

ORIGINAL ARTICLE

Meta-analysis on the comparison between two topical calcineurin inhibitors in atopic dermatitis

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ABSTRACT

Topical calcineurin inhibitors have proved to be suitable for the treatment of AD. We conducted a meta-analysis comparing efficacy and tolerance of tacrolimus with pimecrolimus in treatment of AD. According to our meta-analysis, tacrolimus 0.1% was more effective than pimecrolimus 1% in adult patients (week 3: risk ratio [RR] 0.55, 95% confidence interval [CI] 0.42–0.73), and tacrolimus (a combination of 0.03% and 0.1%) was also more effective than pimecrolimus 1% in pediatric patients (week 6/end of study: RR 0.76, 95% CI 0.63–0.92). Regardless of age or illness severity, tacrolimus 0.1% had higher efficacy than pimecrolimus 1% in the treatment of AD (week 3: RR 0.55, 95% CI 0.42–0.72). In adult patients, tacrolimus 0.1% had more adverse events than pimecrolimus 1% (RR 1.30, 95% CI 1.02–1.66), but the incidence of adverse events between tacrolimus 0.1% (or 0.03%) and pimecrolimus 1% was not significantly different in pediatric patients. No matter whether the patients were adult or pediatric, more pimecrolimus-treated patients withdrew from the trials because of a lack of efficacy. Regardless of age and illness severity, more pimecrolimus 1%-treated patients withdrew from the trials because of a lack of efficacy, compared with tacrolimus 0.1% (or 0.03%)-treated patients. More pimecrolimus-treated pediatric patients withdrew from the trials because of adverse events (RR 0.26, 95% CI 0.1–0.68). More pimecrolimus 1%-treated patients withdrew from the trials because of adverse events, compared with tacrolimus 0.03%-treated patients, regardless of age (RR 0.1, 95% CI 0.02–0.53). In conclusion, tacrolimus ointment has higher efficacy and better tolerance than pimecrolimus cream in treatment of AD.

Key words: atopic dermatitis, calcineurin inhibitor, meta-analysis, pimecrolimus, tacrolimus.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disorder which typically commences in early childhood and is characterized by recurrent episodes of relapse and periods of remission. Conventional therapy for AD is based on the use of emollients as maintenance therapy, coupled with a short course of topical corticosteroids (TC) to treat AD flares. TC are rapidly effective in treating the acute symptoms of AD, but their use for long-term control of AD is not ideal because of the risk of side-effects, such as skin atrophy and hypothalamic–pituitary–adrenal axis suppression, which frequently occur in children.¹

Two topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, have been used for the treatment of AD over the past 10 years and have proved to be suitable for the treatment of both AD flares and long-term control. Some randomized controlled trials (RCT)^{2,3} have compared tacrolimus with pimecrolimus in treatment of AD, but the sample size of each study was not large

enough to draw definitive conclusions. El-Batawy *et al.*⁴ have reported a systematic review and meta-analysis on the effectiveness of TCI in treatment of AD, only in comparison to TC and/or placebo. Another meta-analysis⁵ has compared two TCI for the treatment of AD, however, only in pediatric patients. Herein, we conducted a comprehensive meta-analysis of RCT to compare efficacy, incidences of adverse events and withdrawal of tacrolimus ointment versus pimecrolimus cream in AD.

METHODS

Published work search and data extraction

We constructed an English-language published work search of PubMed, EMBASE and the Cochrane Database of Systematic Reviews from 1998 to October 2011 and considered all RCT comparing tacrolimus ointment with pimecrolimus cream in treatment of AD. The search words were “atopic”, “tacrolimus” and “pimecrolimus”.

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Data were extracted from each study by two investigators. Basic information obtained from each eligible study included proportion of patients achieving success from therapy at week 1, week 3 and week 6/end of study (EOS), proportion of patients with any adverse events, patients withdrawing due to a lack of efficacy and patients withdrawing due to adverse events for each study. Articles were examined to eliminate duplicate reports of the same trial.

Inclusion and exclusion criteria

The inclusion criteria included: (i) RCT comparing tacrolimus 0.1% (or 0.03%) with pimecrolimus 1% in treatment of AD; (ii) study medi-

cation was applied twice daily to the affected area(s) for up to 6 weeks or until 1 week after the affected area(s) were entirely cleared, whichever came first; and (iii) other medicated agents for the treatment of AD were not permitted during the trials.

