pruritus	5	1883	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.17, 1.95]
4.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%	2	998	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.00, 1.88]

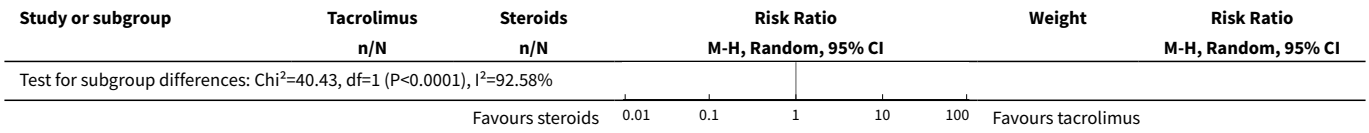
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Tacrolimus 0.03% versus steroids of moderate potency	3	885	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.18, 2.80]
5 Adverse effects: skin infection	4	1643	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.69, 1.66]
5.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%	2	788	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.49, 1.79]
5.2 Tacrolimus 0.03% versus steroids of moderate potency	2	855	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.65, 2.18]

Analysis 3.1. Comparison 3 Tacrolimus 0.03% versus steroids, Outcome 1 Physician's assessment of global response of improvement, clear or excellent.

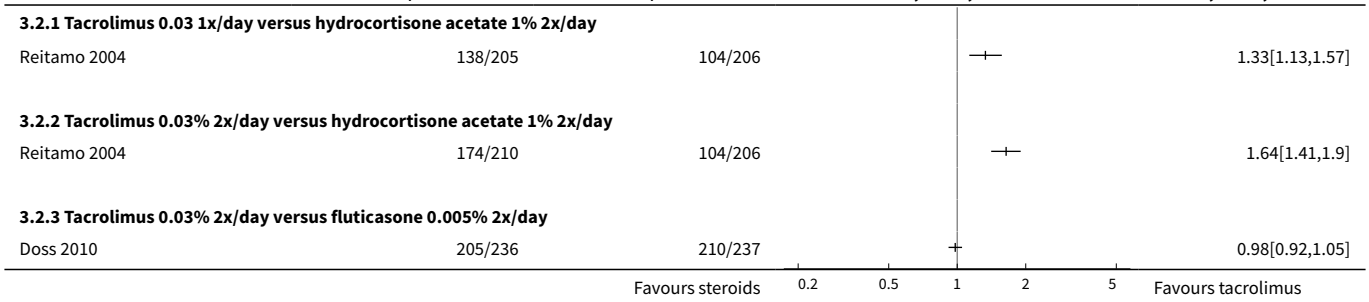
Study or subgroup	Tacrolimus n/N	Steroids n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Tacrolimus 0.03% 1x/day versus hydrocortisone acetate 1% 2x/day					
Reitamo 2004	57/205	28/206		100%	2.05[1.36,3.08]
Subtotal (95% CI)	**205**	**206**		**100%**	**2.05[1.36,3.08]**
Total events: 57 (Tacrolimus), 28 (Steroids)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.43(P=0)					
3.1.2 Tacrolimus 0.03% 2x/day versus hydrocortisone acetate 1% 2x/day					
Reitamo 2002b	73/189	29/185		51.04%	2.46[1.69,3.6]
Reitamo 2004	77/210	28/206		48.96%	2.7[1.83,3.97]
Subtotal (95% CI)	**399**	**391**		**100%**	**2.58[1.96,3.38]**
Total events: 150 (Tacrolimus), 57 (Steroids)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%					
Test for overall effect: Z=6.84(P<0.0001)					
3.1.3 Tacrolimus 0.03% 2x/day versus steroids moderate potency 2x/day					
Reitamo 2002a	73/193	96/186		63.12%	0.73[0.58,0.92]
Sikder 2005	2/15	10/15		36.88%	0.2[0.05,0.76]
Subtotal (95% CI)	**208**	**201**		**100%**	**0.45[0.13,1.57]**
Total events: 75 (Tacrolimus), 106 (Steroids)					
Heterogeneity: Tau^2=0.62; Chi^2=3.6, df=1(P=0.06); I^2=72.19%					
Test for overall effect: Z=1.25(P=0.21)					
3.1.4 Tacrolimus 0.03% 2x/day versus methylprednisolone 0.03% 1x/day					
Bieber 2007	91/136	86/129		100%	1[0.85,1.19]
Subtotal (95% CI)	**136**	**129**		**100%**	**1[0.85,1.19]**
Total events: 91 (Tacrolimus), 86 (Steroids)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					



