THE UNIVERSITY
OF BIRMINGHAM

A Systematic Review of Effectiveness and Cost Effectiveness of Tacrolimus Ointment for Topical Treatment of Atopic Dermatitis in Adults and Children

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The West Midlands Health Technology Assessment Collaboration produces rapid systematic reviews about the effectiveness of health care interventions and technologies, in response to requests from West Midlands Primary Care Trusts. Reviews take approximately 6 months and aim to give a timely and accurate analysis of the available evidence, with an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

Contributions of authors

Blanca Penaloza Hidalgo was the lead reviewer for this study and designed the protocol, undertook the searches, selected, appraised and extracted data from the included studies and wrote the report.
Dr Trudy Knight helped with the selection of studies, data extraction and quality assessment.
Dr Amanda Burls was the senior lead and advised on the protocol, review methods and methodological problems arising in the course of the report, she read and edited the draft report.

Conflicts of interest

None.

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West Midlands Regional Evaluation Panel Recommendation:

A recommendation for the effectiveness and cost effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children was not made as the topic has been referred to National Institute for Clinical Excellence (NICE). Since the REP report completion have published their guidance

http://www.nice.org.uk/page.aspx?o=218149

Anticipated expiry date:

- This report was completed in September 2003
- The searches were completed in April 2003

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ABBREVIATIONS

AD	Atopic Dermatitis
AE	Adverse Events
BID	Twice a day
BNF	British National Formulary
BSA	Body Surface Area
CEA	Cost effectiveness analysis
CI	Confidence Interval
DCD	Disease-Controlled Day
FDA	Food and Drug Administration
HPTC	High-Potency Topical Corticosteroids
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ID	Identification (in tables only)
ITT	Intention to Treat
mEASI	Modified Eczema Area and Severity Index
NHS	National Health System
NICE	National Institute for Clinical Excellence
NNH	Number Needed to Harm
NNT	Number Needed to Treat
Oint.	Ointment (in tables only)
PGA	Physician's Global Assessment of Clinical response
QoL	Quality of Life
R & D	Review and Dissemination
RCT	Randomised controlled trial
RD	Risk Difference
RR	Relative Risk
SCORAD	Severity Scoring of Atopic Dermatitis
S.E.	Standard Error
UID	Once a Day
UK	United Kingdom
US	United States

GLOSSARY OF DERMATOLOGICAL TERMS

Atopic dermatitis: A chronic inflammatory skin disease characterised by an itchy red rash with manifestations that vary according to the age of presentation.

Atopic ezcema: Atopic dematitis.

Erythema: A redness of the skin resulting from inflammation.

Lichenification: An accentuation of skin markings commonly associated with a thickening of the epidermis usually caused by scratching and rubbing.

Xerosis: Dry condition (in this case, of the skin)

Excoriation: Linear crusts and erosions due to scratching

EXECUTIVE SUMMARY

Background

Atopic dermatitis is a chronic recurrent inflammatory disease that affects 15-20% of children and adults. It results in considerable costs to health services and society. Current mainstream treatment is based on topical use of steroids of varying potency according to the age of patients and severity of the disease. However, long-term use of these drugs is limited because of adverse events.

New immunosuppressive drugs such as tacrolimus have emerged as an alternative to steroids for treating patients with moderate to severe AD, but they have not yet been systematically reviewed.

It is also important to assess the cost-effectiveness of this drug.

Questions Addressed by this review

What is the effectiveness of tacrolimus ointment for the topical treatment of atopic dermatitis, the frequency and severity of adverse events when used in adults and children 2 years and over?
What is the cost-effectiveness of tacrolimus compared to current treatments?

Methods

A systematic review of RCTs and economic evaluations addressing the above questions was undertaken. The main electronic databases, websites of conference proceedings and references of relevant articles were searched. Additionally, a handsearch was carried out to localise abstracts of conference proceedings and the pharmaceutical company that produces tacrolimus. Relevant authors were contacted to obtain additional information.
The quality of studies was assessed using the checklist proposed by the Skin Group of the Cochrane Collaboration. Findings were summarized qualitatively and meta-analyses of the effectiveness of tacrolimus compared with vehicle and topical steroids were conducted.

Economic evaluations found in the literature were appraised using a validated checklist.[1]

Results

Effectiveness

228 studies were found but only 25 were RCTs that met all the inclusion criteria. Of these, five studies were eliminated because they were duplicate reports.

11 studies of the 20 finally included trials compared tacrolimus against vehicle and 9 against steroids. 4 studies were published in Japanese.

The quality of the studies varied. Studies published in Japanese were analysed without an ITT analysis.

Meta-analysis using physician's assessment scales of studies comparing tacrolimus with vehicle (i.e. thought to be an inactive treatment) revealed that tacrolimus 0.03% and 0.1% were superior, with a RR of 2.87(95% CI 2.40, 3.43) and 3.42 (95% CI 2.88,4.09). However, 0.1% did not provide additional benefits in children compared with 0.03%.

Tacrolimus proved to be more effective than mild to moderately potent steroids with a RR of 1.67 (95% CI 1.27, 2.19). However, when compared with high-potency steroids it showed only a slight superiority, with a RR of 1.13 (95% C1 0.98, 1.31). These results are limited by the exclusion of 2 studies that did not provide enough information to be included in the meta-analyses.

Sensitivity analysis considering a higher cut-off point of clinical improvement (90% instead of 75% improvement) and ITT analysis resulted in an increase of the effectiveness of tacrolimus compared with mild topical steroids, while its effectiveness decreased compared with high-potency corticosteroids.

Economic Evaluation

Only one complete economic evaluation was found: a CEA comparing tacrolimus against high-potency steroids. This was sponsored by the pharmaceutical company that produces tacrolimus.

The study was based on a Markov model and concluded that tacrolimus is more cost-effective than high-potency topical steroids used for 2 weeks and almost equivalent to them used for 4 weeks. However, it does not provide an ICER to compare alternatives.

Conclusions

Tacrolimus ointment at 0.03% and 0.1% is more effective than vehicle for treatment of AD in adults and children in the short-term.

Tacrolimus was also more effective than mild to moderately potent topical steroids. It was marginally more effective than high-potency topical steroids, though this superiority was less evident when variables were changed in sensitivity analysis.

Additional data to allow inclusion of all studies found would permit more definitive conclusions to be drawn. Primary research is required to assess the long-term effectiveness of tacrolimus, especially with high-potency steroids.

1 Aims of the Review

This review aims to address the following issues:

- To assess the effectiveness of tacrolimus ointment for the topical treatment of atopic dermatitis in adults and children 2 years and over.

- To assess the frequency and severity of adverse events associated with the use of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 years and over, compared with vehicle and topical steroids.

- To assess cost-effectiveness of tacrolimus ointment for the topical treatment of atopic dermatitis in adults and children 2 years and over compared with an active treatment.

2 Background

What is atopic dermatitis?

a) Definition and diagnosis

Atopic dermatitis (AD) or atopic eczema is a chronic inflammatory skin disease characterised by an itchy red rash with manifestations that vary according to the age of presentation.[2] [3]AD can occur in three different age-related stages that may be separated by periods of remission or overlap: the infantile stage up to the age of 2, the childhood stage form 2 to 12 years and the adult stage from puberty onwards. Characteristics of the disease vary in each of these steps.[3]

AD typically starts in the early period of life, with 80% of cases starting before the age 5 and clearing in 60- 70% of children by adolescence.[2]

Since there is no objective laboratory marker for the disease, diagnosis is mainly based on clinical findings. The subjectivity of this issue has produced some controversies in the research field. Diagnostic criteria were established for the first time by Rajka and Hanifin in 1980[4] and helped to standardise diagnostic criteria for clinical and research proposes. Rajka and Hanifin are the most used criteria and are based on the presence of three basic features: pruritus, personal or family history of atopy and the presence of typical lesions with a characteristic distribution (see Appendix 1).

Later refinements to these initial criteria were developed by the UK working party, mainly for epidemiological studies. [5]

Additionally, the most widely used criteria to assess the severity of the disease were proposed by Rajka and Langeland in 1989.[6] According to these authors, AD can be classified as mild, moderate or severe depending on the extent, course and intensity of the disease. (See Appendix 2).

Rajka and Langeland criteria are used as selection criteria for entry in many trials, but they are not sensitive enough to detect short-term changes after an intervention.[7] There is no agreement about which is the best method for this and thus, several different score methods have been proposed. This has made the interpretation of outcomes results of individual trials and the comparison of results between different studies very difficult.[8]

Finlay[7] reviewed the different techniques designed to assess activity of AD in 1996. She analyzed 25 different scales with their different components: most of them considered pruritus, assessment of the presence of a series of clinical signs such as erythema, papules, lichenification etc. combined with an estimation of the body area affected. This last component was found as being the weakest aspect of the clinical scoring systems.

Additionally, and more recently, Charman et al[8] reviewed the validity and reliability of scales used to assess severity of AD.

They found 13 different named scales, of which only one had data published about its validity, reliability, sensitivity and acceptability (SCORAD index). Additionally, they found several other unnamed scores used in different clinical trials that combine clinical parameters in different ways (erythema, excoriations, lichenification, edema, induration, etc).

Moreover, authors suggest in a more recent publication[9] that most clinically relevant outcomes are those assessed by the patients and by the physicians, even though the precision may be better with other types of score (SCORAD, mEASI) which are less relevant from a clinical point of view. (See appendix 3).

b) Aetiology of AD

Familiar occurrence of the disease and a high concordance rate of 77% in monozygotic twins suggest a genetical origin of atopic dermatitis.[10]
The major immunopathogenic abnormality under AD is related to T-helper cell function. These are the cells of the immune system that recognise antigens and modulate immune responses.

In addition to genetical factors, there are also environmental variables related to AD. S*taphylococcus aureus*, a bacterium is found in 93% of AD skin lesions compared to only 5% of non-atopic subjects and p*ytirosporum ovale*, a yeast commonly found on the head and neck, are among the identified microbiological agents that can exacerbate the disease.[10]

Possible contact allergens that can exacerbate AD are also nickel, latex, balsam of Peru, fragrances and preservatives in vehicles and topical preparations. Contact irritants include wool, disinfectants and solvents [10]

Foods such as egg, wheat, milk soy and peanuts can exacerbate AD by immunological and non-immunological mechanisms.[10]

c) Epidemiology of Atopic Dermatitis

Atopic eczema is a very common health problem, especially in children in the first 5 years of life. There is some evidence to suggest that its prevalence has increased two- to three-fold over the last 30 years.[2] A prevalence study in Northern Europe (Germany, Sweden and Denmark) at the beginning of the 1990s suggests that it affects 15- 20% of children of under 7 years old.[11]

Data from the UK are similar, Kay et al [12] found in an study published in 1984 a prevalence of 15 – 20% in school children and 2 – 3% in adults. Fortunately, most of these cases are mild, Emerson et al [13] found in a study conducted on children at Nottingham, an overall prevalence of AD in a 12- month period of time of 16.5% with 84% mild cases, 14% moderate disease and only 2% of the severe category.

d) Burden of disease

AD can reduce the quality of life of patients and their families, which is exacerbated because it is a chronic disease. Pruritus and stigmatisation, the need for special clothing and bedding and avoidance of some activities such as swimming, especially in the case of children, are among the most important factors that affect the quality of life.[2]

A study done in Sweden[14] that assessed the quality of life of patients with AD and psoriasis with a SF-36 questionnaire revealed that both groups had a lower health-related quality of life compared with the general Swedish population.

In financial terms, atopic dermatitis has important costs for health systems. In the UK, a study published in 1996[15] estimated the mean personal cost to a patient with AD at £25.90 on a base of a two-month period of treatment, with a mean cost for the health system of £16.20.

Estimations made by other authors establish that the annual global costs for the whole health system at the estimated prevalence of the disease could reach £125 million. Considering the additional costs for individuals and to society for loss of working days, the estimated of annual global costs of atopic dermatitis could be as high as £465 million per year.[2]

What is the current treatment and service provision for atopic dermatitis?

Most of the cases of AD in the UK are treated in the primary care setting. According to Emerson et al,[13] only 4% of children with atopic eczema are referred to a dermatologist for continuing therapy.

Traditionally, the standard treatment of AD has included multiple interventions, pharmacological and non-pharmacological. A recent systematic review of all therapeutic alternatives revealed that most of them are poorly evidence-based.[2]

The cornerstone of the treatment is topical corticosteroids. They are classified according to potency, the greater the potency, the greater the therapeutic efficacy but also the greater the adverse events (See appendix 4).[16] Its regular use is restricted to the face, neck and intertriginous areas due to skin atrophy, telangectasia, striae, and hypopigmentation or secondary infection, especially with long-term use.

Due to these adverse events, the use of steroids in children is restricted to only moderate and severe cases, with mild topical corticosteroids such as 1-% hydrocortisone ointment. More potent steroids are contraindicated in children less than 1 year old and should generally be avoided in older children or, if necessary, used for short periods.

In adults, the use of mild to potent steroids, according to the severity of the disease, is essential for the treatment of AD together with oral antibiotics that could help to treat secondary infections when they exist.

In addition to steroids, other potent immunosuppresors such as cyclosporine have been used to treat severe cases, but with a limited use because of adverse effects.

According to evidence-based recommendations, the interventions with reasonably established efficacy are topical steroids, oral cyclosporine, and the use of ultraviolet light and psychological approaches. Interventions such as the use of emollients, antihistamines, dietary restrictions and house dust mite reduction, do not have enough evidence to be recommended.

What is tacrolimus and what is its role in the treatment of AD?

Tacrolimus is an immunosuppressant macrolide-type drug that was first isolated in Japan in 1984 from the soil fungus *Streptomycin tsukabaensis*. It acts on the cytoplasm of T-cells producing an inhibition in the process of immune reaction against a foreign substance through blocking calcineurin activation inside the cell.[17]

Tacrolimus is produced by Fujisawa Healthcare Inc. and was first licensed in Japan in 1993 to be used orally or intravenously to prevent liver transplant rejection, after that its use was extended to prevent rejection of other organ transplants.[18]

Its use for dermatological purposes was incorporated more recently. In 1999 it was launched in Japan as a topical ointment (Protopic® by Fujisawa laboratories) for the treatment of atopic dermatitis for adults over 16 years old. Subsequently, it was approved for use in adults and children aged 2 to 15 with moderate to severe atopic dermatitis who failed to achieve adequate response or who were intolerant to conventional treatment. In the UK it was approved on April 2002.[19]

Tacrolimus has been licensed as an ointment in 0.03% and 0.1% formulations and it is indicated for moderate to severe eczema unresponsive to conventional therapy. The BNF recommends its use twice a day for up to 3 weeks and then once daily until lesion clears.[20] Its net price is £19.44 for 30g at 0.03% and £21.60 for 0.1%. The quantity required for a treatment is variable and depends on the area affected.

What is already known about this topic?

NHS R&D Health Technology Assessment Programme published a systematic review of treatments for atopic dermatitis in 2000. This review concluded that there was not enough evidence to assess the effectiveness of new therapies such as tacrolimus and additional primary research was required.[2]

However, the situation has changed over recent years. A search of the literature on February 2003 found no systematic reviews of the effectiveness of topical tacrolimus for atopic dermatitis, but several primary studies were published after the publication of the aforementioned HTA report. Only the Canadian Agency of Health Technology Assessment have published a short non-systematic review of this topic, in 2001.[21]

The Cochrane Library has recently included a protocol for a systematic review of tacrolimus in atopic dermatitis. Just as this review was nearing completion, NICE prioritised the appraisal of tacromlimus for the use in atopic dermatitis together with pimecrolimus, another calcineurin inhibitor for topical treatment of AD. However, NICE guidance will not be available until the end of 2004, so it was decided to proceed with the publication of this report in the interim.

3 Clinical Effectiveness

3.1 Methods

This review was prepared following the WMHTAC handbook methods, the guidelines developed by the University of York[22] and, when possible, the methods proposed by the Cochrane Collaboration in its handbook[23] together with those suggested by the Skin Group of the Cochrane Collaboration on its website.[24]

Minor amendments to the initial protocol were made during this review to improve the rigour of this report. These were made prior to detailed evaluation of the results of included studies (see Appendix 5).

3.1.1 Search strategy

Electronic database
A systematic search was done of the following electronic databases:
MEDLINE (1966 through present)
EMBASE (1974 through present)
CINAHL
The Cochrane Controlled Trials Register (CENTRAL)

Search terms included synonyms of atopic dermatitis and all terms for tacrolimus using filters for RCTs proposed by Cochrane Collaboration. Details of the full search strategy are available in Appendix 6.

Hand searching
Hand searching to look for publications or relevant abstracts of dermatological proceedings available in the British Library was performed. The following journals were examined:
Journal of the European Academy of Dermatology and Venereology. 2001-2002
Annales de Dermatologie et de Venereologie 2002-2003

Additional search strategies
Reference lists of relevant articles and reviews found on databases were searched to identify further studies.
Conference proceedings: electronic search was done on web sites of The British Medical Library, The Institute of Scientific Information of Science for UK education.
To find ongoing trials, the website of the National Research Register and the National Library of Medicine Clinical Trials Register were searched.
The website of Fujisawa Healthcare Inc., that produces tacrolimus (Protopic®), was searched and additionally, the Department of Medical Information was contacted to ask for additional information about studies developed related with tacrolimus and AD.
US Food and Drug Administration web site
Web sites of HTA agencies
Contact with one main author of studies asking for additional studies was made (see appendix 7).

No language restrictions were applied.

3.1.2 Criteria used to decide Inclusion/ Exclusion of studies for this review

Studies were *included* in the final analysis of the review if they met all the following criteria:

Study design
Only randomised clinical trials (RCT) were included.

Population
Adults or children 2 years and over with atopic dermatitis of any intensity and in any part of the body diagnosed by a physician.

Intervention
Topical application of tacrolimus ointment in any concentration

Comparator
Any other topical treatment (placebo, corticoids)

Outcomes
Primary Outcome:
Clinical improvement assessed by any clinical score or symptom changes assessed by the patient or the physician.

Secondary outcomes: - Adverse effects
- Quality of life

Publication status
All studies were included, regardless of publication status

Reporting
All RCTs that completed recruitment were included

Additionally, the following *exclusion criteria* were applied:

- Any study design that was not an RCT.
- Studies where outcomes included *only* non-clinical parameters such as blood tests and/or cellular mechanism assessed by laboratory exams or biopsy.
- Studies that compared only different dosages of tacrolimus without any different comparator.
- Studies in animals

Inclusion/Exclusion criteria were applied to all studies found by the search strategy to decide their inclusion in the review (See appendix 8 for Inclusion/Exclusion form).