The exclusion criteria were: (i) substudy RCT of other eligible RCT; (ii) randomized patients who did not apply any study medication from the safety (adverse events/withdrawal) analyses; and (iii) safety cohort patients who had any major randomization violation from the efficacy analyses.

Definition of main outcomes

The definition of “success of therapy” was achieving a score of “clear” or “almost clear” based on the Investigator’s Global Atopic Dermatitis Assessment. Those patients who used forbidden concomitant medication during the study were excluded in the final efficacy analyses, and we did not regard the efficacy of those patients as “success of therapy”. In each excluded study, if all treated areas entirely cleared before the week-6 visit, treatment continued in all areas for 1 additional week, followed by an EOS assessment, but no treatments were continued beyond 6 weeks.

Statistical analysis

The methodological quality of the included RCT was assessed by Jadad scale. Analysis was performed using the Review Manager ver. 5.0.25. Statistical heterogeneity assumption among studies was checked by the χ^2 -test based Q-test. When I^2 was no more than 50%, risk ratio (RR) and 95% confidence intervals (CI) were calculated using the fixed effect model. While significant heterogeneity among the studies was detected, a random effect model was adopted. Estimation of publication bias was made by funnel plot.⁶

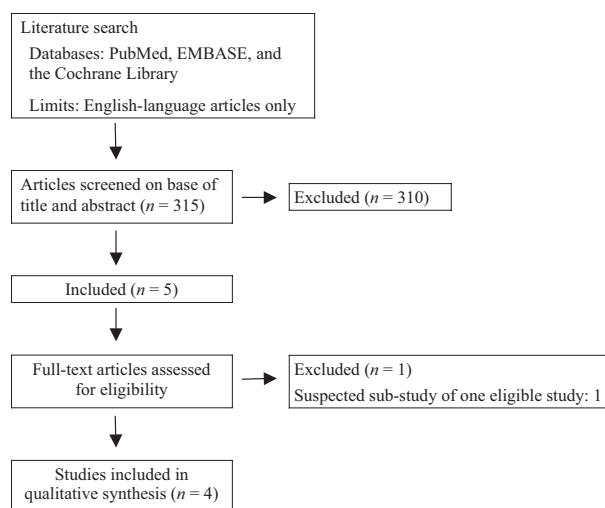


Figure 1. Flow diagram of study selection.

Table 1. Proportion of patients achieving success of therapy at week 1, week 3, and week 6/EOS for each study

Study	Combined analysis		Adult		Pediatric mild AD		Pediatric moderate AD		Pediatric moderate to very severe AD	
	Tacrolimus	Pimecrolimus	Tacrolimus 0.1%	Pimecrolimus 1%	Tacrolimus 0.03%	Pimecrolimus 1%	Tacrolimus 0.03%	Pimecrolimus 1%	Tacrolimus 0.1%	Pimecrolimus 1%
Kempers (2004)										
Patients (n)	70	71	0	0	0	0	70	71	0	0
Success of therapy (n)										
Week 6/EOS	27	18	–	–	–	–	27	18	–	–
Paller (2005)										
Patients (n)	528	532	210	203	207	216	0	0	111	113
Success of therapy (n)										
Week 1	75	67	32	25	40	38	–	–	3	4
Week 3	153	110	69	37	67	63	–	–	17	10
Week 6/EOS	229	163	96	55	97	88	–	–	36	20
Fleischer (2007)										
Patients (n)	141	140	141	140	0	0	0	0	0	0
Success of therapy (n)										
Week 1	18	13	18	13	–	–	–	–	–	–
Week 3	39	21	39	21	–	–	–	–	–	–
Week 6/EOS	57	31	57	31	–	–	–	–	–	–
Kirsner (2010)										
Patients (n)	171	176	61	67	69	71	0	0	41	38
Success of therapy (n)										
Week 1	18	16	–	–	–	–	–	–	–	–
Week 3	41	27	–	–	–	–	–	–	–	–
Week 6/EOS	63	36	–	–	–	–	–	–	–	–

AD, atopic dermatitis; EOS, end of study.