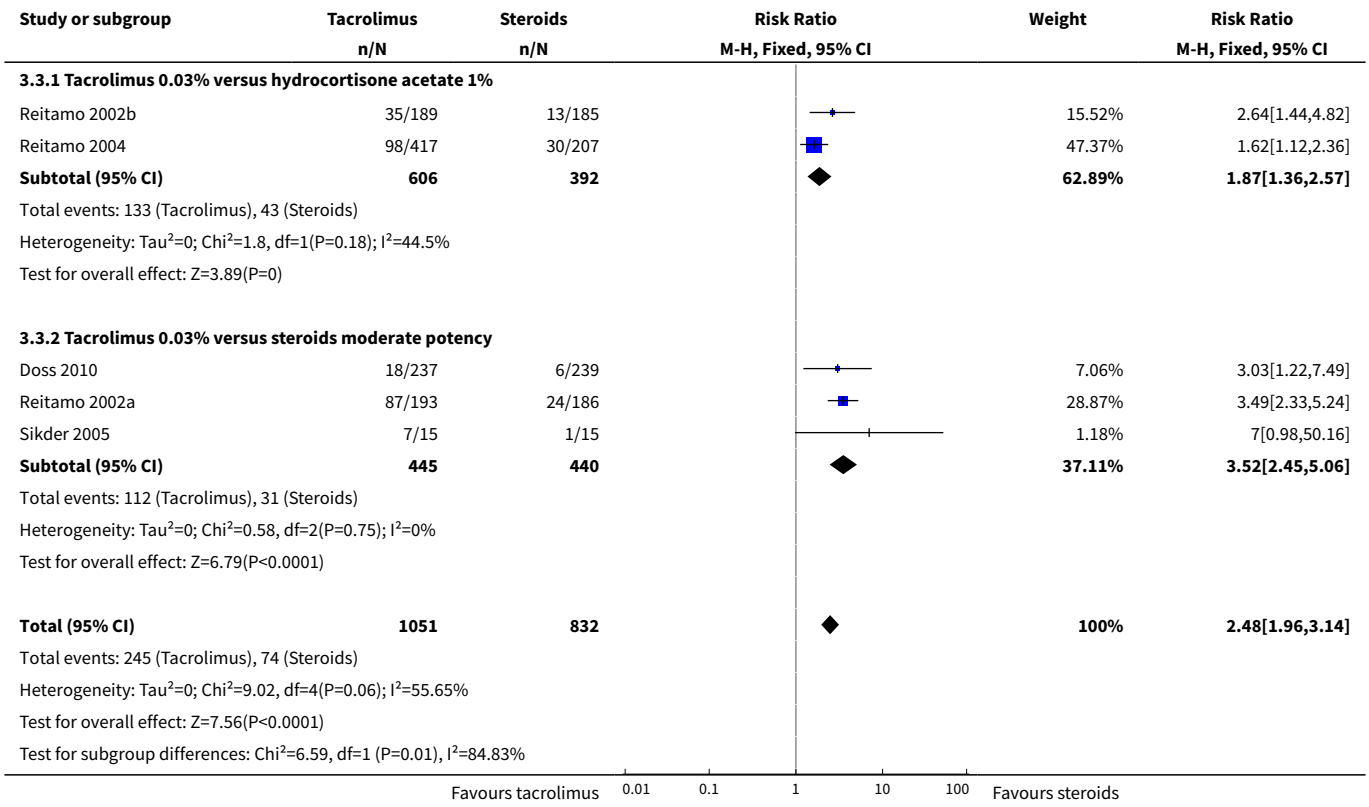
Favours steroids — Favours tacrolimus



Analysis 3.2. Comparison 3 Tacrolimus 0.03% versus steroids, Outcome 2 Participants's assessment of global response of improvement better or much better.

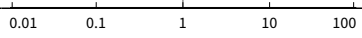


Analysis 3.3. Comparison 3 Tacrolimus 0.03% versus steroids, Outcome 3 Adverse effects: burning.



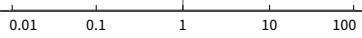
Analysis 3.4. Comparison 3 Tacrolimus 0.03% versus steroids, Outcome 4 Adverse effects: pruritus.

Study or subgroup	Tacrolimus n/N	Steroids n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%					
Reitamo 2002b	25/189	14/185		16.35%	1.75[0.94,3.26]
Reitamo 2004	83/417	33/207		50.96%	1.25[0.86,1.8]
Subtotal (95% CI)	**606**	**392**		**67.31%**	**1.37[1,1.88]**
Total events: 108 (Tacrolimus), 47 (Steroids)					
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					
3.4.2 Tacrolimus 0.03% versus steroids of moderate potency					
Doss 2010	10/237	8/239		9.2%	1.26[0.51,3.14]
Reitamo 2002a	39/193	18/186		21.18%	2.09[1.24,3.52]
Sikder 2005	3/15	2/15		2.31%	1.5[0.29,7.73]
Subtotal (95% CI)	**445**	**440**		**32.69%**	**1.81[1.18,2.8]**
Total events: 52 (Tacrolimus), 28 (Steroids)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=2(P=0.62); I^2=0%					
Test for overall effect: Z=2.69(P=0.01)					
Total (95% CI)	**1051**	**832**		**100%**	**1.51[1.17,1.95]**
Total events: 160 (Tacrolimus), 75 (Steroids)					
Heterogeneity: Tau^2=0; Chi^2=2.88, df=4(P=0.58); I^2=0%					
Test for overall effect: Z=3.2(P=0)					
Test for subgroup differences: Chi^2=1.05, df=1 (P=0.31), I^2=4.89%					



Analysis 3.5. Comparison 3 Tacrolimus 0.03% versus steroids, Outcome 5 Adverse effects: skin infection.

Study or subgroup	Favours tacrolimus n/N	Steroids n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%					
Reitamo 2002b	6/189	4/185		11.15%	1.47[0.42,5.12]
Reitamo 2004	11/207	14/207		38.61%	0.79[0.37,1.69]
Subtotal (95% CI)	**396**	**392**		**49.76%**	**0.94[0.49,1.79]**
Total events: 17 (Favours tacrolimus), 18 (Steroids)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=0.19(P=0.85)					
3.5.2 Tacrolimus 0.03% versus steroids of moderate potency					
Doss 2010	7/237	5/239		13.73%	1.41[0.45,4.39]
Reitamo 2002a	15/193	13/186		36.51%	1.11[0.54,2.27]
Subtotal (95% CI)	**430**	**425**		**50.24%**	**1.19[0.65,2.18]**
Total events: 22 (Favours tacrolimus), 18 (Steroids)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%					
Test for overall effect: Z=0.58(P=0.57)					
Total (95% CI)	**826**	**817**		**100%**	**1.07[0.69,1.66]**
Total events: 39 (Favours tacrolimus), 36 (Steroids)					
Heterogeneity: Tau^2=0; Chi^2=1.11, df=3(P=0.77); I^2=0%					



Study or subgroup	Favours tacrolimus	Steroids	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Test for overall effect: Z=0.29(P=0.77)					
Test for subgroup differences: Chi^2=0.28, df=1 (P=0.59), I^2=0%					

Favours tacrolimus 0.01 0.1 1 10 100 Favours steroids

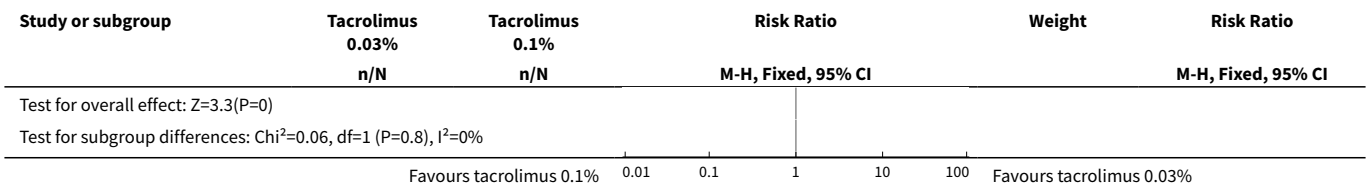
Comparison 4. Tacrolimus 0.03% versus tacrolimus 0.1%