All those studies that met all inclusion and no exclusion criteria were selected on the basis of an initial review of titles and/or abstract. All studies that provided insufficient information to make a decision about inclusion were reviewed in their full text to make a final decision.

One reviewer assessed all studies identified and a second reviewer checked these findings, reviewers were not blinded. Disagreements were resolved by consensus.

A different reviewer (Dr Fukuoka) decided inclusion of studies only in the case of studies found in Japanese. Criteria used were discussed with the first reviewer.

All included and excluded studies with reason of exclusion are summarised in tables (see results section).

3.1.3 Data extraction and quality assessment

After the selection of studies to be included in the review, data were extracted using the data extraction form defined in the protocol, adapted from the form proposed by the Skin Group of The Cochrane Collaboration[24] (see appendix 9). A second reviewer checked the first reviewer‘s work, disagreements were resolved by consensus.

In the case of Japanese studies, data extraction was carried out by another reviewer and the results were compared with those in the Briefing Document “Tacrolimus Ointment in atopic dermatitis NDA 50- 777” published on the FDA website[25]

The quality of included studies was assessed using the quality checklist proposed by the Skin Group of the Cochrane Collaboration[24] that includes main quality items suggested by NHS Centre for R&D and the Cochrane Collaboration[23] (See appendix 9):

- Randomisation: random sequence generation and appropriate concealment allocation.
- Blindness: non-blinded, simple or double-blinded study.
- Loss of follow-up and intention to treat analysis (ITT).

When studies did not provide enough information to judge if methods were adequate, the item was qualified as unclear, although in many cases, authors stated that a randomisation was done or that the study was double-blinded.

In the case of ITT analysis, studies were considered appropriate when all patients included in the randomisation were also included in the analysis or missing outcome data was not substantial or if exclusion was defined prior to collection of data.

No quality assessment score was calculated and the results of quality assessment are presented descriptively in tables (see results section).

As with data extracted, a second reviewer checked the first reviewer’s work. Quality was assessed by a different reviewer (Dr Fukuoka) only in the case of studies in Japanese, and criteria were clarified with the first researcher.

3.1.4 Methods of analysis and synthesis

Once all the data from the included studies were available, the Pharmaceutical Company (Fujisawa Healthcare Inc.) that produces tacrolimus and one of the authors (Dr Reitamo) were contacted to ask for information about new studies and to identify duplicate publications of trials. They were also asked for additional information to complete the data of studies whose results were incompletely published. Information provided by both of them is included in this review.

According to this information, publications were mapped to individual trials and summarised in tables.

The included non-duplicate studies were analysed and summarised qualitatively to assess variation in main study characteristics such as research methods, populations, comparators and outcomes.

Studies were grouped according to comparators: those that compared tacrolimus against a placebo were presented separately from those that compared tacrolimus against another active drug (corticosteroids).

During detailed analysis of the results a large number of different scales to assess outcomes were found and different measures reported e.g. means or medians.

Following the recommendation of experts, assessment of clinical improvement for AD was based on patient's assessment[8,9] and when this information was not available, physician's assessment scales were use instead.

We were unable to include in the meta-analysis studies that did not report results on these scales and for which no additional information could be obtained.

Meta-analysis was done where appropriate using Rev Man software version 4.2 and according to the following criteria:

- Separate meta-analysis was done according to comparators: vehicle or active therapy (steroids) and according to the licensed dose of tacrolimus: 0.03% and 0.1%.
- According to expert suggestions (Dr Hywell Williams) the data of results using tacrolimus 0.3% were not analysed in this report (this dose has not been licensed for clinical use).

- For meta-analysis of tacrolimus compared with vehicle, sub-group analysis by age group (adults and children) was done, obtaining a partial and overall estimator.
- Additionally, in the group of studies that compare tacrolimus with steroids, a sub-group analysis was done according to potency of steroids used as comparators. In this case, an overall estimator was calculated as well.

- Due to lack of sufficient data, a summary of the results of clinical effectiveness was done using physician's assessment scales instead of patient's assessment. The most widely used scale was Physician's Global Assessment of Clinical Response (PGA), but other scales were also used by several studies. According to available data, a cut-off point of "marked" or more improvement was considered for the baseline-case. (See appendix 3)

- For assessment of adverse events, incidence rate of skin burning and pruritus, the most frequent adverse events observed were the outcome measure used for meta-analysis.

- Relative Risk was chosen as the most meaningful summary statistic for clinical effectiveness and random and fixed effect models were used for meta-analysis. The most conservative results were reported, even though all graphs are available in Appendix 14.

- As additional valuable clinical information, and when appropriate, results were reported also using Risk Differences to allow estimation of NNT.
- In the case of adverse events, RD was preferred to estimate NNH when results were statistically significant.

- To allow the inclusion in meta-analysis, of studies where the number of patients per treatment group was not specified and only overall number was reported, it was assumed that all treatment groups had the same number of participants. This is the case of studies of Ohtsuki et al and Hanifin et al, where the authors reported only the total number of participants. The number of participants per arm was estimated dividing the total number by the number of arms in the study.

- Additionally, there was one study (study No. 247[26]) that had two arms for tacrolimus: 0.03% and 0.1%, but only reported overall results comparing with vehicle. For this reason, this study was excluded from the analysis comparing both tacrolimus concentrations.

- ITT analysis: the baseline case was made using data as reported by authors.

- Heterogeneity among studies included in meta-analyses was explored with forest plots and x^2 statistical test in each case.

Sensitivity analysis

Sensitivity analysis was considered to assess the effect on meta-analysis results of the following variables:

- Effect of variation on the cut-off point to assess clinical improvement using PGA or other scales were explored using a 90% improvement level or equivalent to “excellent improvement or cured”. However, this was possible only when studies reported both results.
- Effect of using ITT analysis in all studies that did not use this analysis.

3.2 Results

3.2.1 Studies identified

A final number of 228 studies were identified as potentially relevant trials. Of these, 185 were identified in electronic bibliographic databases (Medline, EMBASE and Cochrane Library), 10 were found on websites of Conference Proceedings, 12 came from reference lists from reviews and relevant primary articles, 17 came from a manual search of journals and 4 were provided by the Pharmaceutical Company or its website.

Excluded studies

The total number of studies identified by the search strategy followed a selection process (See Fig.1) according to the inclusion/exclusion criteria. As a result of this, 25 articles were selected as included in the systematic review and 203 were finally excluded. The list of all excluded studies with reasons for exclusion is presented in Appendix 10.

The main reasons for exclusion were study design (non-RCTs), intervention different to topical tacrolimus and studies in animals.

Included studies

25 articles met all inclusion and no exclusion criteria and were selected for the review. The sources of included and excluded studies are presented in Table 1.

Table 1 - Source of included and excluded studies

Source	Included	Excluded	Total
Electronic databases	9	176	185
Conference proceedings	0	10	10
Handsearch	6	11	17
References	8	4	12
Fujisawa Ltd	2	2	4
Total	25	203	228

It is interesting to observe that less than 50% of the included studies came from electronic databases: 60% were identified by handsearch or examining references of relevant studies and reviews.

As a second step, contact with Fujisawa Company and one author of trials was made to identify repeated reports of the same trials. Mapping of trials is presented in Appendix 11.

As a result of information obtained, 20 different trials were finally identified assessing tacrolimus ointment for topical treatment for atopic dermatitis to be included in the synthesis and analysis of this review.

There was one study that is probably an abstract reporting the same data of another study published in Japanese, both of them comparing tacrolimus with alclometasone. This suspicion is based on the information available in the Briefing Document NDA 50- 777[25] published on the FDA website, where only one study comparing tacrolimus against alclometasone was identified. However, as the Pharmaceutical Company did not confirm this information, both studies were included in the review.

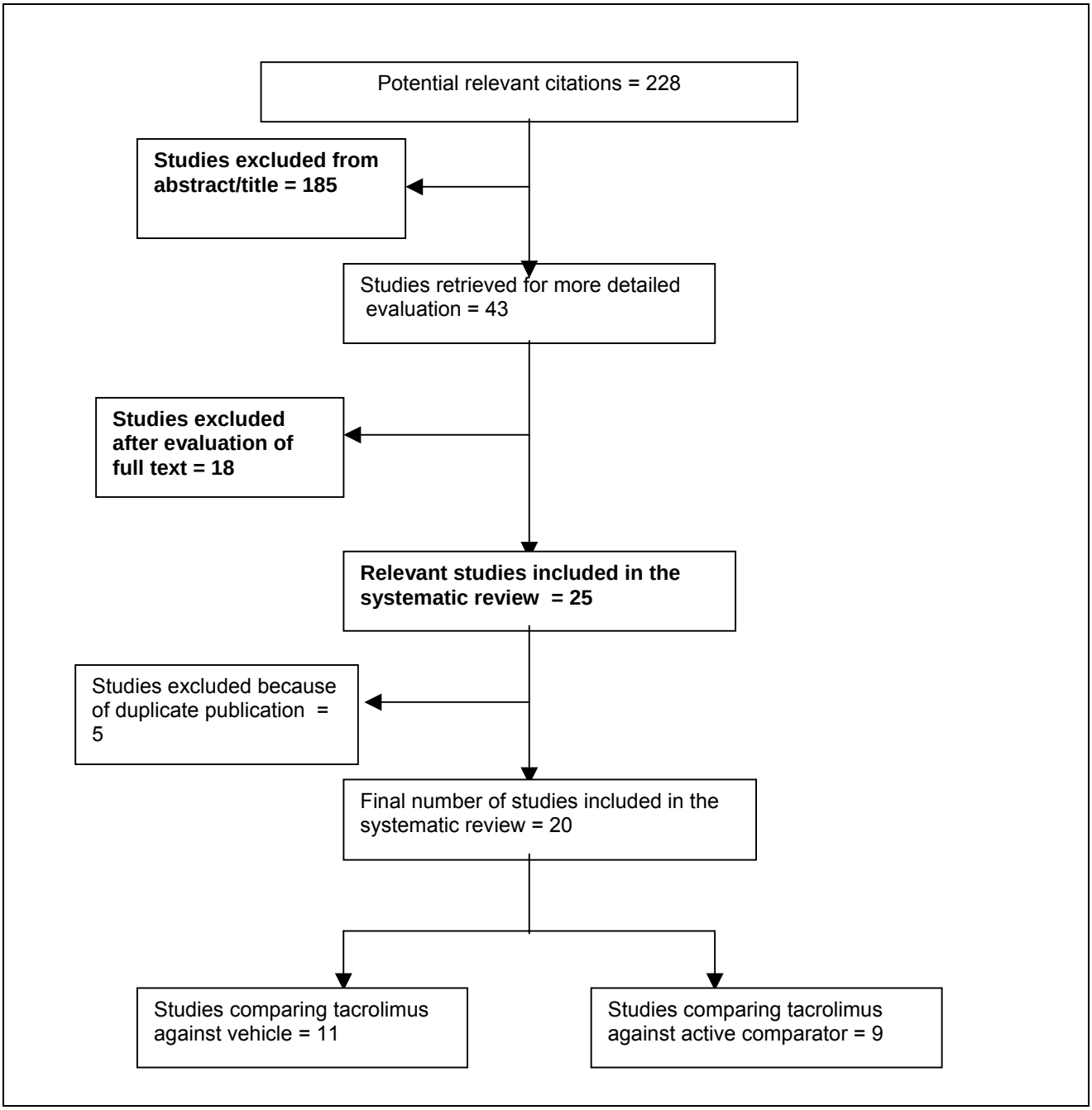
After the information of repeated reports of trials was received, Table 1 was re-built as shown in Table 2.

Table 2 - Source of included studies after elimination of repeated publications

Source	Included	Repeated	Final included
Electronic databases	9	0	9
Conference proceedings	0	0	0
Handsearch	6	4	2
References	8	0	8
Fujisawa Ltd	2	1	1
Total	**25**	**5**	**20**

Thus, although hand searching was initially an important source of identification of included studies, several of them corresponded to abstracts of trials already published as complete articles elsewhere. Nonetheless, more than 50% of finally included studies were missed by the electronic databases.

Figure 1 - Flow diagram of study selection process



3.2.2 Characteristics of included studies.

i) General characteristics

The 20 included studies are presented in Table 3. All studies included were RCTs and most of them were double-blinded. The status of publication varied, 14 studies were published as complete articles, while 6 trials were reported only as abstracts, limiting the available information to assess the quality and data available to be considered in meta-analysis.

Most of the studies included were short-term trials that have a treatment and follow-up period equal to or less than three weeks. Only one trial on children[27] and one trial on adults [28] had a longer treatment and follow-up period, equal to 12 weeks, these trials reported different outcomes in diverse publications.[29,30]

According to information provided by Fujisawa, there was an ethical limitation to allow longer studies when steroids were used as comparator because long-term side effects.

Two studies found with longer periods of follow-up are not included in this review as they were non-controlled clinical trials.[31 32]

Finally, according to information provided by Fujisawa, there are other two on-going studies open-label phase III long-term safety trials comparing tacrolimus ointment to vehicle, one up to 3 years and the other beyond three years, still in progress.

Ten of the 20 studies included reported that Fujisawa Healthcare Inc. sponsored them. The remaining 10 studies did not report sponsorship.

Table 3 - Main characteristics of included studies

Study Identification	Publication state	Sample size	Inclusion criteria	Treatment duration	Interventions and number recruited	Sponsorship
55 Hanifin et al[31]	Complete article	633	Adults with at least moderate AD	12 weeks	211Tacrolimus oint 0.03% tacrolimus oint 0.1% 212 vehicle oint BID	Fujisawa
54 Soter et al [34]	Complete article	631	Adults with at least moderate AD	12 weeks	211Tacrolimus oint 0.03% 209 tacrolimus oint 0.1% 212 vehicle oint BID	Fujisawa
68 Ruzicka et al [37]	Complete article	215	Adult patients with moderate to severe AD with a symptomatic area of at least 200 cm2.	3 weeks	54Tacrolimus oint 0.03% 51 tacrolimus oint 0.1% 51 tacrolimus oint 0.3% 54 vehicle BID	Fujisawa
245Kang et al [38]	Abstract	26	Adults with moderate to severe AD at least 76% of BSA	3 weeks	7 Tacrolimus ointment 0.03% tacrolimus oint 0.1% 7 tacrolimus □int 0.3% 6 vehicle BID	Not reported
263FK506 oint group[39]	Complete article	212	Adult patients with chronic-type AD on the trunk / extremities (16- 62 y)	3 weeks	70 tacrolimus oint. 0.03% 69 tacrolimus oint. 0.1% 72 vehicle BID	Not reported
53 Paller et al[30]	Complete article	351	Pediatric patients 2- 15 y with moderate to severe AD with 10 to 100% of BSA	12 weeks	117 Tacrolimus oint 0.03% 287 tacrolimus oint. 0.1% 117 vehicle BID	Fujisawa
247 Hanifin JMI [26]	Abstract	33	Pediatric patients with moderate to severe AD 3-6 y.	3 weeks	12 Tacrolimus oint. 0.03% 13 tacrolimus oint 0.1% 8 vehicle BID	Not reported
232 Boguniewicz et al [40]	Complete article	180	Children 7- 16 y with moderate to severe AD with 5 % to 30% of BSA	22 days	**Tacrolimus ointment 0.03% tacrolimus ointment 0.1% tacrolimus ointment 0.3% vehicle**	Fujisawa
250 Ohtsuki et al [25]	Abstract	221	Pediatric patients 2- 15 y with moderate to severe AD	3 weeks	Tacrolimus oint 0.03% tacrolimus oint 0.1% vehicle	Not reported
15 Drake et al[29]	Complete article	-579 adults 178 children - 145 toddlers	Adults and children with AD	12 weeks	Tacrolimus oint 0.03% tacrolimus ointment 0.1% vehicle	Fujisawa
285 Reitamo[45]	Abstract	972	Adults with AD	6 months but only 12 weeks reported	487 tacrolimus oint. 0.1% BID on the whole body 485 0.1% hydrocortisone butyrate on trunk and extremities and1% hydrocortisone acetate on the face and neck	Not reported

Table 3 - Main characteristics of included studies - continued

Study Identification	Publication state	Sample size	Inclusion criteria	Treatment duration	Interventions and number recruited	Sponsorship
116 Fleischer et al [33]	Complete article	631 adults 351 children	Adults and children with moderate to severe AD	12 weeks	Tacrolimus ointment 0.03% tacrolimus ointment 0.1% vehicle	Fujisawa
264 FK506 oint.study group [47]	Complete article	264	Adults 16 y or more with AD on face or neck	1 week	75 tacrolimus oint 0.1% 76 Alclometasone oint 0.1%	Not reported
246 Gutgesell et al [39]	Abstract	7	Adults with severe, longstanding AD.	3 weeks	7 Tacrolimus ointment 0.1% in one body half 7 hydrocortisone 3% in the other body half. BID in neck, face and forearms	Not reported
24 Reitamo et al[42]	Complete article	570	Adults >15 y with moderate to severe AD with at least 5% of total BSA	3 weeks	186 0.1% hydrocortisone butyrate 193 tacrolimus oint 0.03% 191 tacrolimus oint 0.1%	Fujisawa
258 FK506 oint. Study group[46]	Complete article	181	Adults 16 y or more with AD on trunk or limbs	3 weeks	89 Tacrolimus ointment 0.1% 92 betamethasone 0.12% oint	Not reported
262 Fk 506 oint study group[37]	Complete article	195	Adults 16 y or more with chronic lesions of AD on their trunk or extremities	3 weeks	51 tacrolimus ointment 0.1% 47 tacrolimus oint 0.3% 49 tacrolimus oint 0.5% 48 betamethasone 0.12%	Not reported
265 Nakagawa et al[38]	Abstract	?	Patients with AD on face and neck	1 week	tacrolimus oint 0.1% Alclometasone oint 0.1%	Not reported
14 Reitamo et al [41]	Complete article	560	Children 2- 15 y with moderate to severe AD at least 5% and no more than 50% of total BSA	3 weeks	185 1% hydrocortisone acetate oint 189 tacrolimus 0.03% BID 186 tacrolimus 0.1% BID	Fujisawa
243 Bos et al [48]	Complete article (in press)	624	Children 2- 15 y with moderate to severe AD	3 weeks	1% hydrocortisone acetate oint tacrolimus 0.03% UID tacrolimus 0.03% BID	Fujisawa

ii) Interventions and comparators

Studies were divided into two groups: those comparing tacrolimus against a placebo and those comparing the drug against topical corticosteroids.

a) Tacrolimus against a placebo

A total of 11 studies comparing tacrolimus against a placebo were found, five of them reporting results on adults and four on children. Two studies reported data for both populations.