RESULTS

Five available RCT^{2,3,7-9} of high quality (Jadad score ≥ 4) met with the inclusion criteria. However, the RCT reported by Abramovits *et al.*⁹ was excluded because it was suspected to be a substudy of another RCT (Fig. 1).⁷ A total of 1834 patients were included: 913 to tacrolimus treatment and 921 to pimecrolimus treatment. The cohort for efficacy analyses was composed of 910 tacrolimus patients and 919 pimecrolimus patients (Table 1), whereas the cohort for adverse events/withdrawal analyses comprised 912 tacrolimus patients and 920 pimecrolimus patients (Table 2).

The evaluable efficacy parameter was “success of therapy” by achieving a score of “clear” or “almost clear”. According to our meta-analysis, tacrolimus 0.1% was more effective than pimecrolimus 1% in the treatment of adult patients (week 3: RR 0.55, 95% CI 0.42–0.73; week 6/EOS: RR 0.58, 95% CI 0.46–0.72), and tacrolimus (a combination of 0.03% and 0.1%) was also more effective than pimecrolimus 1% in pediatric patients (week 6/EOS: RR 0.76, 95% CI 0.63–0.92), which particularly showed that tacrolimus 0.1% had higher efficacy than pimecrolimus 1% in pediatric moderate to very severe AD patients (week 6/EOS: RR 0.55, 95% CI 0.34–0.88).

Regardless of age or illness severity, tacrolimus 0.1% had higher efficacy than pimecrolimus 1% in the treatment of AD (week 3: RR 0.55, 95% CI 0.42–0.72; week 6/EOS: RR 0.57, 95% CI 0.47–0.69), however, the efficacy between tacrolimus 0.03% and pimecrolimus 1% was not significantly different. The combined analysis comparing efficacy showed that tacrolimus was more effective than pimecrolimus (week 3: RR 0.67, 95% CI 0.56–0.80; week 6/EOS: RR 0.65, 95% CI 0.57–0.75) (Fig. 2), where the corresponding funnel plot showed a symmetric distribution of studies. Therefore, publication bias did not seem likely.

According to our meta-analysis comparing incidences of adverse events (mostly application site reactions: burning, pruritus, pain and erythema; skin infection; acne; herpes simplex), tacrolimus 0.1% produced more adverse events than pimecrolimus 1% in adult patients (RR 1.30, 95% CI 1.02–1.66), however, the incidence of adverse events between tacrolimus 0.1% (or 0.03%) and pimecrolimus 1% was not significantly different in pediatric patients. Regardless of age or illness severity, the incidence of adverse events of tacrolimus 0.1% versus pimecrolimus 1% and tacrolimus 0.03% versus pimecrolimus 1% were both similar. The combined analysis comparing incidence of adverse events showed that there was not significantly different between

Table 2. Proportion of patients with any adverse event, patients withdrawing due to a lack of efficacy, and patients withdrawing due to adverse event, for each study

Study	Combined analysis		Adult		Pediatric mild AD		Pediatric moderate AD		Pediatric moderate to very severe AD	
	Tacrolimus	Pimecrolimus	Tacrolimus 0.1%	Pimecrolimus 1%	Tacrolimus 0.03%	Pimecrolimus 1%	Tacrolimus 0.03%	Pimecrolimus 1%	Tacrolimus 0.1%	Pimecrolimus 1%
Kempers (2004)										
Patients (n)	70	71	0	0	0	0	70	71	0	0
Any adverse event	59	60	–	–	–	–	59	61	–	–
Withdrawal										
Due to a lack of efficacy	0	3	–	–	–	–	0	3	–	–
Due to adverse event	1	5	–	–	–	–	1	5	–	–
Paller (2005)										
Patients (n)	530	533	210	203	208	217	0	0	112	113
Any adverse event	113	106	67	47	32	36	–	–	14	23
Withdrawal										
Due to a lack of efficacy	13	35	3	11	4	13	–	–	6	11
Due to adverse event	10	20	6	5	0	10	–	–	4	5
Fleischer (2007)										
Patients (n)	141	140	141	140	0	0	0	0	0	0
Any adverse event	42	35	42	35	–	–	–	–	–	–
Withdrawal										
Due to a lack of efficacy	1	10	1	10	–	–	–	–	–	–
Due to adverse event	3	5	3	5	–	–	–	–	–	–
Kirsner (2010)										
Patients (n)	171	176	61	67	69	71	0	0	41	38
Any adverse event	41	45	–	–	–	–	–	–	–	–
Withdrawal										
Due to a lack of efficacy	4	10	–	–	–	–	–	–	–	–
Due to adverse event	3	10	–	–	–	–	–	–	–	–

AD, atopic dermatitis.