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement, clear or excellent	6	1640	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.72, 0.92]
1.1 3 weeks	4	985	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.96]
1.2 12 weeks	2	655	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 0.99]
2 Adverse effects	4	986	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.06]

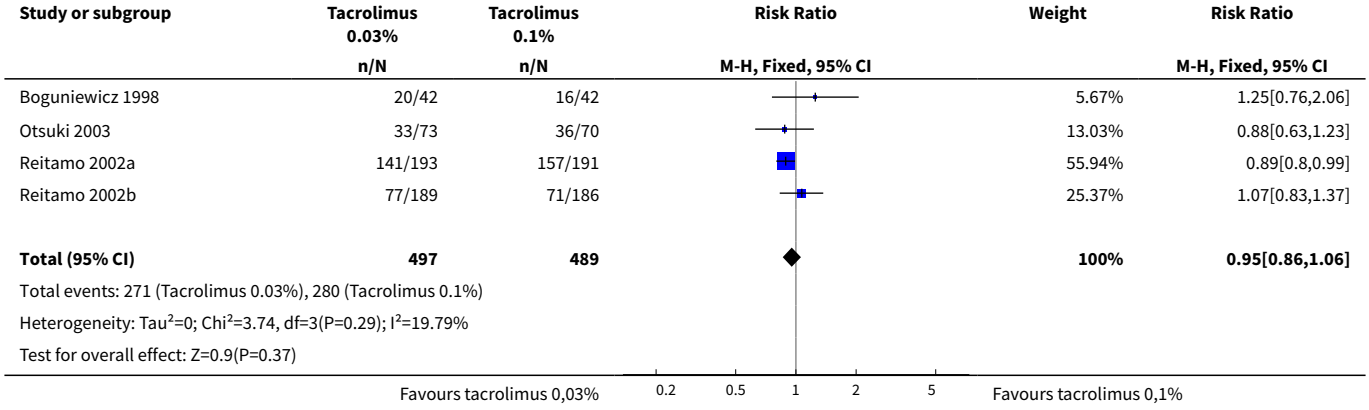
Analysis 4.1. Comparison 4 Tacrolimus 0.03% versus tacrolimus 0.1%, Outcome 1 Physician's assessment of global response of improvement, clear or excellent.

Study or subgroup	Tacrolimus 0.03%	Tacrolimus 0.1%	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
4.1.1 3 weeks					
Boguniewicz 1998	25/42	21/42		5.95%	1.19[0.8,1.76]
Otsuki 2003	18/72	21/70		6.04%	0.83[0.49,1.43]
Reitamo 2002a	73/193	94/191		26.79%	0.77[0.61,0.97]
Reitamo 2002b	73/189	90/186		25.72%	0.8[0.63,1.01]
Subtotal (95% CI)	**496**	**489**		**64.51%**	**0.83[0.71,0.96]**
Total events: 189 (Tacrolimus 0.03%), 226 (Tacrolimus 0.1%)					
Heterogeneity: Tau^2=0; Chi^2=3.8, df=3(P=0.28); I^2=21.04%					
Test for overall effect: Z=2.57(P=0.01)					
4.1.2 12 weeks					
Hanifin 2001	58/211	77/209		21.94%	0.75[0.56,0.99]
Paller 2001	42/117	48/118		13.55%	0.88[0.64,1.22]
Subtotal (95% CI)	**328**	**327**		**35.49%**	**0.8[0.64,0.99]**
Total events: 100 (Tacrolimus 0.03%), 125 (Tacrolimus 0.1%)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=2.07(P=0.04)					
Total (95% CI)	**824**	**816**		**100%**	**0.82[0.72,0.92]**
Total events: 289 (Tacrolimus 0.03%), 351 (Tacrolimus 0.1%)					
Heterogeneity: Tau^2=0; Chi^2=4.48, df=5(P=0.48); I^2=0%					

Favours tacrolimus 0.1% 0.01 0.1 1 10 100 Favours tacrolimus 0.03%



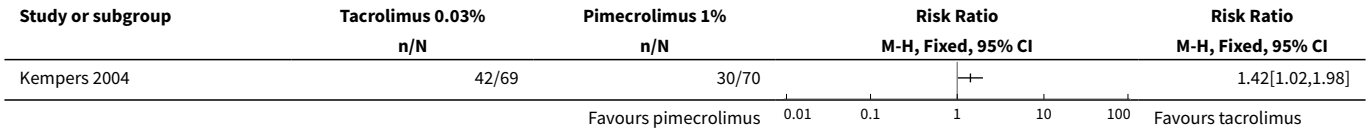
Analysis 4.2. Comparison 4 Tacrolimus 0.03% versus tacrolimus 0.1%, Outcome 2 Adverse effects.



Comparison 5. Tacrolimus 0.03% versus pimecrolimus 1%

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Application site reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Burning	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Itching	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Erythema	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Tacrolimus 0.03% versus pimecrolimus 1%, Outcome 1 Physician's assessment of global response of improvement.



Analysis 5.2. Comparison 5 Tacrolimus 0.03% versus pimecrolimus 1%, Outcome 2 Adverse effects.

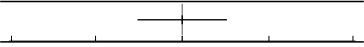
Study or subgroup	Tacrolimus 0.03% n/N	Pimecrolimus 1% n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Application site reaction				
Kempers 2004	18/70	17/71		1.07[0.6,1.91]
5.2.2 Burning				
Kempers 2004	12/70	14/71		0.87[0.43,1.75]
5.2.3 Itching				
Kempers 2004	14/70	6/71		2.37[0.96,5.81]
5.2.4 Erythema				
Kempers 2004	13/70	6/71		2.2[0.89,5.46]

Comparison 6. Tacrolimus 0.1% versus ciclosporin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 SCORAD	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2.1 14 days	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 21 days	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 28 days	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 35 days	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 42 days	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

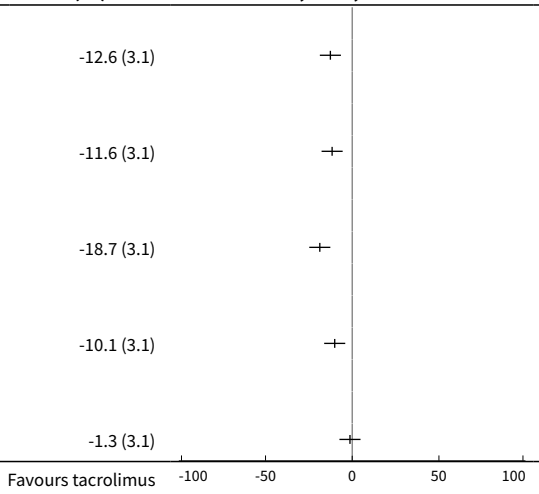
Analysis 6.1. Comparison 6 Tacrolimus 0.1% versus ciclosporin, Outcome 1 Adverse effects.