There were two studies, No. 54[30] and No. 55,[28] which reported different outcomes for the same sample of adult patients, adverse events and effectiveness respectively. Additionally, study No. 15[29] reported the quality of life for adults and children (the same samples of studies No. 53[27] and 55[28]).

Finally, study No. 116[33] reported infectious adverse events for 5 studies: 3 randomised and 2 non-randomised trials. For the effect of this review, only data from randomised studies were considered and they corresponded to the same samples of studies No. 53[27] and No. 55[28]

The longest interventions were of 12 weeks of treatment and in most studies patients received treatment for only 3 weeks.

In most studies tacrolimus was applied in concentrations of 0.03% and 0.1% that correspond to licensed dosage. Additionally, 3 studies,[34 35 36] published between 1997 and 1998 (see table No.3), included also tacrolimus 0.3% that remains used only for research applications.

b) Tacrolimus against steroids

There were 9 trials that compared tacrolimus ointment with corticosteroids, two were conducted on children and seven on adults. Tacrolimus was used mainly in concentrations of 0.1% and only 3 studies also included 0.03%. There is one Japanese study[37] published in 1998, that also included a concentration of 0.5%, of no clinical use.

Corticosteroids used as comparators were of different potency. As mentioned previously, this is an important issue to take into consideration when making comparisons, as the therapeutic effect and adverse events of steroids are proportional to their potency.[16] (See appendix 4).

The two studies conducted on children used a low-potency drug: 1-% hydrocortisone acetate.

On the other hand, three of the seven studies on adults compared tacrolimus against a potent topical steroid, one used 0.1% hydrocortisone butyrate and two-used 0.12% betamethasone. From the remaining four studies, one compared tacrolimus against hydrocortisone, a mild steroid, two studies against alclometasone, a steroid of moderate potency. The last study compared tacrolimus against a high-potency steroid used in the trunk and extremities and a mild steroid used in the neck and face of patients. Details of these comparators are presented in table No.4.

Table 4 - Main characteristics of studies comparing tacrolimus against corticosteroids (*)

Study ID	Population	Intervention	Comparator	Corticosteroids' potency (*)
24 Reitamo et al [42]	Adults >15 y with moderate to severe AD with at least 5% of total BSA	tacrolimus oint. 0.03% tacrolimus oint 0.1% BID	0.1% hydrocortisone butyrate BID	Class 2 potent
258 FK506 oint. Study group [46]	Adults 16 y or more with AD on trunk or limbs	Tacrolimus oint 0.1%	Betamethasone 0.12% oint.	Class 2 potent
262 Fk 506 oint study group[37]	Adults 16 y or more with chronic lesions of AD on their trunk or extremities	tacrolimus oint 0.1% tacrolimus oint 0.3% tacrolimus oint 0.5%	betamethasone 0.12%	Class 2 potent
246Gutgesell et al[39]	Adults with severe, longstanding AD.	Tacrolimus oint 0.1% on one body half Twice daily on neck, face and forearms	hydrocortisone 3% on the other body half	Class 4 mild
264 FK506 oint.study group[47]	Adults 16 y or more with AD on face or neck	tacrolimus oint 0.1%	Alclometasone oint. 0.1%	Class 3 moderately potent
265 Nakagawa et al[38]	Patients with AD on face and neck	tacrolimus oint 0.1%	Alclometasone oint.0.1%	Class 3 moderately potent
14 Reitamo et al[41]	Children 2- 15 y with moderate to severe AD at least 5% and no more than 50% of total BSA	tacrolimus 0.03% tacrolimus 0.1%	1% Hydrocortisone	Class 4 mild
243 Bos et al[48]	Children 2- 15 y with moderate to severe AD	tacrolimus 0.03% BID and tacrolimus 0.03% UID	1% hydrocortisone acetate oint.	Class 4 mild
285 Reitamo[45]	Adults with AD	Tacrolimus 0.1% BID	1% hydrocortisone acetate oint. in the neck and face and 0.1% hydrocortisone butyrate in the trunk and extremities	Class 4 mild Class 2 potent

(*) Classification according to Branzzini and Pimpinelli [16]

iii) Characteristics of studied populations

a) Studies comparing tacrolimus against vehicle.

The diagnostic criteria most frequently used by authors to decide the inclusion of patients in studies were those of Hanifin and Rajka (see appendix No.1). Additionally, all studies considered in this review included patients with moderate to severe AD, most of them according to the Rajka and Langeland severity criteria (see appendix 2).

Age and sex baseline distributions were balanced among different intervention groups and most studies in adults included populations with mean age around 30 -35 years. In children, all studies included patients between 2 and 15 years old (see appendix 11).

b) Studies comparing tacrolimus against topical steroids

In the case of studies that compared tacrolimus with steroids, all of them included patients with moderate to severe AD, even though four of the nine studies did not report the diagnostic and severity criteria used.(See appendix 12)

The proportion of moderate/severe patients included in trials was balanced in all studies. Only one very small study of 7 patients included only severe patients.[39]

Age and sex baseline characteristics were balanced in all arms of studies that provided data. Detailed characteristics of patients included in each study are presented in Appendix 12.

iv) Outcome assessment

a) Clinical improvement

The most widely used scales to assess clinical improvement were Physician's Global Assessment of clinical response (PGA) and the modified Eczema area and severity index (mEASI) (See appendix 3). However, different studies reported their results using mEASI with different statistics: median improvement and interquartile range,[41-43] or means and SE. [27,36]

In the case of the PGA scale, results were reported more homogeneously and variations were only observed in cut-off points used by researchers to decide "success" of the interventions. Most frequent cut-off points used were 90% or 75% and more improvement. Fortunately, with some exceptions most studies reported both data; thus variations were considered in the sensitivity analysis.

There were several studies that presented their own scales based on physicians' assessment of clinical improvement. In particular, all the Japanese studies used a "final global improvement rating" determined by the physician. This included assessment of rush, papule infiltration or lichenification and itching. They graded results in 6 levels from "cured" to "worse" and established a cut-off point to consider the therapy successful or not. This graduation was similar to that of the Physician's Global Assessment (PGA) mentioned previously. (See appendix 3)

Studies that assessed clinical effectiveness with a scale based on physician assessment were considered together in the meta-analysis even though a complete equivalence between different scales could not be established and thus should be considered carefully as a source of heterogeneity in the final interpretation of numerical results.

Tables No.5 and 6 summarise different scales used to assess outcomes in trials that compared tacrolimus with vehicle and tacrolimus against steroids respectively

Table 5 - Assessment methods of clinical improvement used in included studies that compare tacrolimus against a placebo

Study ID	PGA	mEASI or EASI	SCORAD	Percentage of BSA affected	Patient's assessment pruritus or overall response	Other method
55 Hanifin et al[28]	% of patients with ≥ 90% improvement	Least square mean ± S.E.		secondary	secondary	Physician's assessment of clinical signs
68 Ruzicka et al[34]					% of patients markedly improved or more	Score 1 and score 2 (*) (Median decrease) Physician overall assessment (% patients markedly improved or more)
245Kang et al[35]				Mean BSA change		1.Clinical improvement not specified. (% of patients with marked or excellent improvement)
263 FK506 oint group[49]						1. Final global improvement assessed by physician (ad hoc Japanese score)
53 Paller et al[27]	% of patients with ≥ 90% improvement	Least square mean ± S.E.		Least square mean	Least square mean	
247 Hanifin JMl [26]	% of patients with marked to excellent (≥ 75% improvement)			Mean change from baseline		
232 Boguniewicz et al[36]	% of patients with marked to excellent (≥ 75% improvement)	mean ± S.E.			Mean % improvement	
250 Ohtsuki et al[44]						Score for skin signs not specified (Patients with 67% or more improvement)
15 Drake et al[29]						Quality of life during the last week of treatment
116 Fleischer et al[33]						Incidence of skin infections
54 Soter et al[30]						Incidence of adverse events

(*)Score 1: sum of scores for Erythema, oedema and pruritus in treated areas. Score 2: score 1 plus the sum of the scores of oozing or crusting, excoriation and lichenification of involved skin and dryness of non-involved skin in the treated area.

Table 6 - Assessment methods of clinical improvement used in included studies that compare tacrolimus against steroids

Study ID	PGA	mEASI or EASI	SCORAD	Percentage of BSA affected	Patient's assessment pruritus or overall response	Other method
246Gutgesell et al[39]			primary			
24 Reitamo et al[42]						Overall clinical improvement
258 FK506 oint. Study group[46]						1. Final global improvement assessed by physician (ad hoc Japanese score)
262 FK 506 oint study group[37]						1. Final global improvement assessed by physician (ad hoc Japanese score)
264 FK506 oint.study group[47]						1. Final global improvement assessed by physician (ad hoc Japanese score)
265 Nakagawa et al[38]						Clinical improvement (score not specified)
14 Reitamo et al[41]	% patient excellent improv.(≥ 90%)	Median improv.		% change BSA affected		
243 Bos et al[48]	% patients excellent (≥ 90%) or marked improvement (≥ 75%)	% decrease of baseline				
285 Reitamo[45]	Secondary outcome not reported	Response rate (60% or more improvement from baseline at 12 week)				

b) Adverse events (AE)

Incidence rates of adverse events were reported in 13 of the 20 studies divided in AE on the application site and non-application site, all of them in the short-term. Most studies presented incidence rates by type of AE, but overall incidence in the population treated was not available in all trials. Details of specific rates for each study are reported in Appendix 13.

In the 11 studies comparing tacrolimus against vehicle, there were 2 studies that reported AE data of other trials. Study No 54 (Soter et al) [30] reported adverse events of study No. 55, [28] while study No. 116 (Fleischer et al) [33]reported infectious events of trials No. 55 [28] and 53 (Paller et al). [27]

Additionally, three studies published as abstracts reported only general data of AE without incidence rates.

Most frequent AE reported with tacrolimus and vehicle were skin burning, pruritus and skin erythema, while less frequent adverse events on the non-application site were headache, flu-syndrome and sinusitis for all groups. All AE were more frequent in tacrolimus groups.

In studies comparing tacrolimus with steroids, only one study on adults and two on children specified incidence rates of AE. In both groups the most frequent events reported were skin burning, pruritus and folliculitis, while flu-syndrome and headache were most frequent non-application site AE in adults and in children flu-syndrome, fever and rhinitis were most reported.

In children only skin burning was statistically significantly most frequent in tacrolimus groups than with steroids, whereas in adults both skin burning and pruritus were statistically significantly more frequent in the tacrolimus groups.

Finally, study No. 116 (Fleischer et al) [33] reported infectious adverse events for adults and children. The incidence of overall cutaneous infections was not statistically significantly higher in any tacrolimus group compared with vehicle.

c) Quality of life

Only one of the studies found assessed the quality of life of patients treated with tacrolimus or vehicle.[29]

This study reports quality of life data for children, toddlers and adults during the last week of treatment assessed with the Dermatology Life Quality Index (DLQI) in adults, the Children's DLQI in children and in toddlers, a modified version of CDLQI.

Results reported a significant improvement of QoL in all assessed areas for patients treated with tacrolimus 0.03% and 0.1% compared with a placebo in all ages.

v) Validity of included studies

As defined in the protocol, quality assessment was based on a checklist including main methodological issues to avoid bias in RCTs (See appendix 9).

Publication status was a key issue in assessing internal validity properly. Studies published as abstracts did not report enough information to judge the main methodological issues.

Tables No.7 and 8 summarise the assessment of different items considered on the checklist. The studies are presented in two groups, those that compare tacrolimus versus a placebo and those with steroids.

The quality of the studies was heterogeneous. The studies of highest quality were Boguniewicz et al [36] and Reitamo et al[41] which provided enough information to assess properly all items and were considered as "adequate" in all of them.

Several studies were qualified as "unclear" because they did not provide enough information to assess items. This was not only for those published as abstracts, but also for some complete articles.

Table 7 – Internal Validity of Studies Comparing Tacrolimus Against Placebo

Study identification	Adequate random allocation	Adequate concealment allocation	Blindness Assessors	Care provider	Participants	Adequate ITT with minimal missing data
55 Hanifin et al[28]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
54 Soter et al[30]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
68 Ruzicka et al[34]	Unclear	Unclear	Yes	Yes	Yes	Yes
245Kang et al[35] (*)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
263FK506 oint. Group[49]	Unclear	Yes	Yes	Yes	Yes	No
53 Paller et al[27]	Unclear	Unclear	Yes	Yes	Yes	Yes
247 Hanifin JMI [26] (*)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
232 Boguniewicz et al[36]	Yes	Yes	Yes	Yes	Yes	Yes
250 Ohtsuki et al[44]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
15 Drake et al[29]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
116 Fleischer et al [33]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes

(*) Studies reported as abstract

Table 8 – Internal Validity of Studies Comparing Tacrolimus Against Steroids

Study identification	Adequate random allocation	Adequate concealment allocation	Blindness Assessors	Care provider	Participants	Adequate ITT with minimal missing data
24 Reitamo et al[42]	Yes	Yes	Yes	Yes	Yes	Yes
258 FK506 oint. Study group[46]	Unclear	Yes	Yes	Yes	Yes	No
262 FK 506 oint study group[37]	Unclear	Yes	No	No	No	No
246Gutgesell et al[39] (*)	No	No	Unclear	Unclear	Unclear	Yes
264 FK506 oint.study group[47]	Unclear	Yes	Unclear	Unclear	Unclear	No
265 Nakagawa et al[38] (*)	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
14 Reitamo et al[41]	Yes	Yes	Yes	Yes	Yes	Yes
243 Bos et al[48] (*)	Unclear	Unclear	Yes	Yes	Yes	Yes
285 Reitamo[45] (*)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

(*) Studies reported as abstract

Finally, all the studies published in Japanese did not undertake ITT analysis – the authors, after data collection, decided to exclude several patients from the analysis because they did not apply the ointment properly. Additionally, one of the Japanese studies was not blinded properly. [37]

3.3 Assessment of effectiveness

3.3.1 Meta-analyses of clinical effectiveness of tacrolimus compared with vehicle.

First, meta-analyses were done comparing separately tacrolimus 0.03% and 0.1% with vehicle.

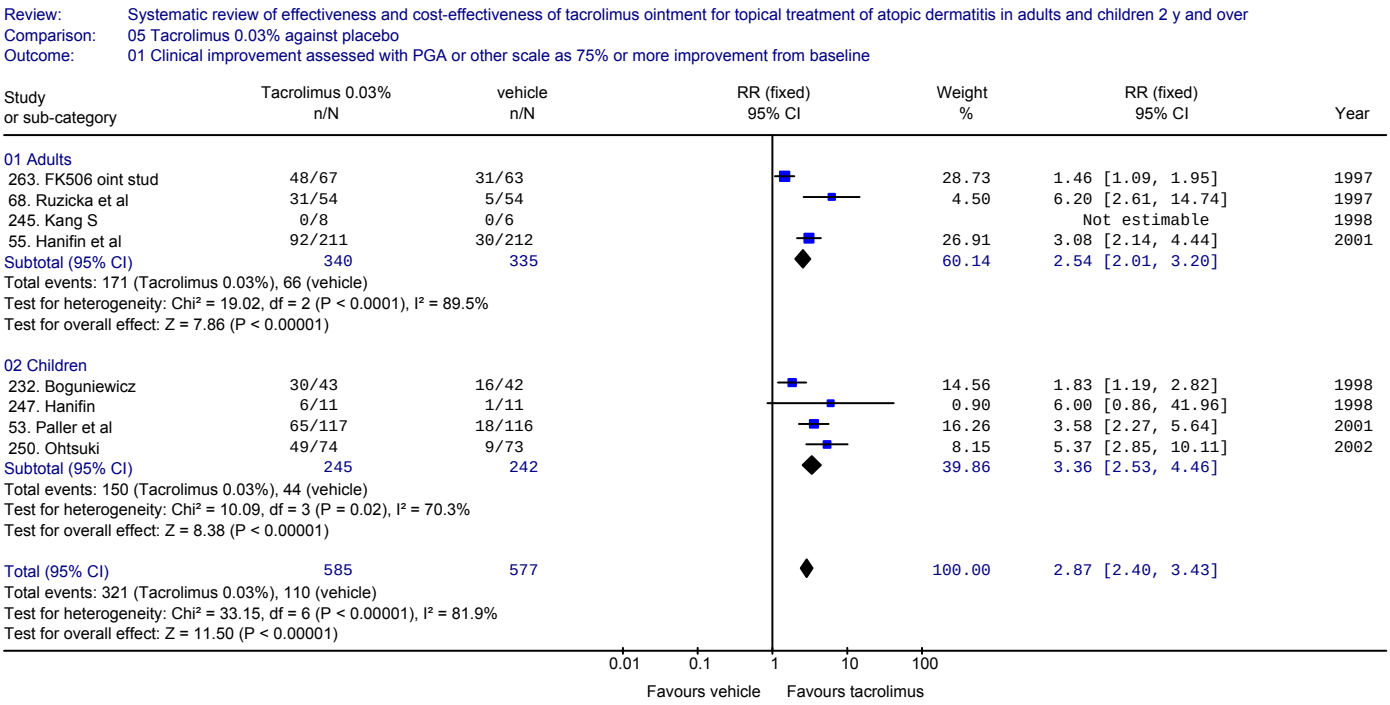
There were 11 three-arm studies that compared tacrolimus 0.03%, 0.1% and vehicle, but only 8 were included in the graphs because the studies that reported different outcomes of the same populations were excluded to avoid double-counting patients (studies No. 54 [30], 15 [29] and 116 [33]).

Sub-group analysis was done dividing studies according to the age of populations studied that is children and adults and ordered by year of publication. Four trials included adults and the other four included children. Sub-group analysis and overall results are reported.

In both meta-analyses (see fig. 2 and 3) the overall results as well as partial result for children and adults, favour tacrolimus, with a discrete strongest effect with 0.1% dosage.
In the meta-analysis of tacrolimus 0.03%, results with fixed and random effect models were very similar, but fixed-effect model resulted in the most conservative overall result, with tacrolimus being 2.87 times more effective than vehicle (See appendix 12 for additional graphs).

Additionally, all studies in adults had a statistically significantly more favourable effect for the active treatment and the same was observed in children with the exception of one small study, with a very large non-significant 95% CI due to the small sample size.