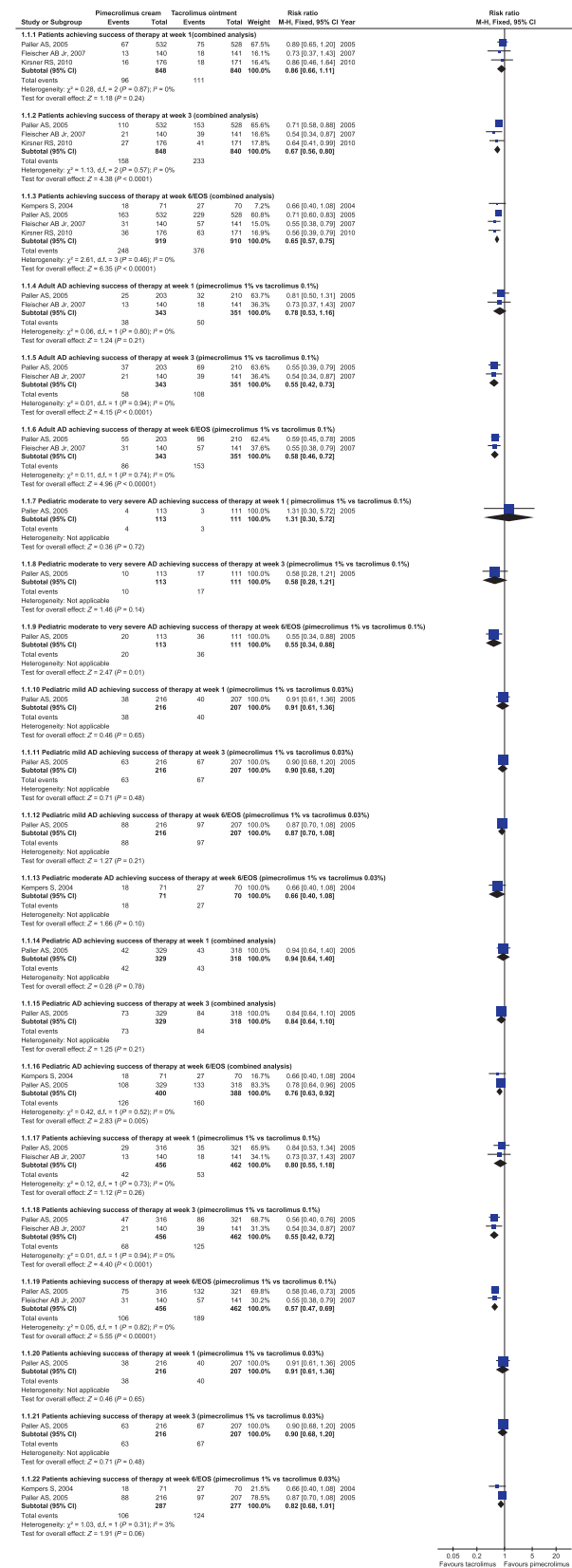


Figure 2. Forest plot with the fixed effect model comparing the efficacy of pimecrolimus cream vs tacrolimus ointment at week 1, week 3 and week 6/EOS. Risk ratio and 95% CI for each study and the combined