Study or subgroup	Tacrolimus 0.1% n/N	Ciclosporin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Pacor 2004	4/15	4/15		1[0.31,3.28]



Analysis 6.2. Comparison 6 Tacrolimus 0.1% versus ciclosporin, Outcome 2 SCORAD.

Study or subgroup	Tacrolimus 0.1% N	Ciclosporin N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
6.2.1 14 days					
Pacor 2004	15	15	-12.6 (3.1)		-12.6[-18.68,-6.52]
6.2.2 21 days					
Pacor 2004	15	15	-11.6 (3.1)		-11.6[-17.68,-5.52]
6.2.3 28 days					
Pacor 2004	15	15	-18.7 (3.1)		-18.7[-24.78,-12.62]
6.2.4 35 days					
Pacor 2004	15	15	-10.1 (3.1)		-10.1[-16.18,-4.02]
6.2.5 42 days					
Pacor 2004	15	15	-1.3 (3.1)		-1.3[-7.38,4.78]



ADDITIONAL TABLES

Table 1. Characteristics of treatment and participants in included studies

Study	Number of participants (n = 5885)	Age	Intervention	Follow up	Classification of AD
Antiga 2010	24	Adults (21 to 65 years)	Tacrolimus 0.1% ointment vs hydrocortisone butyrate 0.1% ointment (BID)	3 weeks	Moderate to severe (SCORAD)
Bieber 2007	265	Children (2 to 15 years)	Tacrolimus 0.03% ointment (BID) vs methylprednisolone aceponate 0.1% ointment (evening) and vehicle ointment (morning)	2 to 3 weeks	Severe flare (IGA > 4) history of moderate to severe AD
Boguniewicz 1998	169	Older children (7 to 16 years)	Tacrolimus 0.03% ointment vs tacrolimus 0.1% ointment vs tacrolimus 0.3% ointment vs vehicle ointment (BID)	3 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989))
Caproni 2007	16	Adults	Tacrolimus 0.1% ointment vs hydrocortisone butyrate 0.1% ointment (BID)	3 weeks	Moderate to severe (SCORAD)
Doss 2010	473	Children (2 to 15 years)	Tacrolimus 0.03% ointment vs fluticasone 0.005% ointment (BID)	3 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989)) and with prior inadequate response to topical corticosteroids
Dou 2006	202	Adults (> 18 years)	Tacrolimus 0.03% ointment vs tacrolimus 0.1% ointment vs vehicle ointment (BID)	3 weeks	Moderate to severe

Table 1. Characteristics of treatment and participants in included studies *(Continued)*

Draelos 2005	37	Adults	Tacrolimus 0.1% ointment vs pimecrolimus 1% cream (BID)	2 weeks	Moderate to severe (IGA)
Fleischer 2007	281	Adults (> = 16 years)	Tacrolimus 0.1% ointment vs pimecrolimus 1% cream (BID)	6 weeks	Moderate to severe (IGA)
Hanifin 2001	632	Adults (> = 16 years)	Tacrolimus 0.1% ointment vs tacrolimus 0.03% ointment vs vehicle ointment (BID)	3 months	Moderate to severe (Rajka and Langeland (Rajka 1989))
Hung 2007	60	Adults and children (9 months to 33 years)	Tacrolimus 0.03% ointment (BID) alone or with fusidic acid 2% cream vs fluticasone propionate 0.05% cream (BID) alone or with fusidic acid 2% cream	6 months	Moderate to severe (Rajka and Langeland (Rajka 1989))
Kempers 2004	141 (for safety) 139 (for efficacy)	Children (2 to 17 years)	Tacrolimus 0.03% ointment vs pimecrolimus 1% cream (BID)	6 weeks	Moderate (IGA)
Otsuki 2003	213	Children (2 to 15 years)	Tacrolimus 0.03% ointment vs tacrolimus 0.1% ointment vs vehicle ointment (BID)	3 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989))
Pacor 2004	30	Adults and children (13 to 45 years)	Tacrolimus 0.1% ointment (BID) vs ciclosporin 3 mg/kg orally	6 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989))
Paller 2001	351	Children (2 to 15 years)	Tacrolimus 0.03% ointment vs tacrolimus 0.1% ointment vs vehicle ointment (BID)	3 months	Moderate to severe (Rajka and Langeland (Rajka 1989))
Paller 2005	225	Children (2 to 15 years)	Tacrolimus 0.1% ointment vs pimecrolimus 1% cream (BID)	6 weeks	Moderate to severe (IGA)
Reitamo 2002a	570	Adults (16 to 70 years)	Tacrolimus 0.1% ointment vs tacrolimus 0.03% ointment vs hydrocortisone butyrate 0.1% ointment (BID)	3 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989))
Reitamo 2002b	560	Children (2 to 15 years)	Tacrolimus 0.1% ointment vs tacrolimus 0.03% ointment vs hydrocortisone acetate 1% ointment (BID)	3 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989))
Reitamo 2004	621	Children (2 to 15 years)	Tacrolimus 0.03% ointment (OD) vs tacrolimus 0.03% ointment (BID) vs hydrocortisone acetate 1% ointment (BID)	3 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989))
Reitamo 2005	972	Adults (> = 18 years)	Tacrolimus 0.1% ointment vs hydrocortisone butyrate 0.1% ointment (on trunk and extremities) and hydrocortisone acetate 1% ointment (on face and neck) (BID)	Up to 6 months	Moderate to severe (Rajka and Langeland (Rajka 1989))
Sikder 2005	45	Older children (7 to 15 years)	Tacrolimus 0.03% ointment (BID) vs clobetasone butyrate 0.05% cream (BID)	4 weeks	Moderate to severe (Rajka and Langeland (Rajka 1989))

Table 1. Characteristics of treatment and participants in included studies *(Continued)*

				vs clobetasone butyrate 0.05% cream (morning) and tacrolimus 0.03% ointment (evening)	

AD: atopic dermatitis.
BID: twice a day.
IGA: Investigators' Global Assessment.
OD: once daily.
SCORAD: SCORing Atopic Dermatitis.
vs: versus.