Figure 2 – Meta-analysis comparing clinical effectiveness of tacrolimus ointment 0.03% against placebo in adults and children with RR and fixed-effect model

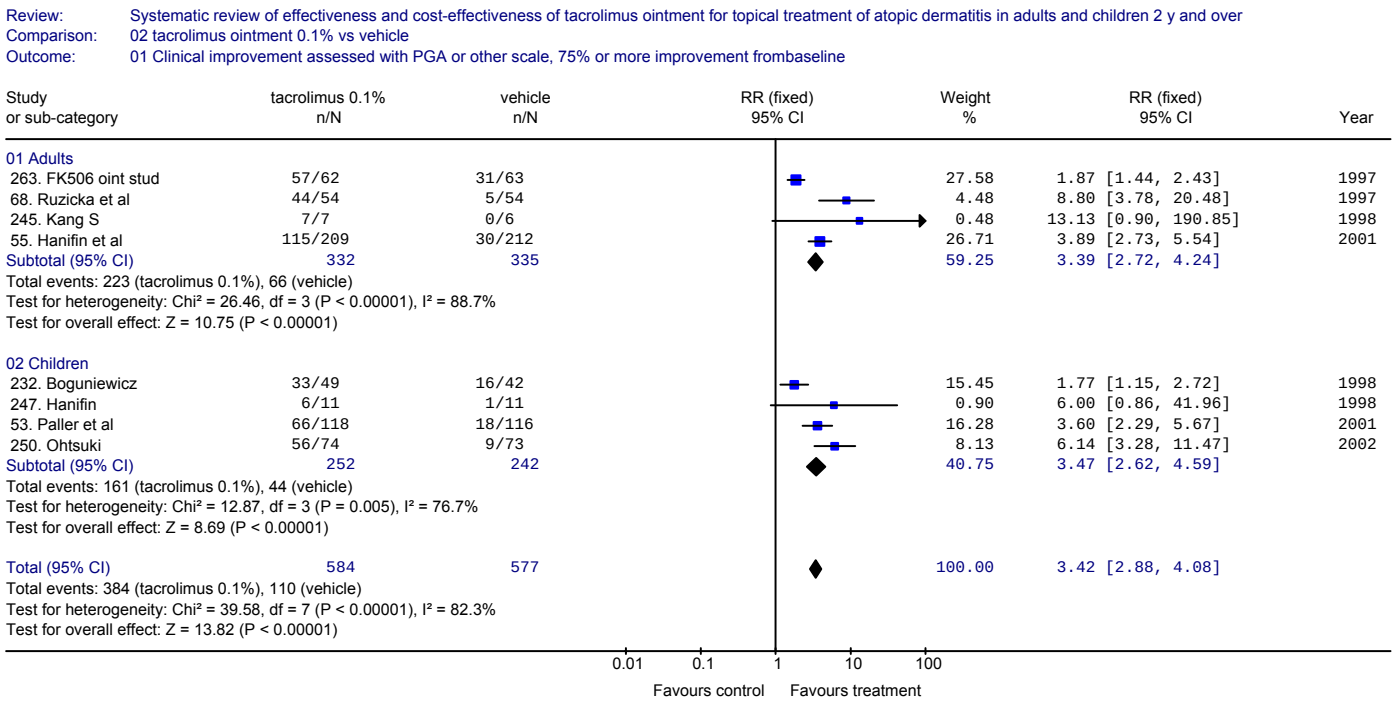


Even if all studies have a result that favours tacrolimus in the forest plot, they are statistically significantly heterogeneous when considered together.

In the case of the tacrolimus 0.1%, the overall RR estimated with fixed-effect model was the most conservative result with tacrolimus being 3.42 times more effective than placebo, with a significant 95% CI (2.88, 4.08) (See figure 3). Similar results were obtained also with fixed-effect model (See appendix 14).

The treatment effect in sub-groups was similar; both concentrations of tacrolimus had the strongest effect on children. However, for the highest concentration, there was a slight difference between adults and children.

Figure 3 – Meta-analysis comparing tacrolimus 0.1% against vehicle using RR and fixed-effect model.



In this case, studies were statistically significantly heterogeneous in sub-groups of adults and children and also when considered all together.

The main sources of heterogeneity could be attributed to the use of different assessment scales and diversity in quality levels.

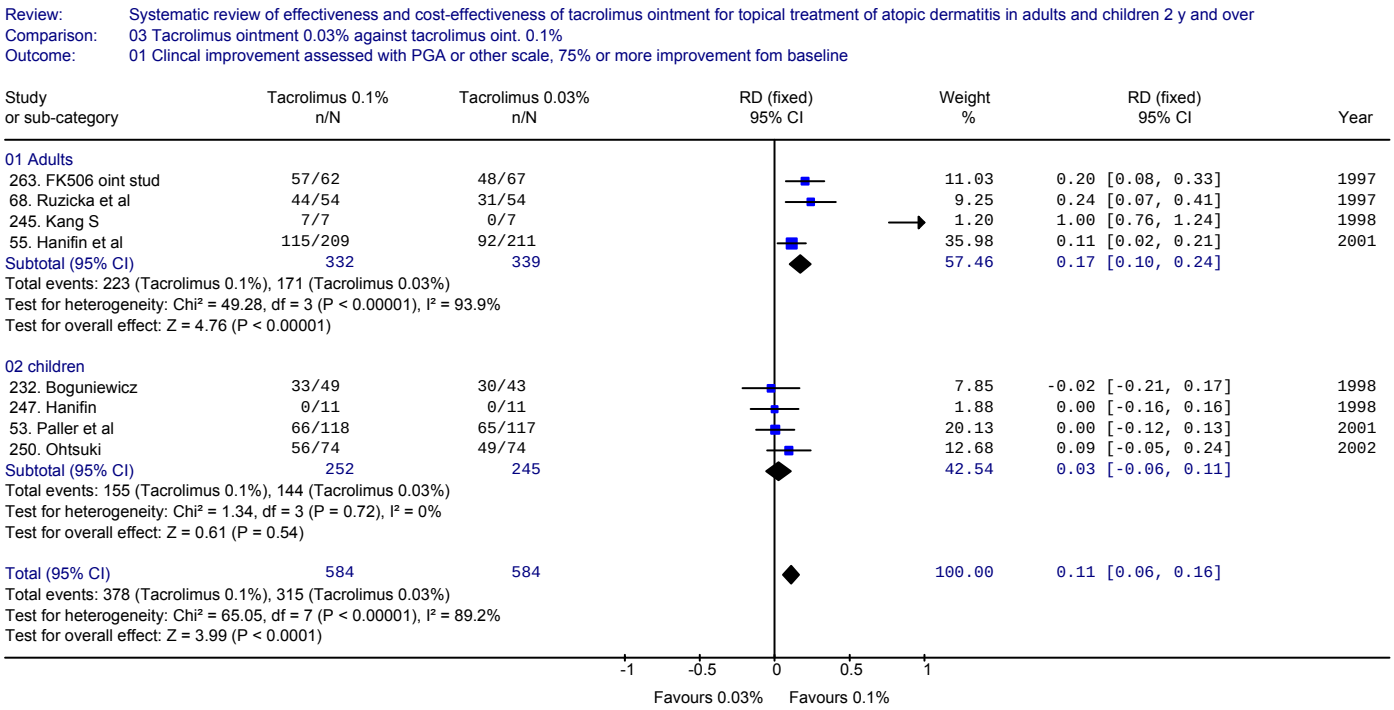
Additionally, meta-analysis using RD was done to estimate NNT with tacrolimus compared with vehicle. In the case of tacrolimus 0.03%, the most conservative result was using fixed-effect model with a statistically significant overall risk difference of 0.36 (0.31, 0.41) with a NNT of 3. For tacrolimus 0.1%, the RD estimated with fixed-effect model was the most conservative with a RD of 0.47 (0.42, 0.51) with a NNT of 2 (See Appendix 13 for graphs).

Finally, considering that all included studies were three-arm trials, a comparison between tacrolimus 0.03% and 0.1% was done to estimate the incremental effect of the higher concentration (See figure 4).

An overall effect slightly favourable to 0.1% was observed, with an overall RD of 0.11 (95% CI of 0.04, 0.14) with a NNT of 9. This means that 9 patients would have to be treated with tacrolimus 0.1% to produce 1 additional cured patient compared with the use of a concentration of 0.03%. This result is a consequence of the superiority of 0.1% in adults where the NNT is 6, but not in children, where the NNT is 33.

These results suggest that there is no evidence to support the use of tacrolimus 0.1% in children.

Figure 4 – Meta-analysis comparing tacrolimus 0.03% and 0.1% using RD and fixed effect-model



3.3.2 Meta-analyses of tacrolimus compared with steroids

In the case of comparison of tacrolimus with steroids most of data available were comparing steroids with tacrolimus 0.1%. Only one study in children compares them with tacrolimus 0.03%.

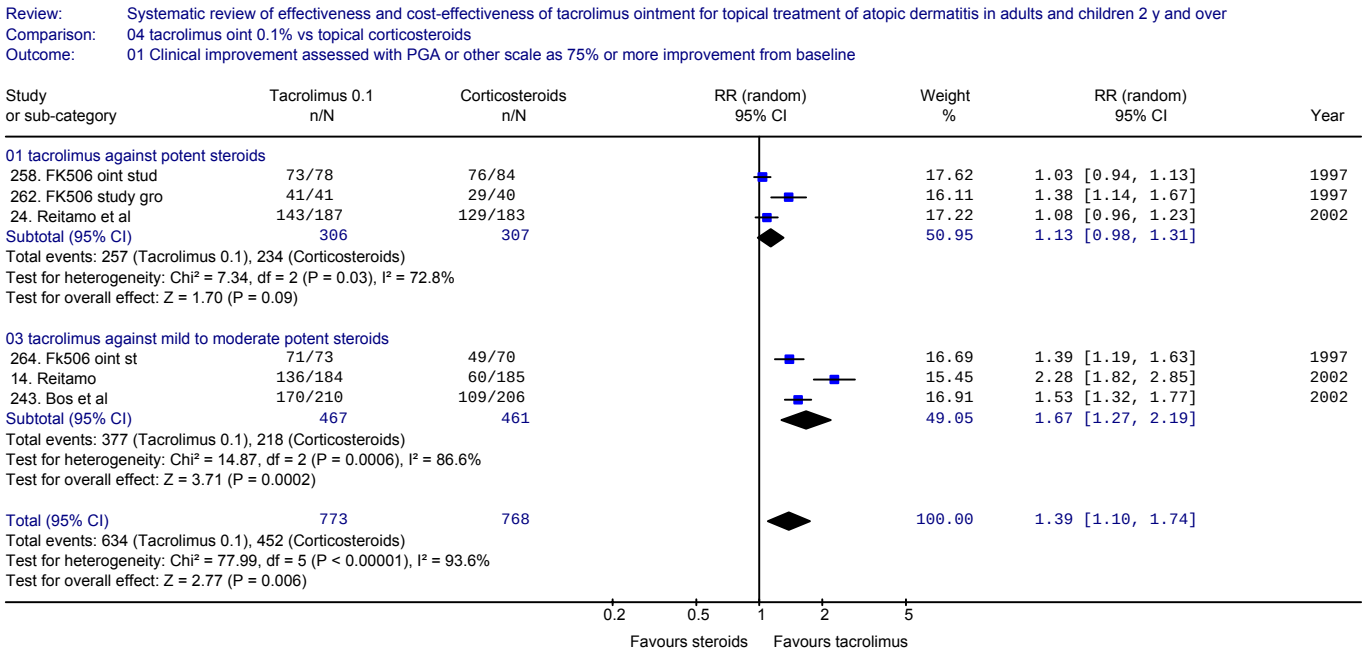
The meta-analysis included six of 9 trials found. Three studies were not considered because they were abstracts without enough data to allow inclusion. Nonetheless, they were included on graphs and correspond to study No. 265[38], with no quantitative data and probably a repeated publication of study No. 264 [47]; study No. 246[39], with a very small sample of 7 patients without numerical results reported and an abstract by Reitamo [45] that reported results only using mEASI scale.

The included studies are three trials in adults comparing tacrolimus with high-potency topical steroids and three publications comparing it with a steroid of mild to moderate potency.

Both random and fixed effect models gave very similar results, but the most conservative was obtained with random-effect model (see appendix 12). Tacrolimus was more effective than potent steroids with a RR of 1.13 almost statistically significant (95% CI of 0.98, 1.31) (See figure 5). For milder steroids the result was more favourable to tacrolimus, with a RR of 1.67 with a statistically significant 95% CI (1.27, 2.19).

The overall result considering all steroids was favourable to tacrolimus with a RR of 1.39 with a significant 95% CI (1.10,1.74), very similar with random and fixed-effect models.(See appendix 12).

Figure 5 – Meta-analysis comparing tacrolimus with steroids in adults and children using RR and random-effect model



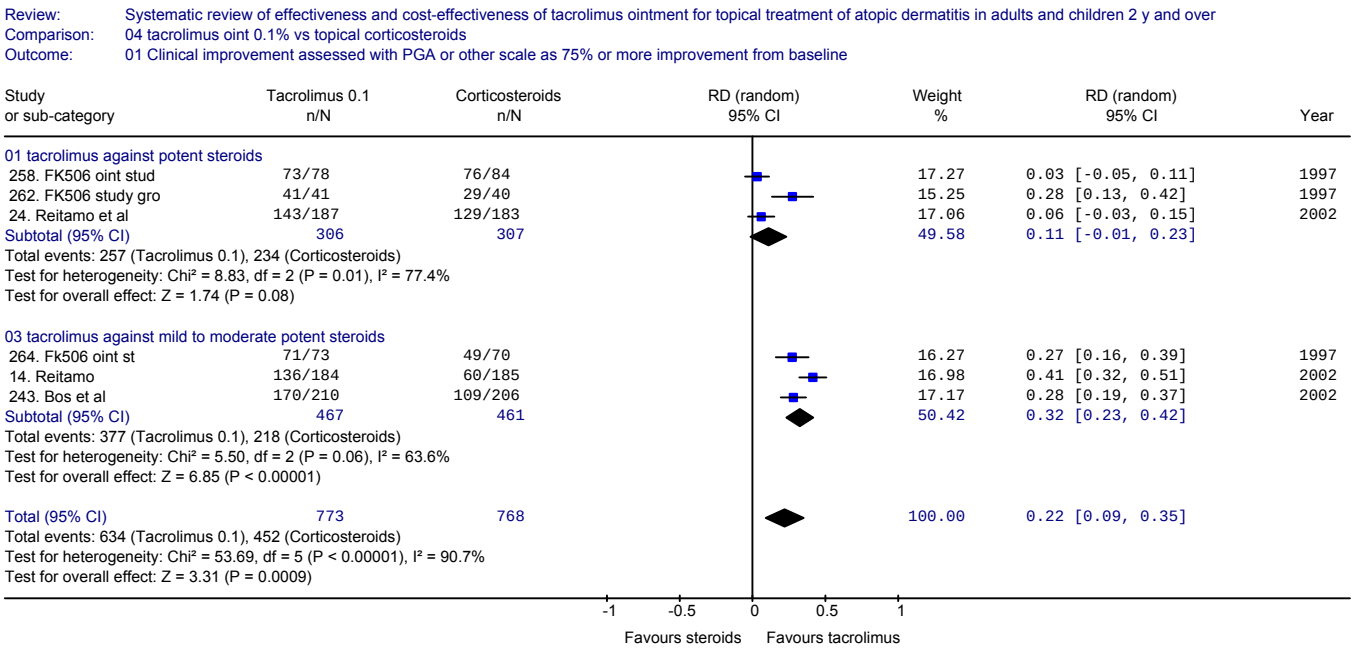
In this case all the studies together have statistically significant heterogeneity, while the 3 studies that compared tacrolimus with potent steroids were homogeneous. However, this information should be considered cautiously given the small number of studies included.

Moreover, this series of studies have numerous sources of heterogeneity, mainly because of the different comparators and different scales used to assess outcomes together with the different ages of the populations.

Meta-analysis of these studies using RD as a summary statistic gave an overall effect for tacrolimus of 0.22 with a statistically significant 95% CI (0.09, 0.35) with a NNT of 5. It means that 5 patients would have to be treated with tacrolimus 0.1% to produce 1 additional cured patient compared with the use of steroids.

This analysis produced different results when sub-groups are considered. With random-effect model, tacrolimus is superior to potent steroids, with a RD of 0.11 almost statistically significant (95% CI 0.01, 0.23) resulting in a NNT of 9. A comparison with mild to moderate potency steroids gives an NNT of 3 (See figure 6).

Figure 6 - Meta-analysis comparing tacrolimus with steroids in adults and children using RD and random-effect model



The results of the comparison of tacrolimus with steroids should be interpreted cautiously. Even though there is a clear tendency to a more favourable effect for tacrolimus, 3 of the 6 studies included were Japanese studies without ITT analysis. This is especially relevant in the case of the comparison of tacrolimus with potent steroids, where the superiority of tacrolimus is even smaller. This situation is considered in the sensitivity analysis.

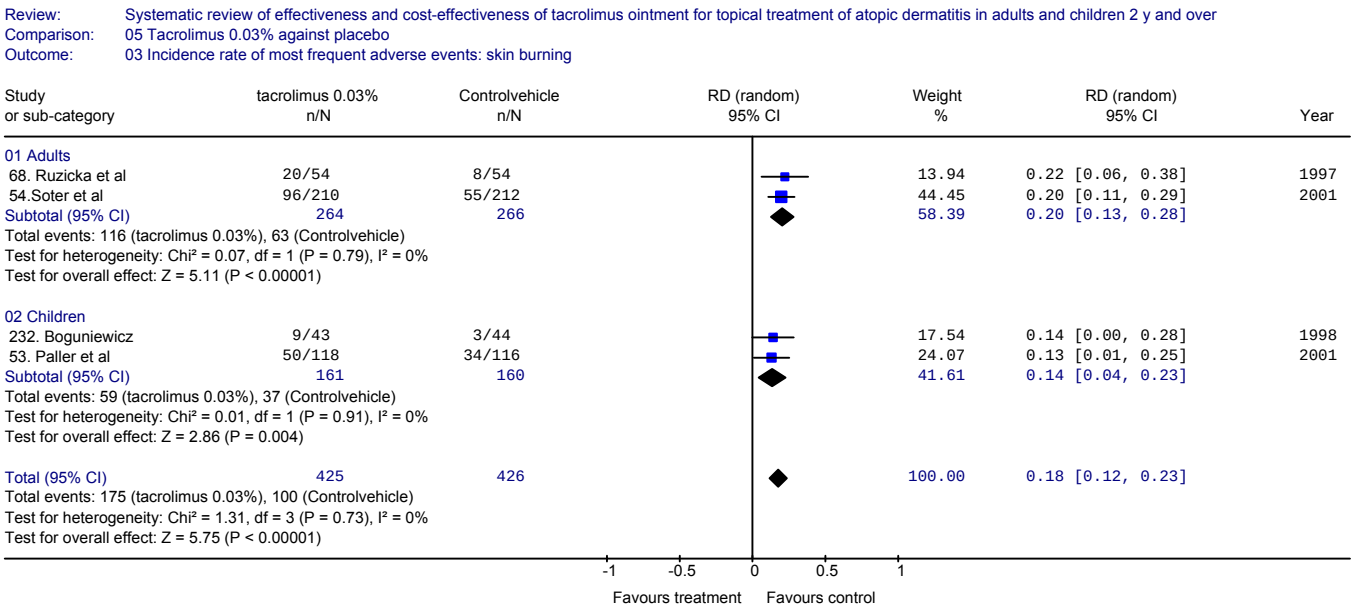
3.3.3 Meta-analysis comparing incidence of adverse events.