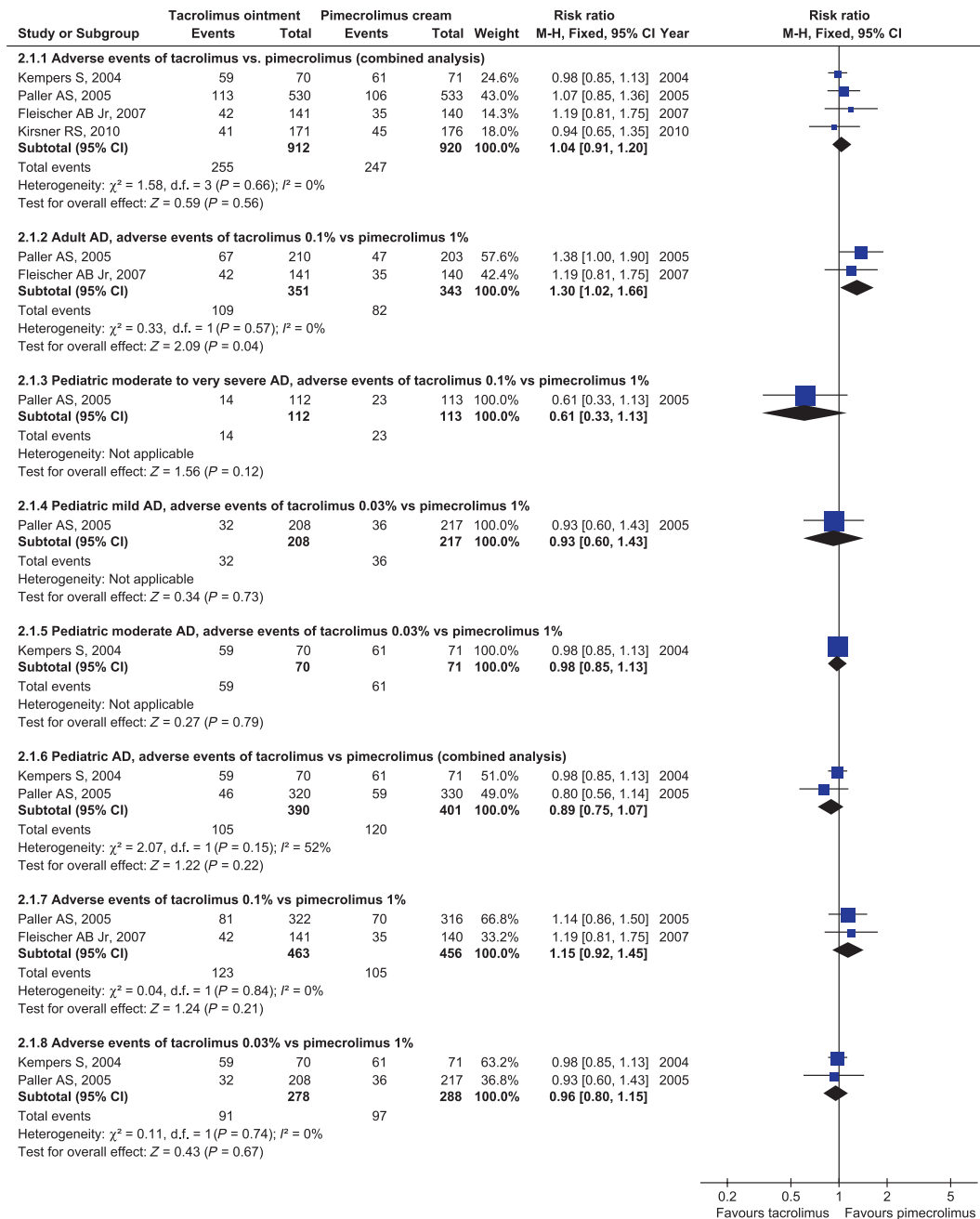


Figure 3. Forest plot with the fixed effect model comparing tacrolimus ointment with pimecrolimus cream in occurrences of adverse events. Risk ratio and 95% CI for each study and the combined estimate of adverse events with its CI are plotted on the graph. AD, atopic dermatitis; CI, confidence interval.

versus pimecrolimus cream in treatment of AD, because only one study concerning cost-effectiveness could be found, which reported that tacrolimus 0.1% might yield better clinical outcomes and lower costs of care than pimecrolimus 1% in adults with AD.¹⁰ Third, there is probable publication bias in Figure 4, where absence of plot in the bottom-right area indicates that there was no published negative data. Unpublished and non-English-language studies were not

included, so the possibility of publication bias exists. Fourth, our analysis has only compared the short-term efficacy and safety of tacrolimus ointment versus pimecrolimus cream in the treatment of AD because the long-term data comparing tacrolimus ointment with pimecrolimus cream is scarce at present.