Table 2. Spontaneous reported malignancies in association with topical tacrolimus use

Malignancy	Age (years)	Application site	Occurence site	Comment	Exposure to onset (days)
B-cell lymphoma, EBV-associated, and primary lung carcinoma	49	Face	Kidney	-	730
Cutaneous Kaposi sarcoma	28	Axilla, groin	Axilla, groin	HIV patient on HAART, treated for inverse psoriasis, developed KS at these sites, which metastasised, and the patient died	30
Hepatoblastoma	5	-	Liver	Considered unrelated	455
Lymphadenopathy – possible lymphoma	40	Application site	Application site	Pre-existing lymphoma lesions 'looked like' lymphoma and resolved spontaneously*	-
Lymphoma or Sézary syndrome	16	Face	Lymph nodes	Participant also had been on systemic ciclosporin	730
Metastatic angiosarcoma	16	Face/neck	Clavicle	Present before treatment but increased rapidly in size	105
Metastatic melanoma	39	-	Generalised	Metastatic disease newly detected from primary 3 years early	21 to 28
Metastatic sweat gland carcinoma	43	Not axilla	Axilla	-	4 years
Nodular follicular lymphoma	60	Lower limbs, face	-	May be associated with EBV	504
Non-Hodgkin lymphoma	52	-	-	Used tacrolimus for 6 months. Insufficient evidence	365
Non-Hodgkin lymphoma	54	-	-	Used tacrolimus on extensive areas: 50% of body. Died from lymphoma. Insufficient evidence	-
Oesophageal cancer with metastases	49	-	Oesophagus	-	122

Table 2. Spontaneous reported malignancies in association with topical tacrolimus use *(Continued)*

Panniculitis-like T-cell lymphoma	53	Trunk, limbs	Trunk, limbs	Also used pimecrolimus	240
Squamous cell carcinoma	34	Face	Face	UV therapy, outdoor sports	-
Squamous cell carcinoma	57	Penis	Penis	Treated for balanitis considered to be lichen sclerosus et atrophicus; non-specific biopsy	70
Squamous cell carcinoma	51	-	Mouth	Long history of pipe smoking	-
Squamous cell carcinoma recurrence	75	Vulva	Vulva	Treated for lichen sclerosus et atrophicus	42
T-cell lymphoma, anaplastic large cell	50	Right hip	Right hip	Insufficient evidence	-

EBV: Epstein–Barr virus.
HIV: human immunodeficiency virus.
HAART: highly active antiretroviral therapy.
KS: Kaposi sarcoma.
UV: ultraviolet.
*Questionable if this should be classed as malignant.
Data shown in Ormerod 2005.

Table 3. Lymphoma risk

Study	Study population	Follow-up	Comparisons	Results related to lymphoma risks
Arellano 2007	294 cases/293,000 controls	-	TCIs and TCS in participants with AD	- Increased risk in AD participants (related to severity) - No evidence of increased risk with any of the topical treatments
Arellano 2009	> 3,000,000 (cohort)	1992 to 2006	AD, treatment with topical immunosuppressants, or both	- Increase risk in AD participants (related to severity) - Increased risk with topical corticosteroids (related to potency) - Insufficient data to assess TCI-related risks
Hui 2009	953,064 (cohort) (96% unexposed, 4% exposed)	Median 2.4 years	AD or eczema participants exposed or not to TCI	- Increased risk in the exposed group**
Schneeweiss 2009	- 118,863 for pimecrolimus - 38,757 for tacrolimus - 1,043,025 mid to potent corticosteroid - 118,825 untreated dermatitis - 118,863 for general population	2002 to 2006 (median 1.3 years)	See study population	- Increased risk compared with general population* - No risk differences between the 3 treatments

*pre-existing lymphomas misdiagnosed as AD.
**proportion of people who had diagnosis of AD was 2 times higher in the exposed group (i.e., there was a higher prevalence of AD than eczema in the exposed group). See Summary of main results (Risk of malignancies).
AD: atopic dermatitis.
TCI: topical calcineurin inhibitor.
TCS: topical corticosteroids.

Table 4. Non-melanoma skin cancer (NMSC) and melanoma (MM) skin cancer risk

Study	Study population	Follow up	Comparisons	Results related to skin cancer risks
Hui 2009	953,064 (cohort) (96% unexposed, 4% exposed)	Median 2.4 years	AD participants exposed or not to TCI	- Similar risks for NMSC - Lower risks for MM
Margolis 2007	875 cases 1946 controls	-	Dermatitis participants (AD, seborrhoeic dermatitis, rosacea, other dermatitis) with or without use of TCI	- No increased risk of NMSC in TCI-treated participants - MM risk not evaluated
Naylor 2005	9813 tacrolimus-treated participants	3 months to 4 years	AD participants with tacrolimus use compared with an aged cohort in the US	- No increased risk of NMSC in tacrolimus treated participants - MM risk not evaluated

AD: atopic dermatitis.
TCI: topical calcineurin inhibitor.
MM: melanoma.
NMSC: non-melanoma skin cancer.

Table 5. Observational non-comparative studies

Study	1. Population 2. Age group 3. Follow-up	Tacrolimus formulation	Common local effects	Systemic effects	Laboratory values	Malignancies	Others (number of events)	Detectable blood concentration
Gontijo 2008	1. n = 174 2. Paediatric 3. 6 weeks	0.03%	- Burning - Pruritus	-	-	-	- Asthma (2) - Pneumonia (2) - Pyodermitis (1)	-
Koo 2005	1. n = 7923 2. Adult/paediatric 3. Median: 210 days	0.1% (92.7%) 0.03% (7.3%)	- Burning - Pruritus	- Flu-like symptoms - Headache (frequency similar to that expected of the general population)	-	- 13 cases of NMSC (no risk with calculated incidence)	- Alcohol intolerance 3.7%	-
Mandelin 2012	1. n = 50 2. Paediatric (< 2 years) 3. 2 years	0.03%	- Pruritus - Local infection	- Non-serious respiratory infection and gastroenteritis	-	-	-	< 1 ng/ml (in 98%)
Reitamo 2000	1. n = 316 2. Adults 3. 6 to 12 months	0.1%	- Burning - Pruritus - Erythema	-	Normal (only 1 transient increase in liver enzymes)	-	- Alcohol intolerance 5 serious events: - Eczema herpeticum (1) - Cellulitis (1) - Varicella (1) - AD flare-up (1)	Minimal < 1 ng/dl in 76% of participants