Meta-analyses were done comparing incidence rates of the most frequent adverse events: pruritus and skin burning, comparing tacrolimus 0.03% and 0.1% with vehicle. Unfortunately no quantitative synthesis was possible with studies comparing tacrolimus with steroids.

Meta-analyses including all the studies with data of AE, both tacrolimus concentrations produced statistically significantly more pruritus and skin burning than vehicle, with random and fixed effect models. The graph comparing skin burning with tacrolimus 0.03% and vehicle using RD and random-effect model is shown in figure 7. Other graphs are available in appendix 14.

Tacrolimus 0.1% does not have statistically significant more pruritus or skin burning than 0.03% concentration using RD and fixed-effect model. Thus the NNH was not estimated.

Figure 7 – Meta-analysis comparing incidence of skin burning with tacrolimus 0.03% and vehicle in adults and children using RD and random-effect model



3.3.4 Sensitivity Analysis

Sensitivity analysis was done with different cut-off points, and applying ITT analysis in studies where it was not applied, to explore variations in results.

Variations in cut-off points

a) Tacrolimus compared with vehicle

In the case of studies comparing tacrolimus 0.03% and 0.1% against vehicle, trials that were assessed using a higher cut-off point were:

Adults

- Hanifin et al [28] from 75% to 90% cut-off
- FK506 study group [49] from "moderate" to "significant " improvement

Kang et al [35] and Ruzicka et al[34] were considered as in the baseline case because they did not report other cut- off points (only "marked to excellent")

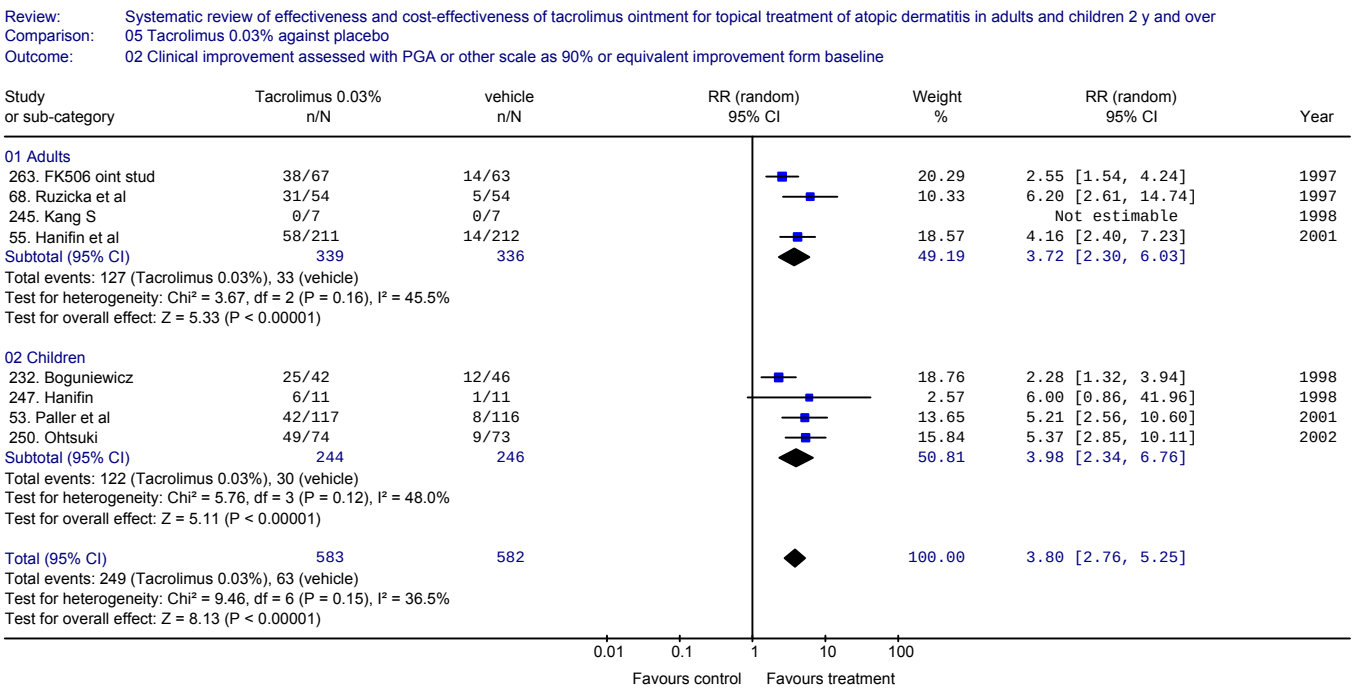
Children

- Boguniewicz et al [36] from 75% to 90% cut-off
- Paller et al [27] from 75% to 90%

Hanifin et al [26] (75% or more) and Ohtsuki [44] (67%) were considered as in the baseline case.

In the case of tacrolimus 0.03%, results with random and fixed effect models were similar, but the most conservative results were obtained with random-effect model: RR was of 3.80 (95% CI 2.76, 5.25), considerable higher than the baseline RR of 2.93 (95% CI 2.45, 3.51) (See figure 8).

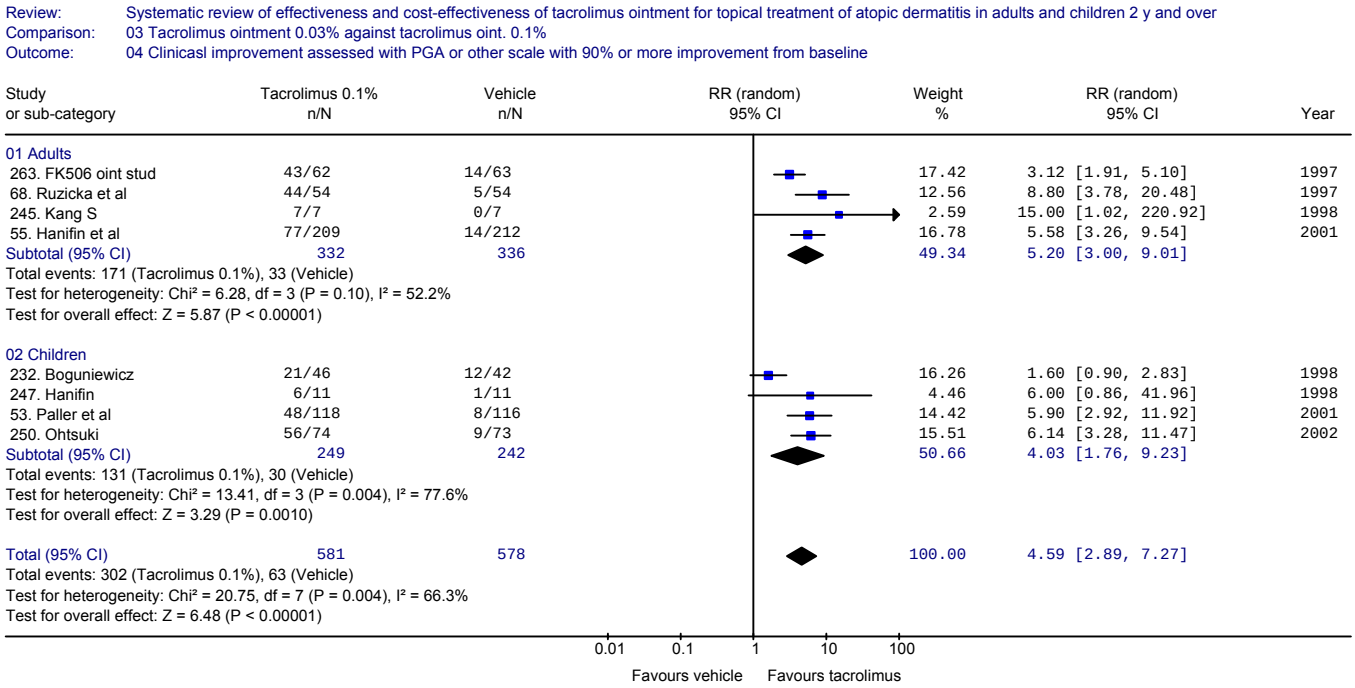
Figure 8 – Meta-analysis comparing clinical effectiveness of tacrolimus 0.03% with vehicle using a higher cut-off point, RR and random-effect model



The studies became statistically homogeneous for sub-groups and overall assessment. Consequently, this variable may explain the heterogeneity found in the baseline case.

In the case of tacrolimus 0.1%, a RR of 4.59 (95% CI 2.89, 7.27) with random-effect model is largely more favourable than the baseline result of RR 3.42 (95%CI 2.88, 4.08) (See figure 9).

Figure 9 –Meta-analysis comparing clinical effectiveness of tacrolimus 0.1% with vehicle using a higher cut-off point, RR and random-effect model



Heterogeneity in this case is statistically significant as it was in the baseline case when considering all studies and child trials, but adult studies this time are statistically homogeneous.

b) Tacrolimus compared with steroids.

In the case of studies comparing tacrolimus 0.1% with steroids, trials with different cut-off points were:

Potent steroids:

- Reitamo et al [41] from 75% to 90% improvement
- FK506 study group[46] from “moderate or more” improvement to “significant or more”.
- FK506 study group [37] from “moderate or more” to “significant or more” improvement.

Mild to moderate steroids

- Reitamo et al [42] and Bos et al [48] from 75% to 90% improvement
- FK506 study group [47] from “moderate or more” to “significant” improvement.

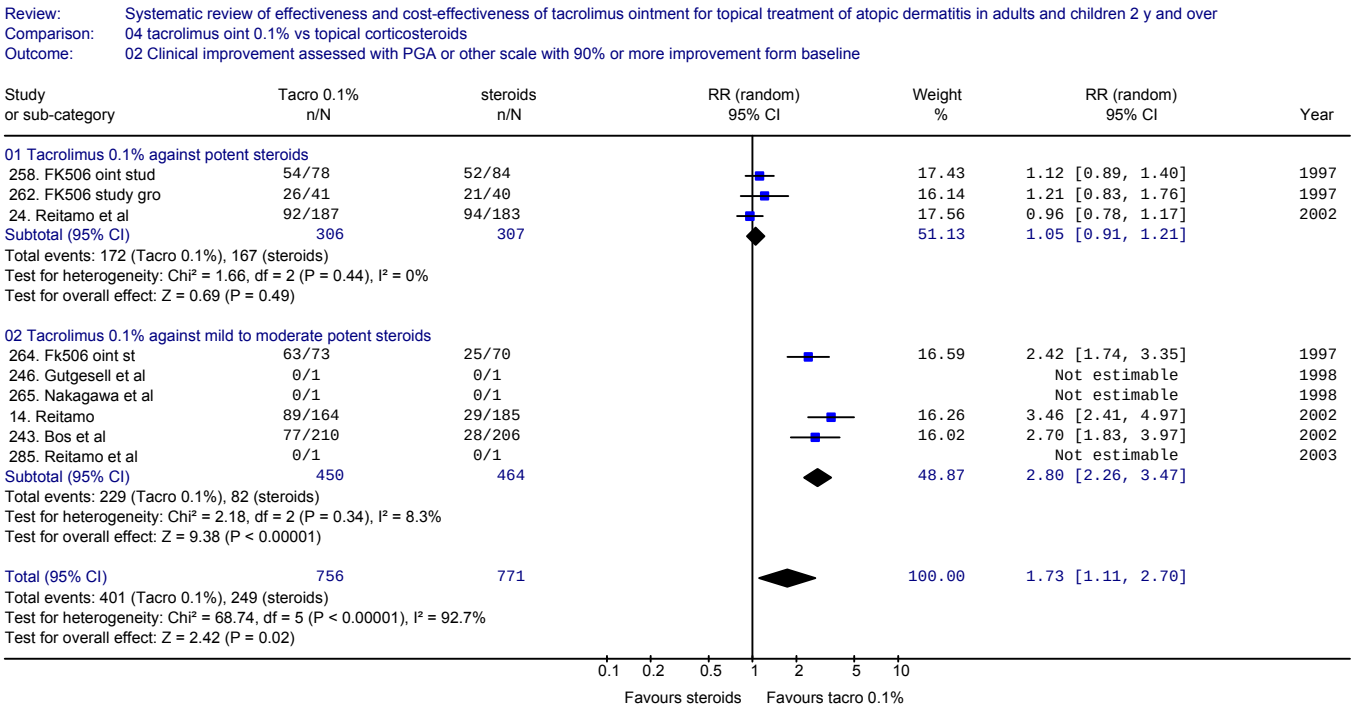
Gutgesell et al [39] data not available

In this case, a meta-analysis with a modification of the cut-off points produced a decrease in the effectiveness of tacrolimus compared with steroids as was observed in the baseline case (see figure 10).

When tacrolimus is compared with potent steroids, its superiority is decreased with a RR (random-effect model) of 1.05 with a no statistically significant 95% CI (0.91, 1.21), compared with the baseline case where RR favoured tacrolimus with 1.13, almost statistically significant (95% CI 0.98, 1.3).

However, when tacrolimus is compared with mild to moderately potent steroids, it is more effective than the baseline case. Tacrolimus is now 2.80 times more effective, compared with RR of 1.67 before, both statistically significant (see figure 10).

Figure 10 – Meta-analysis comparing clinical effectiveness of tacrolimus with steroids using a higher cut-off point, RR and random-effect model



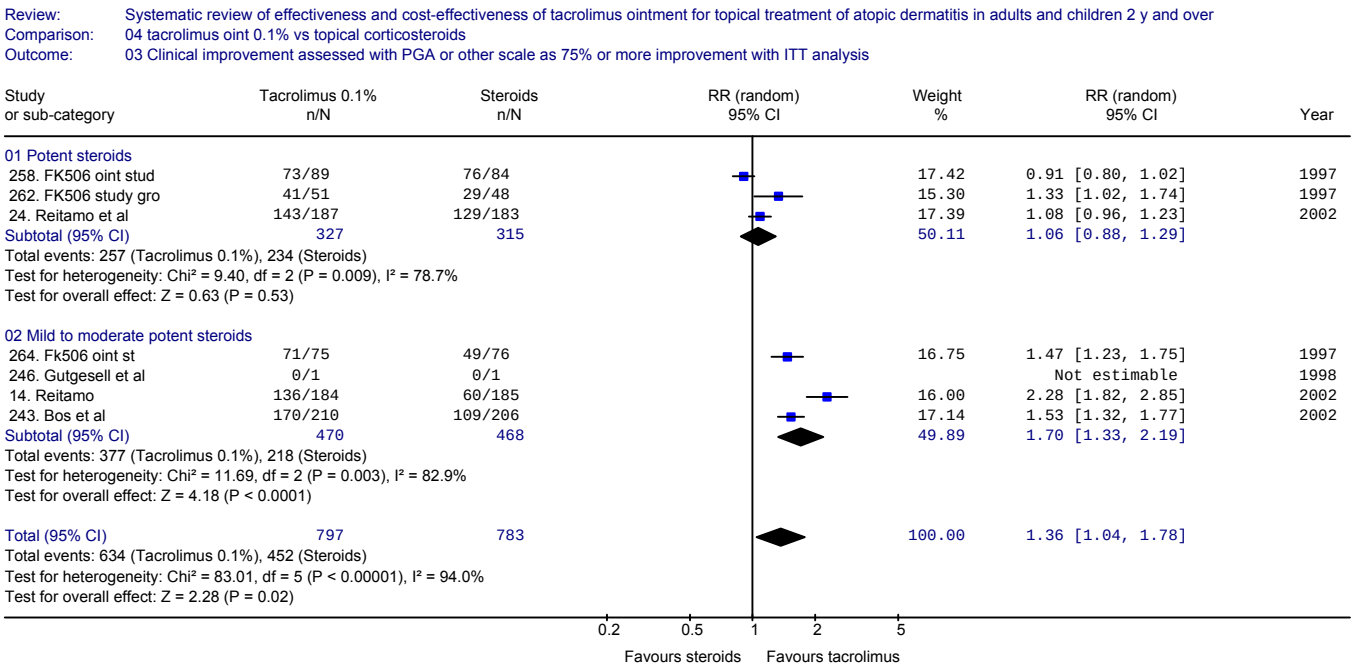
Cut-off point variations eliminated the statistical heterogeneity seen in the baseline case inside sub-groups analysis but this still remains when all studies are considered together.

Variations in ITT analysis

As mentioned previously, the four Japanese studies included in this review did not analyse their results using ITT analysis. As three of these studies compared tacrolimus with steroids, the impact of this methodological defect was assessed only in this case.

For this sensitivity analysis, the data presented by the authors were corrected to include all patients randomised in each group. The new results are presented in figure 11.

Figure 11 – Meta-analysis comparing clinical effectiveness of tacrolimus with steroids using ITT analysis, 75% cut-off, RR and random-effect model



The correction of the results with ITT analysis had a greater impact on the comparison of tacrolimus with potent steroids, as two of the three studies considered changed their data. In the new situation, tacrolimus showed almost no difference to potent steroids, with a non-statistically significant RR of 1.06 (95% CI 0.88, 1.29), compared with the previous RR of 1.13 (95% CI 0.98, 1.31).

In the case of milder steroids, the effect is opposite, with an increase in the superiority of tacrolimus. This time the RR is 1.70 (95% CI 1.33, 2.19) compared with the previous 1.67 (95% CI 1.27, 2.19). However, there were only 3 studies to compare.