In conclusion, tacrolimus ointment has higher efficacy and better tolerance than pimecrolimus cream in treatment of AD.

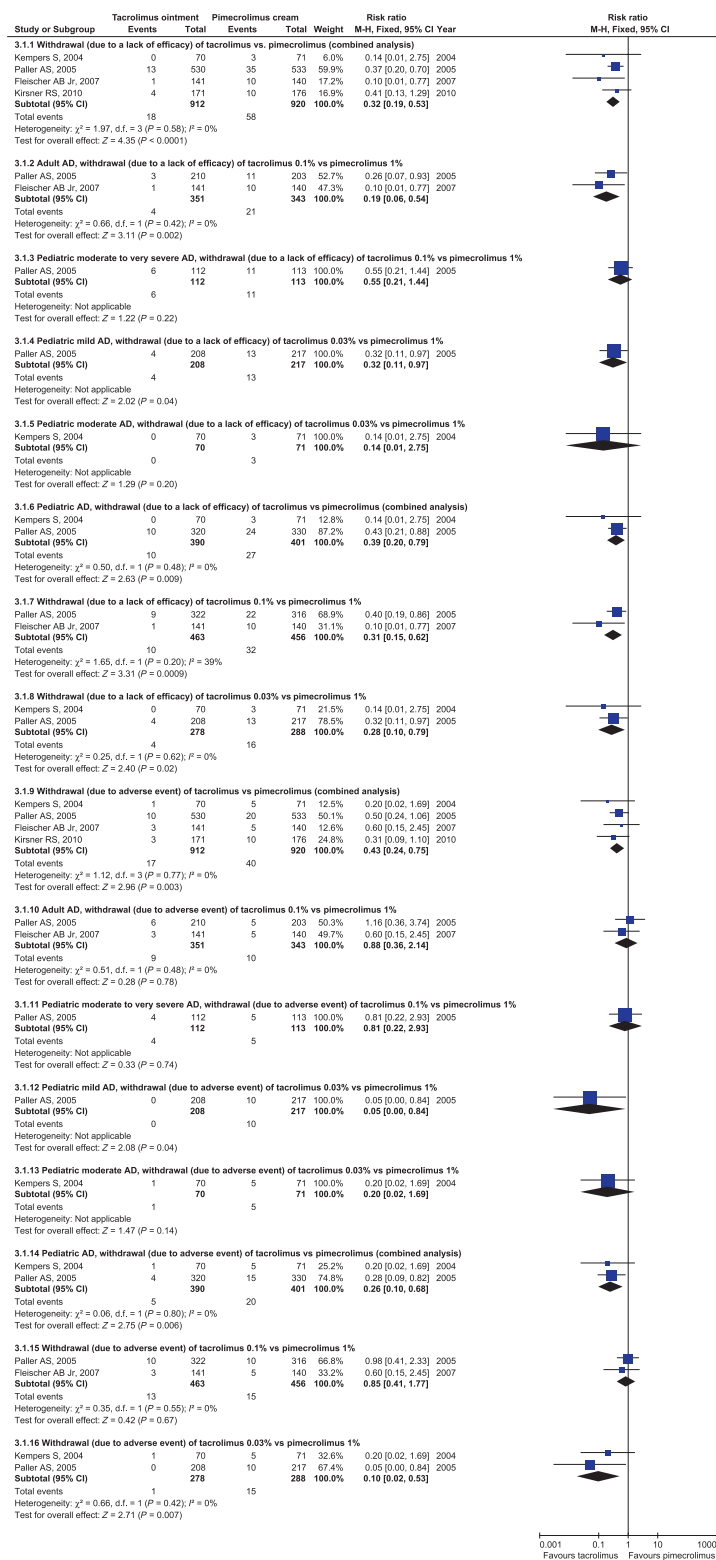


Figure 4. Forest plot with the fixed effect model comparing withdrawal (due to a lack of efficacy and due to adverse event) of tacrolimus ointment vs pimecrolimus cream. Risk ratio and 95% CI for each study and the combined estimate of the withdrawal with its CI are plotted on the graph. AD, atopic dermatitis; CI, confidence interval.

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