Table 5. Observational non-comparative studies *(Continued)*

						- *Staphylococcus aureus* superinfection (1)		
Reitamo 2007	1. n = 672 2. Adults 3. 2 years	0.1%	- Burning - Pruritus	-	-	- 2 cases (Bowen and prostate carcinoma) not related - Benign neoplasm (7)	- Herpes (7%) (expected in AD participants) - Eczema herpeticum (1) - Erythroderma (1) - AD exacerbation (1)	-
Reitamo 2008	1. n = 782 2. Adult/paediatric 3. 4 years (median: 1422 days)	0.1%	- Burning - Pruritus - Skin infection	- Flu-like symptoms (more in children)	-	6 cases - Cervical carcinoma (1) - Acute leukaemia (1) - Chronic leukaemia (1) - Basal cell carcinoma (2 to 3 on the same participant) - 34 benign neoplasms	-	-
Remitz 2007	1. n = 466 2. Paediatric 3. 29.5 months (mean: 16.3 months)	0.03% 0.1%	- Burning - Pruritus	- Seasonal infection (flu-syndrome) - No growth retardation	Normal	-	- Leukopenia (1)* - Herpes (4.9%)/ eczema herpeticum (0.9%)	-

Table 5. Observational non-comparative studies *(Continued)*

							- Molluscum 3%) - Warts (3.6%)	
Saple 2003	1. n = 125 2. 12 to 69 years 3. 5 weeks	0.03%	- Burning - Pruritus - Erythema	-	Normal	-	-	-
Won 2004	1. n = 18 2. Adult/paediatric 3. 4 weeks	0.03%	- Burning - Pruritus	-	Normal	-	Serious events (3): - Flu-syndrome (1) - Severe skin rash (1) - Eczema herpeticum (1)	-
Wong 2003	1. n = 30 2. Adult/paediatric 3. 4 weeks	0.1% adults 0.03% paediatric	- Burning - Pruritus	-	Normal	-	-	2 participants < 5 ng/ml

* 6-year-old participant, at month 6, resolution after withdrawn.
AD: atopic dermatitis.
NMSC: non-melanoma skin cancer.

APPENDICES

Appendix 1. Validated scores and classification criteria

Validated scores, scales, and diagnosis and severity criteria (Charman 2000; Rehal 2011)

- Hanifin and Rajka criteria

"The diagnosis of atopic dermatitis using the Hanifin and Rajka criteria requires that patients have at least 3 of the 4 major criteria and 3 of the 23 minor criteria.

Major criteria:

- Pruritus
- Dermatitis affecting flexural surfaces in adults and the face and extensors in infants
- Chronic or relapsing dermatitis
- Personal or family history of cutaneous or respiratory atopy

Minor criteria can be divided into four categories:

- Facial features: facial pallor, facial erythema, hypopigmented patches, infraorbital darkening, infraorbital folds (Dennie-Morgan folds), cheilitis, recurrent conjunctivitis, anterior neck folds
- Triggers: foods, emotional factors, environmental factors, skin irritants
- Complications: susceptibility to cutaneous infections, impaired cell-mediated immunity, immediate skin-test reactivity, elevated IgE, keratoconus, anterior subcapsular cataracts
- Other: early age of onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris, hand and foot dermatitis, nipple eczema, white dermatographism, perifollicular accentuation" (Hanifin 1980).

- The Rajka and Langeland Scoring System

"It is a simple scale measuring clinical course, intensity, and extent of atopic eczema. It is probably most suitable for baseline categorization of patients rather than to monitor severity changes in trials. The scale involves an assessment of body surface area involvement, albeit into 1 of 3 categories only" (Rajka 1989).

- Severity Scoring of Atopic Dermatitis (SCORAD)

On this score, the disease extent is assessed by the rule of nines* and disease severity is evaluated based on five clinical characteristics: one - erythema, two - edema, three - oozing/crusts, four - excoriation, and five - lichenification. It still evaluates pruritus and sleep loss (subjective symptoms) with Visual Analogue Scales. The combination of the points given to those 3 aspects (extention and severity of disease and subjective symptoms) give a maximum score of 103.

*The rule of 9 is used to calculate the affected area: head and neck representing 9%; each upper limb representing 9%; each lower limb representing 18%; anterior trunk representing 18%; the back representing 18%; genitals, each palm, and the back of each hand representing 1% each.

- Eczema Area and Severity Index (EASI) and modified EASI (mEASI)

On this score, four clinical characteristics (erythema, induration, excoriation, and lichenification) are evaluated on a scale of zero (absent) to three (severe), together with disease extension measured at four body sites (head and neck, upper limbs, trunk, lower limbs). EASI give a maximum score of 72.

mEASI represents a variation of EASI, with the inclusion of the assessment of pruritus, not included on the EASI score (Hanifin 2001b).

- Investigator's Global Assessment (IGA)

"This score uses a 6-point severity scale from clear to very severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease, and 5 = very severe disease). IGA uses clinical characteristics of erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment" (Rehal 2011).

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 (eczema or neurodermatitis or dermatitis):ti,ab,kw
#2 MeSH descriptor Eczema explode all trees
#3 MeSH descriptor Dermatitis explode all trees

#4 MeSH descriptor Neurodermatitis explode all trees
#5 MeSH descriptor Dermatitis, Atopic explode all trees
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 (tacrolimus or protopic or fk506 or "fk 506"):ti,ab,kw
#8 MeSH descriptor Tacrolimus explode all trees
#9 (#7 OR #8)
#10 (#6 AND #9)

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Eczema/ or eczema.mp.
2. exp Dermatitis, Atopic/
3. neurodermatitis.mp. or exp Neurodermatitis/
4. exp Dermatitis/ or dermatitis.mp.
5. or/1-4
6. exp Tacrolimus/
7. topical tacrolimus.mp.
8. Protopic.mp.
9. (tacrolimus adj3 topical$).mp.
10. (tacrolimus adj3 ointment).mp.
11. (fk 506 or fk506).mp.
12. or/6-11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. (animals not (humans and animals)).sh.
22. 20 not 21
23. 5 and 12 and 22

[13-22: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)].