As a consequence, the effect of ITT analysis in the overall result slightly reduce the effectiveness of tacrolimus compared with all steroids (previous RR 1.39 (95% CI 1.10, 1.74) in the baseline case, to a RR of 1.36 (95% CI 1.04, 1.78).

IV. – Economic Analysis

A systematic review of the literature was carried out to find full economic evaluations of treatment for atopic dermatitis with tacrolimus ointment compared to any other active therapy.

3.4 Methods

3.4.1 Search strategy

The following sources were searched to find economic evaluations:

Electronic databases

- Health Economic Evaluation Database (OHE HEED). Issue April 2003.
- EMBASE
- MEDLINE

(These two databases were searched using methodological filters for identifying cost and economic model studies from the Birmingham Technology Assessment Group.)

- DARE
- NHS Economic Evaluations Database (NHS EED)

Additional searches:

- Reference lists of relevant studies found on databases were searched to identify further studies.

No language restriction was imposed.

Details of the full search strategy are available in Appendix No.6.

3.4.2 Inclusion and exclusion criteria

Studies identified with the search strategy were included in the review if they met all the following criteria:

- Type of study: any full economic evaluation study
- Population: adults and children 2 years and over with diagnosis of atopic dermatitis of any intensity and on any part of the body
- Diagnostic criteria: atopic dermatitis diagnosed by a physician
- Intervention: topical application of tacrolimus ointment
- Comparator: any topical active treatment (corticoids or other)
- Outcomes: costs, cost consequences, cost-utility, incremental cost effectiveness ratio.

Exclusion criteria

Studies were excluded if they were not a full economic evaluation and if they compare tacrolimus against a placebo.

Inclusion/Exclusion criteria were applied by a reviewer and studies found were critically assessed using the checklist for decision analytic modelling proposed by Soto,[1] when economic evaluations were modelling-based and for other economic-evaluations, the checklist proposed by Drummond et al.[50]

3.5 Results

3.5.1 Studies identified

45 studies were found by the search strategy but only one of them was a full economic evaluation that met all the inclusion criteria.[51] Thus the remaining 44 studies were excluded from this review (See appendix 14 for full list).

3.5.2 General characteristics of the included study

The included study is a cost-effectiveness analysis of tacrolimus ointment versus high-potency topical steroids (HPTC) in adults with moderate to severe atopic dermatitis.

The study compared 3 different treatment protocols for AD: tacrolimus ointment and two different schedules of HPTC, each as monotherapy applied in adults with moderate to severe AD unresponsive to or not well controlled with mid-potency topical steroids.

The study was conducted from the third–party payer perspective during a 1-year period and applied a Markov model to represent more accurately the cyclic and recursive nature of AD.

It was developed in the US and supported by Fujisawa Healthcare Inc. The pharmaceutical company also sponsored most of the authors that participated in the study.

3.5.3 Critical Appraisal of evidence available

The checklist used to assess this study has 13 items. The full checklist is presented in table 9 and an overall discussion follows.

Table 9 – Appraisal of study included according to checklist for decision analytic modelling

Item	Appraisal
1. Hypothesis and objective	- Study has a clearly defined answerable objective
2. Rationale of the modeling	- Markov model is used and justified adequately to represent the cyclic and recurrent condition of AD.
3. Type and description of the model	Model design seems proper for answering the research question Markov model is explained with detail in each of its steps Diagram of model pathway is provided
4.Time horizon	- 1 year. It seams enough time for a short-term recurrent disease
5.Perspective	Third-party payer perspective. Indirect costs, transportation, over the counter medications, etc were not included. **- It would be more correct to use a societal perspective to consider all costs of the alternatives**.
6.Assessment of comparators	- Accoding to license indications, high-potency topical steroids are adequate comparators, even though, given the long-term horizon, mild and mid-potent steroids would have been more appropriate
7.Model data sources	Data used in the model were obtained from the literature, but did not come from systematic a review. Additional data were provided by a physician pane without clear explanation of methods used for this. **Steroids:** Data were not taken from studies that compare potent steroids with tacrolimus, but from different studies. For data for steroid effectiveness, data were taken from a literature review with meta-analysis, but there were not specifications of which study design was considered (RCT), or which were the comparators. Additionally, the physician panel defined long-term effectiveness of steroids -**Tacrolimus**: Data were taken from two trials found in the literature, one of them done on children (but this is a study on adults) and from other unspecified information provided by the pharmaceutical company. No systematic reviewed was performed. Concentration of tacrolimus used was not defined **Secondary treatment:** - Data were accorded by the physician panel: secondary treatment was defined as mid-potency steroids+ antibiotics
8. Outcomes and probabilities assessment	-Treatment success was defined as “Disease-controlled days”, days in which patients did not required primary prescription of topical therapy. -“Disease controlled” was defined as 75% or more improvement assessed with PGA scale. -Even though they are difficult to obtain, outcome definition did not consider quality if life outcomes, to build QALYs, the most useful method to assess different interventions in economic studies. -Probabilities for each outcome were clearly stated
9. Healthcare resource utilisation	Only costs of drugs, physician visits and prescription of medications were considered -Costs of drugs were according to market prices.
10. Analysis of the results	The study did not report an incremental cost-effectiveness ratio - Only an average cost-effectiveness is reported
11. Sensitivity analysis	Sensitivity analysis was performed considering adequate variables. - Missing consideration of a sensitivity analysis with cheapest and most expensive steroids alternatives and most and less effective alternatives.
12. Discussion and conclusions	-Conclusions are based only in the average cost- effectiveness estimation: Authors concluded that tacrolimus is more cost-effective than HPTC even though they did not estimate ICER.
13. Sponsorship	Fujisawa Healthcare Inc sponsored this study. - Implications of sponsorship were not discussed by authors

3.5.4 Discussion of economic-evaluation results

Authors assessed the cost-effectiveness of tacrolimus against potent topical steroids, the most relevant comparators to be considered. They used a Markov model, appropriate to represent the cyclic and recurrent characteristics of AD.

However, data used to assess the effectiveness of the drugs did not come from RCTs that compare them with each other, for tacrolimus they used data from vehicle-compared trials and from a study done on children, but applied to adults. Thus the information provided by the literature did not come from a systematic review. Effectiveness estimated at 2 and 4 weeks of therapy is lower than the value obtained by this study, but considering different duration of therapies.

Additionally, there was no clarity about the process and criteria used by the physician panel to decide values and variables and there was no discussion about the implications of their sponsorship by Fujisawa Healthcare Inc.

The most relevant issue was that although the authors concluded that tacrolimus was more effective than HPTC used for 2 weeks, they did not present ICER to support this conclusion, but only average cost-effectiveness for each alternative.

With the data offered, the estimation could be made:

	HPTC- 2 weeks	HPTC- 4 weeks	Tacrolimus
Total costs	$1682	$1317	$1323
Total efficacy (in DCD)	185	194	190

$$ICER = \frac{\text{Cost tacrolimus – cost of steroids (2 weeks)}}{\text{Benefit tacrolimus- benefit steroids (2 weeks)}}$$

$$ICER = \frac{\text{US\$ 1323-1682}}{\text{190-185 DCD}} = \text{US\$ - 71.8/ per one disease controlled day}$$

This means that this value is in the 2nd quadrant of the cost-effectiveness plane, thus tacrolimus dominates HPTC used for 2 weeks, saving US$71.8 for each disease controlled day gained.

For the comparison of tacrolimus with HPTC used for 4 weeks, according to values provided in the study:

$$ICER = \frac{\text{Cost tacrolimus– cost of steroids (4 weeks)}}{\text{Benefit tacrolimus – benefit steroids (4 weeks)}}$$

$$ICER = \frac{\text{US\$ 1323-1317}}{\text{190-194 DCD}} = \text{US\$ - 1.5/ per one disease controlled day}$$

This ICER means that HPTC used for 4 weeks slightly dominates tacrolimus, saving $1.5 for each disease-controlled day gained.
These results however considered the average wholesale price of potent steroids, but differences in prices of different types and brands of steroids were considerable, and not clearly equivalent to differences in effectiveness.

Authors comments
This systematic review has shown that tacrolimus is more effective than mild to moderate steroids for treating AD. Since high potency steroids are not used in the long-term we believe this to be the most relevant comparator for the bulk of health service provision.

The BNF for September 2003 gives a price for 0.1% tacrolimus of £21.60 for 30g. Hydrocortisone 0.1% (a mild corticosteroid) has a price of 66p for 30g and clobetasone butyrate (a moederately potent corticosteroid) costs £2.82 for 30g. Both are applied thinly twice daily. Using BNF figures would suggest that tacrolimus will be about 33 times as expensive as using hydrocortisone 0.1% and 7.5 times more expensive than using clobetasone butyrate. This suggests that the approximately equivalent costs used in the published economic evaluation are not applicable in the UK and thus this study's findings were it to be considered valid methodologically are not generalisable to the UK.

In view of the fact that the NCCHTA has commissioned a full HTA and economic evaluation to inform the NICE appraisal process it was not considered an appropriate use of resources for this group to develop and economic model. We therefore limited ourselves to estimating the cost per person "cured" (it must be remembered however that this is a recurrent disease).

The most optimistic calculation for a 75% improvement from baseline is an NNT is 3 (ignoring the fact that some trials fail to report an ITT analysis). Assuming that 30g is sufficient to treat a patient for a similar period to that in the trials, one can estimate the cost to have one additional patient reach this measure of "cure" as follows:

£21.60 X 3 = £64.80 to treat 3 patients with tacrolimus
£2.82 X 3 = £8.46 to treat 3 patients with clobetasone
£64.80 - £8.46 = £56.34/patient "cured"

4 Limitations of this technology assessment

4.1 Potential weaknesses

- Lack of double review for studies in Japanese., although data extracted wereverified with data published in the FDA web site.
- The exclusion from meta-analysis of some included studies because of a lack of complete information, even though contact with the pharmaceutical company was attempted, but without response, until the date of the conclusion of this report.
- Not all data available of different cut-off points was included in the sensitivity analysis.
- A complete economic-evaluation adapted to the UK context was not available
- It is difficult to assess the quality of life implications of the outcome measures used in trials and thereby derive a cost/QALY without considerable modelling being required.

4.1.1 Possible bias in this review

Publication bias in this review was explored with funnel plot graphs of baseline cases. For studies that compared tacrolimus with vehicle, graphs are presented in figures 12 and 13.

Figure 12 – Funnel plot of studies comparing tacrolimus 0.03% against vehicle

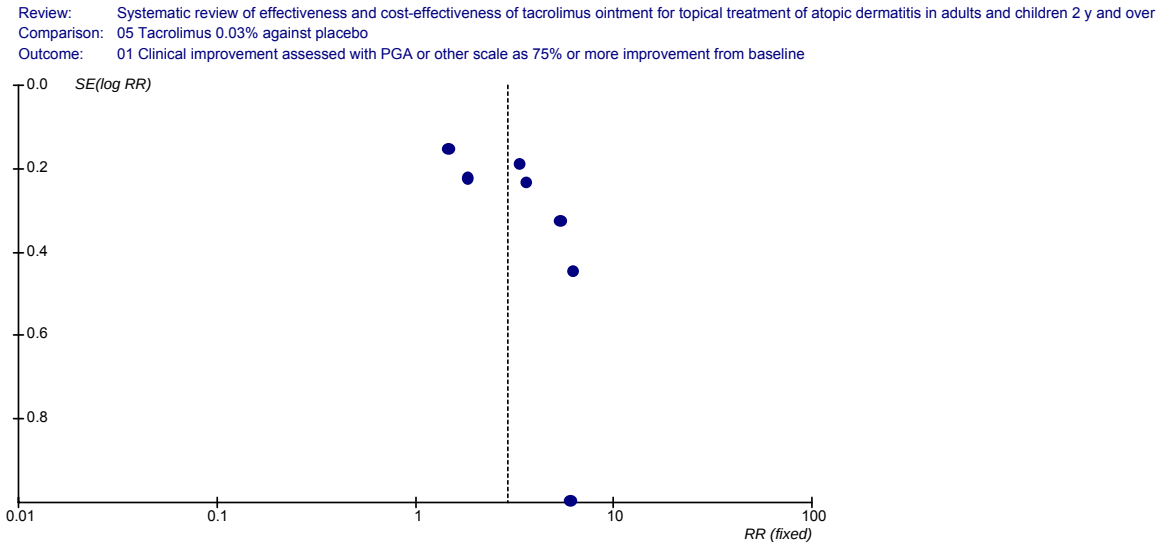
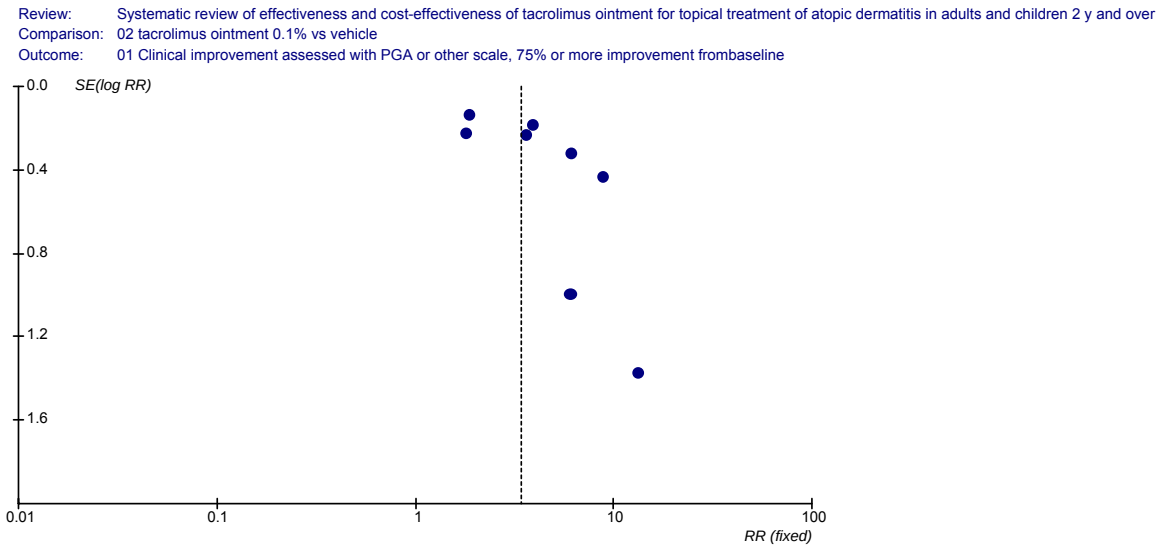


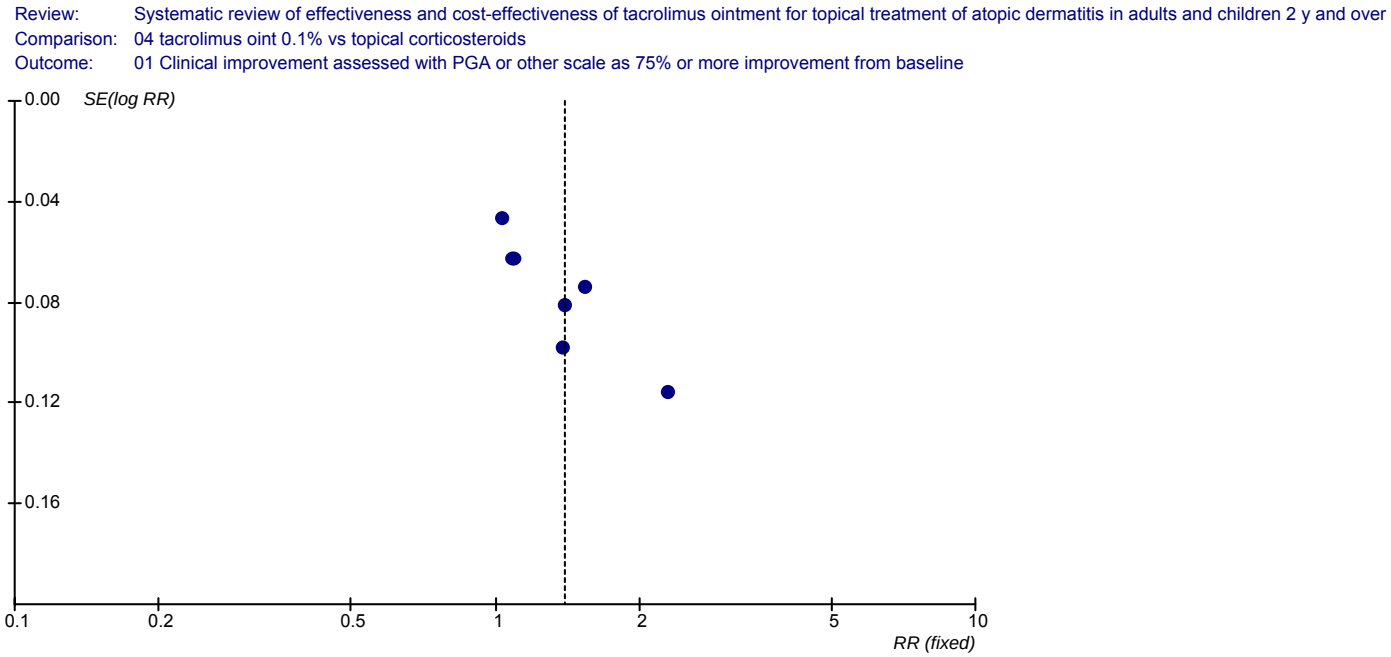
Figure 13 – Funnel plot of studies comparing tacrolimus 0.1% against vehicle



The funnel plots are asymmetrical in both cases, which could be due to true publication bias, and this review could have missed small studies causing a negative effect. However, as there are only a few studies considered asymmetry could also be explained by chance.

This is not clear also in the case of studies comparing tacrolimus with steroids, as only 6 studies had data to be considered (Figure No. 14).

Figure 14 – Funnel plot of studies comparing tacrolimus against steroids



5 Discussion and conclusions

Results from analysing 20 different trials revealed that tacrolimus ointment 0.03% and 0.1% are more effective than vehicle to treat AD in adults and children, however 0.1% did not demonstrate an incremental benefit when compared with tacrolimus 0.03% in children.

Additionally, using physician assessment-based scales to value results, tacrolimus ointment 0.1% was superior to mild and moderate potency topical steroids and slightly superior when compared with high-potency corticosteroids,

One-way sensitivity analysis changing the baseline cut-off point of the assessment of clinical improvement and adjusting the results by ITT analysis when it was not present reinforced the superiority of tacrolimus over mild steroids but decrease it when compared with high- potency corticosteroids. This gives less force to baseline findings with concern to the superiority of tacrolimus compared with these latter drugs.