Appendix 4. EMBASE (Ovid) search strategy

1. eczema.mp. or exp ECZEMA/
2. exp DERMATITIS/ or dermatitis.mp.
3. exp atopic dermatitis/
4. neurodermatitis.mp. or exp NEURODERMATITIS/
5. or/1-4
6. exp tacrolimus/
7. topical tacrolimus.ti,ab.
8. Protopic.ti,ab.
9. (tacrolimus adj3 ointment).ti,ab.
10. (tacrolimus adj3 topical).ti,ab.
11. (fk506 or fk 506).ti,ab.
12. or/6-11
13. random$.mp.
14. factorial$.mp.
15. (crossover$ or cross-over$).mp.
16. placebo$.mp. or PLACEBO/
17. (doubl$ adj blind$).mp.
18. (singl$ adj blind$).mp.
19. (assign$ or allocat$).mp.
20. volunteer$.mp. or VOLUNTEER/
21. Crossover Procedure/
22. Double Blind Procedure/
23. Randomized Controlled Trial/
24. Single Blind Procedure/

25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 5 and 12 and 25

Appendix 5. LILACS search strategy

(eczema or eccema or dermatitis or neurodermatitis) and (tacrolimus or protopic or fk506 or "fk 506")

[Searched using the Controlled clinical trials topic-specific query filter].

Appendix 6. MEDLINE (Ovid) adverse effects search strategy

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
3. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
4. exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
5. side effect$.ti,ab.
6. exp Poisoning/
7. exp hepatitis, toxic/ or exp hepatitis, chronic, drug-induced/
8. exp Substance-Related Disorders/
9. exp Drug Toxicity/
10. exp Abnormalities, Drug-Induced/
11. exp Teratogens/
12. exp Mutagens/
13. exp Carcinogens/
14. metabolite$.ti,ab.
15. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
16. photoallergic reaction$.ti,ab.
17. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
18. phototoxicit$.ti,ab.
19. (sensitization or sensitisation).ti,ab.
20. exp Burning Mouth Syndrome/
21. stinging.ti,ab.
22. burning.ti,ab.
23. fetal abnormalit$.ti,ab.
24. exp Drug Monitoring/
25. drug effect$.ti,ab.
26. Sleep Apnea, Obstructive/
27. ARRHYTHMIA/
28. (safe or safety).ti,ab.
29. toxicity.ti,ab.
30. noxious.ti,ab.
31. complication$.ti,ab.
32. treatment emergent.ti,ab.
33. tolerability.ti,ab.
34. rebound.ti,ab.
35. Hypercalcemia/ci [Chemically Induced]
36. Urinary Calculi/ci [Chemically Induced]
37. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
38. Substance Withdrawal Syndrome/ci, de [Chemically Induced, Drug Effects]
39. ATROPHY/ci [Chemically Induced]
40. TELANGIECTASIS/ci [Chemically Induced]
41. skin thinning.ti,ab.
42. Liver Diseases/ci [Chemically Induced]
43. Kidney Diseases/ci [Chemically Induced]
44. Disseminated Intravascular Coagulation/ci [Chemically Induced]
45. Multiple Organ Failure/ci [Chemically Induced]
46. Stevens-Johnson Syndrome/ci [Chemically Induced]
47. Epidermal Necrolysis, Toxic/ci [Chemically Induced]
48. Heart Block/ci [Chemically Induced]
49. COMA/ci [Chemically Induced]
50. PARALYSIS/ci [Chemically Induced]

51. exp Nausea/
52. exp Vomiting/
53. benign intracranial hypertension.ti,ab. or exp Pseudotumor Cerebri/
54. exp Pigmentation Disorders/ or pigmentation.ti,ab. or exp Pigmentation/
55. lupus induced hepatitis.ti,ab.
56. or/1-55
57. ae.fs.
58. to.fs.
59. co.fs.
60. po.fs.
61. or/57-60
62. exp Tacrolimus/
63. tacrolimus.ti,ab.
64. protopic.ti,ab.
65. (fk506 or fk 506).ti,ab.
66. 62 or 63 or 64 or 65
67. exp Ointments/
68. ointment$.ti,ab.
69. exp Skin Cream/
70. (cream or creams).ti,ab.
71. (lotion or lotions).ti,ab.
72. topical$.ti,ab.
73. epicutaneous.ti,ab.
74. skin.ti,ab.
75. 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
76. 66 and 75
77. 56 and 76
78. 61 and 76
79. 77 or 78

Appendix 7. EMBASE (Ovid) adverse effects search strategy

1. side effect$.ti,ab.
2. metabolite$.ti,ab.
3. photoallergic reaction$.ti,ab.
4. phototoxicit$.ti,ab.
5. (sensitization or sensitisation).ti,ab.
6. stinging.ti,ab.
7. burning.ti,ab.
8. fetal abnormalit$.ti,ab.
9. (toxic effect$ or drug effect$).ti,ab.
10. (safe or safety).ti,ab.
11. toxicity.ti,ab.
12. noxious.ti,ab.
13. complication$.ti,ab.
14. tolerability.ti,ab.
15. treatment emergent.ti,ab.
16. tolerability.ti,ab.
17. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
18. rebound.ti,ab.
19. skin thinning.ti,ab.
20. lupus induced hepatitis.ti,ab.
21. exp postmarketing surveillance/
22. exp drug surveillance program/
23. exp drug hypersensitivity/ or exp hypersensitivity reaction/ or exp delayed hypersensitivity/ or exp hypersensitivity/ or exp immediate type hypersensitivity/
24. exp drug eruption/
25. exp anaphylaxis/
26. exp allergic conjunctivitis/
27. exp atopic dermatitis/
28. exp food allergy/
29. exp respiratory tract allergy/