However, these results are limited because 3 trials were excluded because lack of data to include them in the meta-analysis.

Moreover, most of the studies included in this review were short-term trials that assessed only the effectiveness of this drug over short periods of time. This is relevant considering the chronic condition of AD, where the assessment of effectiveness using a decreased rate of recurrences and increase of the quality of life of patients in the long-term could be clinically more relevant than only short-term improvement, as it has been referred also by other authors.

This short-term horizon does not allow assessing theoretical additional benefits of tacrolimus when compared with topical steroids related with adverse events observed with long-term use of these drugs. According to information provided by Fujisawa, ethical consideration limits the long-term use of steroids because adverse effects and thus, does not allow long-term comparative studies using these drugs.

Moreover, even if populations selected in most trials corresponded to patients with moderate to severe disease, there wasn't homogeneity in selection of patients according to the response to previous therapies. This is an important issue in deciding the indication of tacrolimus as a first or second-line therapy and to assess the license indication of the drug.

Finally, this review revealed a lack of economic evaluations in the UK setting up to April of 2003. Only one economic evaluation has been done to assess the cost-effectiveness of tacrolimus against an active therapy.

The study presents a proper CEA comparing tacrolimus against high-potency topical steroids, one of the most interesting comparator from the clinical point of view. The Markov model used seems appropriate for the cyclical characteristic of the disease. However, the study conclusions of the superiority of tacrolimus against HPTC used for 2 weeks and equivalence compared with its use for 4 weeks are not based on an incremental cost-effectiveness ratio estimation but on the average cost-effectiveness ratio. Moreover the relative costs of the two drugs are completely different to the UK context where corticosteroids are many times cheaper. Thus the results of this study does not allow us to conclude that tacrolimus is more cost-effective than HPTC.

5.1 Implications for other parties

5.1.1 The health system

Tacrolimus ointment is an effective therapy for moderate to severe AD in adults and children compared with vehicle and with mild to moderate potent steroids. Use of concentrations higher than 0.03% does not provide additional benefits in children.

The superior effectiveness of tacrolimus when compared with high-potency topical steroids is less clear and needs more primary research in the short term.

Given the limitations of the use of high-potency steroids in the long-term because adverse events, the most interesting comparator for tacrolimus could be mild steroids where tacrolimus has demonstrated superiority.

Conclusions about the cost-effectiveness of tacrolimus need additional research.

5.1.2 Patients and carers

Undoubtedly, patients and carers are most interested in long-term outcomes rather than short-term ones, especially those concerned with quality of life improvements. Tacrolimus is more effective than vehicle in the short-term and one study demonstrated that this is also true for quality of life, but additional evidence is needed to answer this when compared with other active therapies.

5.1.3 Suggestions for future research

The results of this review reveal that additionally primary research is required to assess the long-term effectiveness of tacrolimus, especially compared with relevant alternative therapies such as mild and mid-potency steroids.

Additionally, the selection of patients in the new trials should be directed to clarify the role of tacrolimus in standard therapy as a first or second line therapy.

An incremental cost –effectiveness analysis is needed to more fully inform decision makers and we anticipate that it will be available in the Technology Assessment Report commissioned to inform the NICE appraisal process by the end of next year (2004).

6 Appendices

Appendix 1 – Criteria for the diagnosis of atopic dermatitis

The Hanifin and Rajka Diagnosis Criteria for atopic dermatitis[4]

Must have 3 or more major features:

Pruritus
Typical morphology and distribution: flexural lichenification of linearity in adults; facial and extensor involvement in infants and children
Chronic or chronically relapsing dermatitis
Personal or family history of atopy (e.g. asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis)

Plus 3 or more minor features:
Xerosis
Itchthyosis/palmar
Immediate (type I) skin test reactivity
Elevated serum IgE
Early age of onset
Tendency towards cutaneous infections
Tendency towards non specific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie- Morgan infraorbital fold
Keratoconus
Anterior sub capsular cataracts
Orbital darkening
Facial pallor/ facial erythema
Pytiriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool or lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by environmental/ emotional factors
White, dermographism/ delayed blanch

Appendix 2 – Grading Score of Rajka and Langeland for Severity of Atopic Dermatitis [6]

Rajka and Langeland developed a simple scoring system for grading the severity of atopic dermatitis.

Parameters of the score:

116 **Extent**

116 Childhood and adult phase

- Less than approx. 9% of the body area 1
- Involvement evaluated to be more then score 1,

Less than score 3 2

- More than approx. 36% of the body area involved 3

b) Infantile phase

- Less than approx. 18% of the skin involved 1
- Involvement evaluated to be more than score 1,

Less than score 3 2

- More than 54% of the skin involved 3

2. COURSE

- More than 3 months of remission during a year* 1
- Less than 3 months remission during a year* 2
- Continuous course 3

3. INTENSITY

- Mild itch, only exceptionally disturbing night's sleep 1
- Itch, evaluated to be more than score 1, less than score 3 2

Severe itch, usually disturbing night's sleep 3

Score summation:
3- 4 = mild
4.5- 7.5 = moderate
8- 9 = severe
When doubt, score 1.5 or 2.5 may also be used.

*May be adjusted in infants or if onset was less than 1 year before grading.

Appendix 3 – Description of endpoints of clinical outcomes.

Physician's Global Assessment of clinical response (PGA) [43]

Level	% Improvement
Cleared	**100**
Excellent improvement	**90- 99**
Marked improvement	**75- 89**
Moderate improvement	**50- 74**
Slight improvement	**30- 49**
No appreciate improvement	**0- 29**
Worse	**< 0**

Eczema Area and Severity Index (EASI/ mEASI)

Erythema, edema-induration- papulation, excoriation and lichenification are rated by investigators on a scale of 0 to 3, 0= absent; 1 = mild; 2 = moderate and 3 = severe

The percentage of the total BSA affected by AD is estimated (0- 100%) for four body regions (head and neck, upper limbs, lower limbs and trunk).
Patients assessed the intensity of itching experienced during the previous 24 hours using a 10-cm visual analogue scale, with 0 cm indicating "no itching" and 10-cm indicating "worst itch imaginable". For each body region the following steps are carried out:

1. An affected area score of 0 to 6 is assigned for the percentage of affected BSA (0-100%)
2. The individual ratings for erythema, edema-induration-papulation, excoriations and lichenification are summed (0-3 for each of the four symptoms)
3. the sum of the individual symptoms (max=12) is multiplied by the affected area score (max =6) for a maximum of 72
4. For 2 to 6-yr olds, the head and neck subtotal was multiplied by 0.2, the upper limb subtotal by 0.2, the trunk subtotal by 0.3 and the lower limb subtotal by 0.4.
5. all components were summed (max EASI = 72)
6. the patients assessment of itching was converted to an ordinal scale from 0- 3 and then multiplied by the investigators total affected area score (0- 6) for a maximum itching score of 18. The EASI was summed with itching score for a maximum mEASI of 90.

Appendix 4 – Classification of steroids according to potency (extraction from Brazzini and Pimpinelli)[16]

Relative potency (concentration as % weight/weight) of topical steroids formulations.

Corticosteroids	**Potency**
Class 1 (very potent)	
Clobetasol propionate	0.05
Diflucortolone valerate	0.3
Fluocinolone acetonide	0.2
Halcinonide	0.1
Class 2 (potent)	
Betamethasone valerate	0.1
Budesonide	0.025
Hydrocortisone butyrate	0.1
Triamcinolone acetonide	0.1
Class 3 (moderate potent)	
Alclometasone dipropionate	0.05
Beclometasone dipropionate	0.025
Betamethasone benzoate	0.025
Betamethasone dipropionate	0.05
Betamethasone valerate	0.025 and 0.05
Clobetasone butyrate	0.05
Hydrocortisone butyrate	0.1
Hydrocortisone valerate	0.2
Class 4 (mild)	
Dexamethasone	0.01- 0.1
Hydrocortisone (alcohol or acetate)	0.1- 1
Methylprednisolone	0.25
Prednisolone	0.5

Appendix 5 – Amendments to protocol

116 Aim of the review was changed from:

“ To assess clinical effectiveness and cost effectiveness of tacrolimus ointment for the topical treatment of atopic dermatitis in adults and children 2 years and over.”

To:

This review aims to address the following issues:

To assess the efficacy and effectiveness of tacrolimus ointment for the topical treatment of atopic dermatitis in adults and children 2 years and over.

To assess the frequency and severity of adverse events associated with the use of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 years and over, compared with vehicle and corticosteroids.

To assess cost-effectiveness of tacrolimus ointment for the topical treatment of atopic dermatitis in adults and children 2 years and over.

II. In Methods.

Search

Journals to handsearch were not specified before

Inclusion/Exclusion criteria

The following exclusion criteria were added:

Studies where outcomes included *only* non-clinical parameters such as blood tests and/or cellular mechanism assessed by laboratory exams or biopsy.

Studies that compared only different dosage of tacrolimus without any different comparator

III.- Economic Analysis

In methods:

Instrument for critical appraisal was changed from checklist of Drummond et al[50] to a specific checklist for studies using modelling by Soto[1]

Appendix 6 – Search strategies

A Clinical Effectiveness

Search strategy for MEDLINE, via OVID with filter for RCT3 from Cochrane Library:

116 TACROLIMUS/
116 tacrolimus.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 FK506.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 protopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 1 or 2 or 3 or 4
116 Dermatitis, Atopic/
116 atopic dermatitis.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 atopic eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 Besnier's prurigo.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 neurodermatitis atopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 flexural eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 6 or 7 or 8 or 9 or 10 or 11
116 5 and 12
116 randomized controlled trial.pt.
116 controlled clinical trial.pt.
116 randomized controlled trials/
116 random allocation/
116 double blind method/
116 single blind method/
116 or/14-19
116 (animal not human).sh.
116 20 not 21
116 clinical trial.pt.
116 exp clinical trials/
116 (clin$ adj25 trial$).ti,ab.
116 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
116 placebos/
116 placebo$.ti,ab.
116 random$.ti,ab.
116 research design/
116 or/23-30
116 31 not 21
116 32 not 22
116 comparative study/
116 exp evaluation studies/
116 follow up studies/
116 prospective studies/
116 (control$ or enereal d $ or volunteer$).ti,ab.
116 or/34-38
116 39 not 21
116 39 not (22 or 33)
116 22 or 33 or 41
116 13 and 42

b) Search strategy for MEDLINE, via OVID with filter for RCT2 from Cochrane Library:

116 TACROLIMUS/
116 tacrolimus.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 FK506.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 protopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 1 or 2 or 3 or 4
116 Dermatitis, Atopic/
116 atopic dermatitis.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 atopic eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 Besnier's prurigo.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 neurodermatitis atopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 flexural eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 6 or 7 or 8 or 9 or 10 or 11
116 5 and 12
116 randomized controlled trial.pt.
116 controlled clinical trial.pt.
116 randomized controlled trials/
116 random allocation/
116 double blind method/
116 single blind method/

116 or/14-19
116 (animal not human).sh.
116 20 not 21
116 clinical trial.pt.
116 exp clinical trials/
116 (clin$ adj25 trial$).ti,ab.
116 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
116 placebos/
116 placebo$.ti,ab.
116 random$.ti,ab.
116 research design/
116 or/23-30
116 31 not 21
116 32 not 22
116 22 or 33
116 34 and 13

c) Search strategy for EMBASE, via OVID:

1. TACROLIMUS/ 2 tacrolimus.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 FK506.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 protopic.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 1 or 2 or 3 or 4
116 Dermatitis, Atopic/
116 atopic dermatitis.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 atopic eczema.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 Besnier's prurigo.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 neurodermatitis atopic.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 flexural eczema.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 6 or 7 or 8 or 9 or 10 or 11
116 5 and 12
116 randomized controlled trial/
116 exp clinical trial/
116 exp controlled study/
116 double blind procedure/
116 randomization/
116 placebo/
116 single blind procedure/
116 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
116 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
116 (placebo$ or matched communities or matched schools or matched populations).mp.
116 (comparison group$ or control group$).mp.
116 (clinical trial$ or random$).mp.
116 (quasiexperimental or quasi experimental or pseudo experimental).mp.
116 matched pairs.mp.
116 or/14-27
116 13 and 28 (140)

d) Search strategy for CENTRAL:
1. TACROLIMUS/ 2 tacrolimus.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 FK506.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 protopic.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 1 or 2 or 3 or 4
116 Dermatitis, Atopic/
116 atopic dermatitis.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 atopic eczema.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 Besnier's prurigo.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]

116 neurodermatitis atopic.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 flexural eczema.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 6 or 7 or 8 or 9 or 10 or 11
116 5 and 12

B Economic Analysis

Search strategy to localize cost studies in MEDLINE:

116 TACROLIMUS/
116 tacrolimus.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 FK506.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 protopic.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 1 or 2 or 3 or 4
116 Dermatitis, Atopic/
116 atopic dermatitis.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 atopic eczema.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 Besnier's prurigo.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 neurodermatitis atopic.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 flexural eczema.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
116 6 or 7 or 8 or 9 or 10 or 11
116 5 and 12
116 cost benefit analysis/
116 cost effectiveness analysis/
116 cost minimization analysis/
116 cost utility analysis/
116 economic evaluation/
116 (cost or costs or costed or costly or costing).tw.
116 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
116 (technology adj assessment$).tw.
116 or/14-21
116 13 and 22

Search strategy to localize cost studies in EMBASE:

116 TACROLIMUS/
116 tacrolimus.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 FK506.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 protopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 1 or 2 or 3 or 4
116 Dermatitis, Atopic/
116 atopic dermatitis.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 atopic eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 Besnier's prurigo.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 neurodermatitis atopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 flexural eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 6 or 7 or 8 or 9 or 10 or 11
116 economics/
116 exp "costs and cost analysis"/
116 cost of illness/
116 exp health care costs/
116 economic value of life/
116 exp economics medical/
116 exp economics hospital/
116 economics pharmaceutical/
116 exp "fees and charges"/
116 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
116 (expenditure$ not energy).tw.
116 (value adj1 money).tw.
116 budget$.tw.

116 or/13-25
116 26 and 12
116 5 and 12
26 and 28

Search strategy to find economic models in MEDLINE:

116 TACROLIMUS/
116 tacrolimus.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 FK506.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 protopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 1 or 2 or 3 or 4
116 Dermatitis, Atopic/
116 atopic dermatitis.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 atopic eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 Besnier's prurigo.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 neurodermatitis atopic.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 flexural eczema.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
116 6 or 7 or 8 or 9 or 10 or 11
116 5 and 12
116 decision support techniques/
116 markov.mp.
116 exp models economic/
116 decision analysis.mp.
116 cost benefit analysis/
116 or/14-18
13 and 19

Appendix 7 – Letter to a relevant author

Dr Sakari Reitamo
Department of Dermatology
Hospital for skin an Allergic Diseases
University of Helsinski
Meilahdentie 2
00250 Helsinski
Finland

Dear Dr Reitamo:

The West Midlands Health Technology Assessment Collaboration based at the Department of Public Health and Epidemiology at the University of Birmingham, England is working on a systematic review on the effectiveness of tacrolimus (Protopic ®) ointment for the treatment of atopic dermatitis. This review is being done in co-operation with the Cochrane Collaboration.

In our systematic search we have localized several studies were you are author or co-author. We would like to ask your help in identifying additional studies you know that have been done to assess effectively and effectiveness of this drug for atopic dermatitis and to let us know which of your published studies report which trials so that we do not double count trials.

We would also like to ask whether you would be willing to provide important data of your studies that we have been unable to find in the published literature.

Please find enclosed a list of the relevant articles. Where it corresponds, we have indicated the missing data.

Thank you very much for your help

Yours

Dr Blanca Penaloza
Department of Public Health and Epidemiology
University of Birmingham, UK

Appendix 8 – Inclusion / Exclusion criteria form

Effectiveness of tacrolimus ointment for treatment of atopic dermatitis in adults and children 2 years and over

Study No.:
Author:
Year: Journal:

Study design:	Is the study an RCT?	Y	N	U
Population:	Is the population patients adults or children 2 years or over with atopic dermatitis?	Y	N	U
Intervention	Is the intervention tacrolimus Ointment applied topically?	Y	N	U
Comparator	Is the comparator any topical Treatment (placebo, corticoids or other)	Y	N	U
Outcomes	Are outcomes: clinical improvement assessed by any clinical score or symptoms changes referred by the patient or the physician, or assessment of QoL or adverse effects? (Exclude studies where assessment has only include blood tests or cellular mechanisms)	Y	N	U

If all answers are Y → included
Conclusion:
__Excluded
__Included
__Unclear
Comments:

Appendix 9 – Quality assessment and data extraction form

116 **Identification**

Date :
Reviewer:
Study ID:
Author:
Year: Journal:

II.- Methodological quality of the study

Criteria	
1.Generation of randomisation sequence: 116 Adequate (computer generated or shuffled envelopes, tossed coins) 116 Unclear, insufficient details provided - Inadequate (DoB, case number, etc)	☐ ☐ ☐
2. Allocation concealment 116 Adequate (third party or opaque envelopes) 116 Unclear, insufficient details provided 116 Inadequate	☐ ☐ ☐
3.Blindness Assessor blinding. Adequate (outcome assessor is blinded and independent) 116 Unclear, insufficient details provided 116 Inadequate, assessor is aware of allocation Care provider 116 Adequate 116 Unclear, insufficient details provided 116 Inadequate, care provider is aware of allocation Patient Adequate 116 Unclear, insufficient details provided - Inadequate, patient is aware of allocation	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
3.ITT analysis and loss of follow up Adequate, ITT analysis with minimal missing outcome data 116 Unclear, insufficient details provided - Inadequate, non ITT analysis OR substantial missing outcome data	☐ ☐ ☐

III.- Methods

116 Study Design

a)Unit of randomisation (e.g. whole person, left/right arm, lesion):
b) Unit of analysis (e.g. whole person, left/ right arm lesion):
c) Design: parallel group/ cross over/ other (describe):

2.Participants

116 Setting (e.g. primary or secondary care)

b) Diagnostic criteria:
c) Disease severity:
e)Entry criteria

116 Interventions

	dose, frequency and duration
Intervention 1	
Intervention 2	
Intervention 3	
Intervention 4	

IV.- Results

116 Study participants. Description of the study population

	Interv 1	Interv 2	Interv 3	Interv 4l	Total	p- value
Number of participants randomized						
Age (No, %) 2- 15 years (mean, SD) 15 years (mean, SD)						
Sex (no, %) Male Female						
Severity of the condition (No. %)						
Race (No %)						
Duration of the disease						

b) Withdrawals

	Interv 1	Interv 2	Interv 3	Interv 3	Total
Number and % of withdrawals					
Reason for withdrawal 1) 2) 3) 4)					
Lost of follow up (No. %)					
Final number of participants assessed					

c) Outcomes

Principal outcome measures(e.g. complete resolution of symptoms) a) b)					
Methods of assessing outcome measures a) b)					
	Interv 1	Interv 2	Interv 3	Interv 4	p- value
Principal outcome a) result					
Principal outcome b) result					
Secondary outcome measure (e.g. itchiness, appearance) 1. 2. 3.					
Method of assessing secondary outcome measure 1. 2. 3.					