30. exp urticaria/
31. exp intoxication/
32. exp toxic hepatitis/
33. exp addiction/
34. exp drug toxicity/
35. exp teratogenic agent/
36. exp mutagenic agent/
37. exp carcinogen/
38. exp contact dermatitis/
39. exp skin allergy/
40. exp irritant dermatitis/
41. exp phototoxicity/
42. exp photodermatosis/ or exp photoallergy/
43. exp burning mouth syndrome/
44. exp drug monitoring/
45. exp sleep apnea syndrome/
46. exp heart arrhythmia/
47. hypercalcemia/
48. urolithiasis/
49. tachyphylaxis/
50. withdrawal syndrome/
51. atrophy/
52. telangiectasia/
53. liver disease/
54. kidney disease/
55. disseminated intravascular clotting/
56. multiple organ failure/
57. Stevens Johnson syndrome/
58. toxic epidermal necrolysis/
59. heart block/
60. coma/
61. paralysis/
62. nausea/
63. vomiting/
64. benign intracranial hypertension.ti,ab. or exp brain pseudotumor/
65. exp pigment disorder/
66. exp pigmentation/
67. pigmentation.ti,ab.
68. exp adverse drug reaction/
69. exp drug safety/
70. exp phase 4 clinical trial/
71. (ae or to).fs.
72. or/1-70
73. exp tacrolimus/
74. tacrolimus.ti,ab.
75. protopic.ti,ab.
76. (fk506 or fk 506).ti,ab.
77. or/73-76
78. exp ointment/
79. ointment$.ti,ab.
80. exp skin cream/
81. (cream or creams).ti,ab.
82. exp lotion/
83. (lotion or lotions).ti,ab.
84. exp topical drug administration/
85. topical$.ti,ab.
86. epicutaneous.ti,ab.
87. skin.ti,ab.
88. or/78-87
89. 77 and 88
90. 72 and 89
91. 71 and 89

92. 90 or 91

Appendix 8. Study selection form

Study eligibility - topical tacrolimus for atopic dermatitis

First author	Journal/Conference proceedings, etc.	Year

RCT	Relevant participants People with atopic dermatitis who have been diagnosed by a physician	Relevant interventions Topical tacrolimus	Relevant outcomes Physician's overall evaluation; patient's self-assessment; rates of improvement as defined in the trial report; improvement in atopic dermatitis severity grade; incidence and severity of adverse effects; dropout rates
Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No*/Unclear

***Do not proceed if any of the above answers are 'No'. If the study is to be included in the 'Excluded studies' section of the review, record below the information to be inserted into the 'Characteristics of excluded studies' tables**

References to trial

Check other references identified in the searches. If there are further references to this trial, link the papers now and list them below. All references to a trial should be linked under one Study ID in Review Manager.

Code each paper	Author(s)	Journal/Conference proceedings, etc.	Year
A	The paper listed above		
B	Further papers		

WHAT'S NEW

Date	Event	Description
19 October 2016	Amended	A search of MEDLINE, PubMed, and Embase in October 2016 found only two relevant studies, which our Co-ordinating Editor and the lead author decided did not merit an update at this time.

Date	Event	Description
		Thus, an update of this review has been postponed. Our Information Specialist will run a new search in October 2017 to re-assess whether an update is needed.

HISTORY

Protocol first published: Issue 5, 2012
Review first published: Issue 7, 2015

Date	Event	Description
21 July 2015	Amended	Typographical error corrected.
2 July 2015	Amended	Author information (affiliation) updated.

CONTRIBUTIONS OF AUTHORS

JCM was the contact person with the editorial base, co-ordinated contributions from the co-authors, and wrote the final draft of the review.
JCM and EMKS screened papers against eligibility criteria.
JCM obtained data on ongoing and unpublished studies.
JCM and EMKS appraised the quality of papers.
JCM and EMKS extracted data for the review, and JCM sought additional information about papers.
JCM entered data into RevMan.
JCM analysed and interpreted data.
JCM and EMKS worked on the methods sections.
JCM drafted the clinical sections of the background and responded to the clinical comments of the referees.
EMKS looked at the methodology and statistics of the final version of the review and comments of the referees.
HAI was the consumer co-author and checked the review for readability and clarity, as well as ensuring that outcomes were relevant to consumers.
JCM is the guarantor of the update.
CM checked the review for English language translation problems.
VA, CM, EMKS, and AFTG reviewed the final paper.

Disclaimer

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DECLARATIONS OF INTEREST

Jade Cury Martins: nothing to declare.
Ciro Martins: nothing to declare.
Valeria Aoki: nothing to declare.
Aecio FT Gois: nothing to declare.
Henrique Akira Ishii: nothing to declare.
Edina MK da Silva: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The National Institute for Health Research (NIHR), UK.

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the Description of the condition section by adding two recent references for systemic treatments: Roekevisch 2014 and Simon 2014.

Within the Objectives section in the published protocol, we stated that we were going to compare topical tacrolimus with "other available topical treatments"; we decided to expand the search to any active treatments, topical or systemic, and therefore, there was a change to "other active treatments". In the same section, we changed the term "effectiveness" to "efficacy", as the latter relates to the circumstances of a randomised controlled trial that might be more ideal than the usual circumstances of healthcare practice.

In the Types of outcome measures section, with regard to 'Timing of outcome assessment', we considered the longer-term data the primary end point, since these are clinically more important as atopic dermatitis is a chronic inflammatory skin condition with a relapsing course. As most of the included studies reported short-term data, we analysed only the rapid onset of improvement and included this comment in this section so that readers can understand the reasons. In the same section, we changed timing for longer-term benefit for "one year or longer", instead of ± 2 years, as we originally planned in the protocol. We added SCORing Atopic Dermatitis (SCORAD) to our secondary outcome measures as another validated or objective measure.

We excluded studies where only a limited area of the body, such as the face or neck, were the subject of the clinical trial because the aim of this review was to look at studies where the whole person was treated and evaluated. Additionally, we also excluded studies where dropout rate was greater than 40%, as we feel the data had lost credibility because of the high degree of dropout.

Dealing with missing data/Sensitivity analysis: we could not impute missing data or perform the planned analyses because of lack of studies.

We amended the thresholds for interpretation of the I^2 statistic in line with Higgins 2011.

We used GRADE to assess the evidence and added 'Summary of findings' tables for the primary outcomes of our review. We did not plan this at the time of publication of the protocol.

NOTES

A search of MEDLINE, PubMed, and Embase in October 2016 found only two relevant studies, which our Co-ordinating Editor and the lead author decided did not merit an update at this time. Thus, an update of this review has been postponed. Our Information Specialist will run a new search in October 2017 to re-assess whether an update is needed.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Calcineurin Inhibitors [administration & dosage] [adverse effects]; Dermatitis, Atopic [*drug therapy] [pathology]; Dermatologic Agents [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Tacrolimus [*administration & dosage] [adverse effects] [analogs & derivatives]

MeSH check words

Humans