	Interv 1	Interv 2	Interv 3	Interv 4
Secondary outcome 1 result				
Secondary outcome 2 result				
Secondary outcome 3 result				
Side effects / adverse events reported. No. patients and No. events				
Assessment of compliance: yes / not stated / no Method:				

V.- Sponsorship

Declared Y / N / unsure if yes, who? _____

VI.- Comments

Appendix 10 – List of References of Excluded Studies with Reasons of Exclusion

Reference	Reason for exclusion
Tacrolimus – PrografI. *Drugs of the Future* 1997;**22**:926.Ref ID: 194	Non RCT
US FDA advisory committee recommends approval of tacrolimus ointment. *Skin Therapy Letter* 2000;**6**:5.Ref ID: 82	Non RCT
Tacrolimus ointment shows promising results in improving atopic eczema. *Pharmaceutical Journal* 2001;**267**:637.Ref ID: 148	Non RCT
Topical tacrolimus for treatment of atopic dermatitis. *Medical Letter on Drugs & Therapeutics* 2001;**43**:33-4.Ref ID: 47	Non RCT
Topical tacrolimus-a role in atopic dermatitis?. [Review] . *Drug & Therapeutics Bulletin* 2002;**40**:73-5. Ref ID: 74	Non RCT
Case histories in drug discovery and design 2001. *Drug News & Perspectives* 2002;**15**:60-4.Ref ID: 134	Non RCT
Topical pimecrolimus (Elidel) for treatment of atopic dermatitis. *Medical Letter on Drugs & Therapeutics* 2002;**44**:48-50. Ref ID: 22	No tacrolimus
Tacrolimus ointment better than topical steroids in atopic dermatitis. *Pharmaceutical Journal* 2002;**269**:517.Ref ID: 115	Non RCT
Ahmed I, Berth-Jones J, Bos JD. Topical tacrolimus and pimecrolimus are not associated with skin atrophy [11]. *British Journal of Dermatology* 2002;**146**:342-3.Ref ID: 133	Non RCT
Alaiti S, Kang S, Fiedler VC, Ellis CN, Spurlin DV, Fader D *et al*. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. *Journal of the American Academy of Dermatology* 1998;**38**:69-76. Ref ID: 67	Non RCT
Alak AM, Moy S, Cook M, Lizak P, Niggebiugge A, Menard S *et al*. An HPLC/MS/MS assay for tacrolimus in patient blood samples. Correlation with results of an ELISA assay. *Journal of Pharmaceutical & Biomedical Analysis* 1997;**16**:7-13.Ref ID: 90	Non RCT
Alak AM, Cook M, Bekersky I. A highly sensitive enzyme-linked immunosorbent assay for the determination of tacrolimus in atopic dermatitis patients. *Therapeutic Drug Monitoring* 1997;**19**:88-91. Ref ID: 69	Non RCT
Allen BR. Tacrolimus ointment: its place in the therapy of atopic dermatitis.[comment]. *Journal of Allergy & Clinical Immunology* 2002;**109**:401-3.Ref ID: 26	Non RCT
Alomar, A. Skin and environment- perception and protection, vols 1 and 2. 2001. 10-10-2001. Ref Type: Conference Proceeding Ref ID: 269	Non RCT
Aoyama H, Tabata N, Tanaka M, Uesugi Y, Tagami H. Successful treatment of resistant facial lesions of atopic dermatitis with 0.1% FK506 ointment [4]. *British Journal of Dermatology* 1995;**133**:494-6. Ref ID: 203	Non RCT (case report)
Assmann T, Homey B, Ruzicka T. Applications of tacrolimus for the treatment of skin disorders. [Review]. *Immunopharmacology* 2000;**47**:203-13. Ref ID: 60	Non RCT
Assmann T, Homey B, Ruzicka T. Topical tacrolimus for the treatment of inflammatory skin diseases. [Review] . *Expert Opinion on Pharmacotherapy* 2001;**2**:1167-75. Ref ID: 42	Non RCT
Augustin M, Brunella B, Klein M. Economic benefits of tacrolimus oinment versus topical enereal d e ds in the treatment of moderate to severe atopic dermatitis: a Markov Model. *Journal European Academy of Dermatology and Venereology* 2002;**16**:129. Ref ID: 235	Non RCT
Barzegar C,.Pradalier A. Therapeutic approach to atopic dermatitis. *Revue Francaise de Allergologie et de Immunologie Clinique* 2002 ;**42** :410-24. Ref ID: 125	Non RCT
Bekersky I, Boswell G, Ohara K, Kuroda Y, Sambuco C. Topical application of tacrolimus ointment did not alter the cutaneous pigmentation of enerea micropigs. *International Journal of Toxicology* 1998;**18**:19-21. Ref ID: 184	In Animals
Bekersky I, Fitzsimmons W, Tanase A, Maher RM, Hodosh E, Lawrence I. Nonclinical and early clinical development of tacrolimus ointment for the treatment of atopic dermatitis. [Review]. *Journal of the American Academy of Dermatology* 2001;**44**:S17-S27. Ref ID: 56	Non RCT
Bekersky I, Lilja H, Lawrence I. Tacrolimus pharmacology and nonclinical studies: from FK506 to enereal. [Review] *Seminars in Cutaneous Medicine & Surgery* 2001;**20**:226-32. Ref ID: 35	Non RCT
Beltrani VS. Tacrolimus ointment: advancing the treatment of atopic dermatitis. *Current Allergy & Asthma Reports* 2001;**1**:307-8. Ref ID: 30	Non RCT
Bergman J,.Rico MJ. Tacrolimus clinical studies for atopic dermatitis and other conditions. [Review] . *Seminars in Cutaneous Medicine & Surgery* 2001;**20**:250-9. Ref ID: 34	Non RCT

Bernard LA,.Eichenfield LF. Topical immunomodulators for atopic dermatitis. [Review] . *Current Opinion in Pediatrics* 2002;**14**:414-8. Ref ID: 18	Non RCT
Bernard LA, Bergman JN, Eichenfield LF. Pimecrolimus 1% cream (Elidel) for atopic dermatitis. *Skin Therapy Letter* 2002;**7**:1-3. Ref ID: 20	No tacrolimus
Bernard LA, Cunningham BB, Al Suwaidan S, Friedlander SF, Eichenfield LF. A rosacea-like granulomatous eruption in a patient using tacrolimus ointment for atopic dermatitis. *Archives of Dermatology* 2003;**139**:229-31. Ref ID: 72	Non RCT (case report)
Bernstein CN. Treatment of the extraintestinal manifestations of inflammatory bowel disease. [Review]. *Current Gastroenterology Reports* 2002;**4**:513-6. Ref ID: 2	Non RCT
Bieber T. Topical tacrolimus (FK 506): A new milestone in the management of atopic dermatitis. *Journal of Allergy & Clinical Immunology* 1998;**102**:555-7. Ref ID: 187	Non RCT
Bigby M. A thorough systematic review of treatments for atopic eczema. [Review] . *Archives of Dermatology* 2001;**137**:1635-6. Ref ID: 37	Non RCT
Bigby M. Editor's comment. *Archives of Dermatology* 2001;**137**:1636. Ref ID: 145	Non RCT
Bird J,.Montana J. New therapeutic approaches to atopic dermatitis. *Expert Opinion on Investigational Drugs* 1996;**5**:1173-80. Ref ID: 201	Non RCT
Bischoff A. New therapeutic approach of atopic eczema and psoriasis with immunosuppressive agents. *Pharmazeutische Zeitung* 1999;**144**:39-40. Ref ID: 181	Non RCT
Boguniewicz, M. Combination therapy and new directions for managing atopic dermatitis. 23, 243-246. 2002. Ref Type: Conference Proceeding Ref ID: 271	Non RCT
Bonifazi E. Anti-inflammatory topical drugs in atopic dermatitis. *European Journal of Pediatric Dermatology* 1998;**8**:157-60. Ref ID: 183	Non RCT
Bornhovd E, Burgdorf WH, Wollenberg A. Macrolactam immunomodulators for topical treatment of inflammatory skin diseases. [Review] . *Journal of the American Academy of Dermatology* 2001;**45**:736-43. Ref ID: 40	Non RCT
Bornhovd EC, Schuller E, Bieber T, Wollenberg A. The use of immunosuppressive macrolides in clinical dermatology. *Hautarzt* 2000;**51**:646-54. Ref ID: 173	Non RCT
Bornhovd EC, Burgdorf WH, Wollenberg A. Immunomodulatory macrolactams for topical treatment of inflammatory skin diseases. [Review] [60 refs]. *Current Opinion in Investigational Drugs* 2002;**3**:708-12. Ref ID: 7	Non RCT
Bos J. Topical tacrolimus and pimecrolimus are not associated with skin atrophy. *British Journal of Dermatology* 2002;**146**:342. Ref ID: 248	Non RCT
Boucher M. Tacrolimus ointment for the treatment of atopic dermatitis. *Issues in Emerging Health Technologies* 2001;1-4. Ref ID: 31	Non RCT
Boucher M. Tacrolimus ointment: For the treatment of atopic dermatitis. *Canadian Pharmaceutical Journal* 2001;**134**:28-31. Ref ID: 127	Non RCT
Brehler R, Hildebrand A, Luger TA. Recent developments in the treatment of atopic eczema. *Journal of the American Academy of Dermatology* 1997;**36**:983-94. Ref ID: 196	Non RCT
Brunner U, Gensthaler BM, Morck H. Seven newcomers on the drug market. *Pharmazeutische Zeitung* 2002;**147**:28-34. Ref ID: 110	Non RCT
Chamlin SL, Frieden IJ, Fowler A, Williams M, Kao J, Sheu M *et al*. Ceramide-dominant, barrier-repair lipids improve childhood atopic dermatitis [7]. *Archives of Dermatology* 2001;**137**:1110-2. Ref ID: 156	Non RCT
Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, Fluhr JW *et al*. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: Changes in barrier function provide a sensitive indicator of disease activity. *Journal of the American Academy of Dermatology* 2002;**47**:198-208. Ref ID: 117	Non RCT
Cheer SM,.Plosker GL. Tacrolimus ointment. A review of its therapeutic potential as a topical therapy in atopic dermatitis. [Review] [112 refs]. *American Journal of Clinical Dermatology* 2001;**2**:389-406. Ref ID: 32	Non RCT
Choi CJ,.Nghiem P. Tacrolimus ointment in the treatment of chronic cutaneous graft-vs-host disease: a case series of 18 patients. *Archives of Dermatology* 2001;**137**:1202-6. Ref ID: 43	Non RCT

Chuang T-Y, Brashear R, Wagner JD, Farmer ER. Principles of evidence-based management using stage I-II melanoma as a model. *International Journal of Dermatology* 2002;**41**:721-8. Ref ID: 108	No tacrolimus, No AD
De Tran QH, Guay E, Chartier S, Tousignant J. Tacrolimus in dermatology. [Review]. *Journal of Cutaneous Medicine & Surgery* 2001;**5**:329-35. Ref ID: 13	Non RCT
DiCarlo JB,.McCall CO. Pharmacological alternatives for severe atopic dermatitis. *International Journal of Dermatology* 2001;**40**:82-8. Ref ID: 165	Non RCT
Drummond A, Campbell FA, Roberts DT. Treatment of atopic eczema in adults and children. *Hong Kong Practitioner* 2002;**24**:480-9. Ref ID: 113	Non RCT
Duarte AM, Garzon MC, Laude T, Siegfried E, Winfield JPA. Proceedings of the Society for Pediatric Dermatology Meeting, Manchester Village, Vermont, August 8-11, 1996. *Pediatric Dermatology* 1997;**14**:158-64. Ref ID: 198	Non RCT
Dubertret L. Which steroids for the treatment of skin disorders on the face? *Journal of the European Academy of Dermatology & Venereology* 2002;**16**:121. Ref ID: 129	Non RCT
Ebihara N,.Suto H. Treatment of atopic blepharitis. *Folia Ophthalmologica Japonica* 2000;**51**:535-9. Ref ID: 172	Non RCT
Eedy DJ. What's new in atopic dermatitis? *British Journal of Dermatology* 2001;**145**:380-4. Ref ID: 151	Non RCT
Eichenfield LF, Lucky AW, Boguniewicz M, Langley RG, Cherill R, Marshall K *et al*. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents.[comment]. *Journal of the American Academy of Dermatology* 2002;**46**:495-504. Ref ID: 12	No tacrolimus
Eichenfield LF, Hanifin JM, Beck LA, Lemanske Jr RF, Sampson HA, Weiss ST *et al*. Atopic dermatitis and asthma: Parallels in the evolution of treatment. *Pediatrics* 2003;**111**:608-16. Ref ID: 91	Non RCT
Ellis CN, Drake LA, Prendergast MM, Abramovits W, Boguniewicz M, Daniel CR *et al*. Cost-effectiveness analysis of tacrolimus ointment versus high-potency topical corticosteroids in adults with moderate to severe atopic dermatitis. *Journal of the American Academy of Dermatology* 2003;**48**:553-63. Ref ID: 231	Non RCT (Economic evaluation)
Fleischer AB, Jr. Treatment of atopic dermatitis: role of tacrolimus ointment as a topical noncorticosteroidal therapy. [Review] [30 refs]. *Journal of Allergy & Clinical Immunology* 1999;**104**:S126-S130. Ref ID: 61	Non RCT
Frankel SJ,.Kerdel FA. Topical tacrolimus. *Skin Therapy Letter* 1995;**6**:1-2. Ref ID: 51	Non RCT
Fuchs M, Schliemann-Willers S, Heinemann C, Elsner P. Tacrolimus enhances irritation in a 5-day human irritancy in vivo model. *Contact Dermatitis* 2002;**46**:290-4. Ref ID: 75	Non RCT
Galli E, Cicconi R, Rossi P, Casati A, Brunetti E, Mancino G. Atopic dermatitis: Molecular mechanism, clinical aspects and new therapeutical approaches. *Current Molecular Medicine* 2003;**3**:127-38. Ref ID: 95	Non RCT
Geba GP, Ptak W, Askenase PW. Topical tacrolimus and cyclosporine A differentially inhibit early and late effector phases of cutaneous delayed-type and immunoglobulin E hypersensitivity. *Immunology* 2001;**104**:235-42. Ref ID: 77	Animals
Gescuk BD,.Davis Jr JC. Novel therapeutic agents for systemic lupus erythematosus. *Current Opinion in Rheumatology* 2002;**14**:515-21. Ref ID: 119	No AD
Gewirtz AT,.Sitaraman SV. Tacrolimus: Fujisawa. *Current Opinion in Investigational Drugs* 2002;**3**:1307-11. Ref ID: 98	No RCT
Ghura HS,.Camp RDR. Scarring molluscum contagiosum in patients with severe atopic dermatitis: Report of two cases [6]. *British Journal of Dermatology* 2001;**144**:1094-5. Ref ID: 139	Non RCT (case report)
Gianni LM,.Sulli MM. Topical tacrolimus in the treatment of atopic dermatitis. [Review] . *Annals of Pharmacotherapy* 2001;**35**:943-6. Ref ID: 44	Non RCT
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Wahn U, Bos JD, Goodfield M, Caputo R, Papp K, Manjra A *et al*. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics* 2002;**110**:e2. Ref ID: 21	No tacrolimus
Wahn V. Immunologic therapies in allergic disorders. *Allergologie* 2000;**23**:371-95. Ref ID: 174	No RCT
Wellington K,.Jarvis B. Topical pimecrolimus: a review of its clinical potential in the management of atopic dermatitis. [Review] [79 refs]. *Drugs* 2002;**62**:817-40. Ref ID: 23	No tacrolimus
Whalley D, Huels J, McKenna SP, Van Assche D. The benefit of pimecrolimus (Elidel, SDZ ASM 981) on parents' quality of life in the treatment of pediatric atopic dermatitis. *Pediatrics* 2002;**110**:1133-6. Ref ID: 10	No tacrolimus
Wollenberg A, Sharma S, von Bubnoff D, Geiger E, Haberstok J, Bieber T. Topical tacrolimus (FK506) leads to profound phenotypic and functional alterations of epidermal antigen-presenting dendritic cells in atopic dermatitis.[comment]. *Journal of Allergy & Clinical Immunology* 2001;**107**:519-25. Ref ID: 50	No RCT
Wollenberg, A. and Bieber, T. Topical immunomodulatory agents and their targets in inflammatory skin diseases. 33, 2212-2216. 2001. Ref Type: Conference Proceeding Ref ID: 272	No RCT
Woodhouse RJ. Report from Great Britain. *Pharmazeutische Industrie* 2003;**65**:53-8. Ref ID: 100	No RCT
Worm M. Novel therapies for atopic eczema. *Current Opinion in Investigational Drugs* 2002;**3**:1596-603. Ref ID: 99	No RCT
Worm M. New compounds for the treatment of eczematous skin diseases. *Expert Opinion on Therapeutic Patents* 2002;**12**:1023-33. Ref ID: 122	No RCT
Xiao T, Kagami S, Saeki H, Sugaya M, Kakinuma T, Fujita H *et al*. Both IL-4 and IL-13 inhibit the TNF-a and IFN-gamma enhanced MDC production in a human keratinocyte cell line, HaCaT cells. *Journal of Dermatological Science* 2003;**31**:111-7. Ref ID: 211	No RCT
Yudate T, Yajima A, Aragane Y, Yamazaki F, Kawada A, Tezuka T *et al*. Clinical effectiveness of tacrolimus ointment (Protopic) on atopic dermatitis other than facial lesions. *Skin Research* 2002;**1**:237-44. Ref ID: 92	No RCT
Zabawski EJ, Jr., Costner M, Cohen JB, Cockerell CJ. Tacrolimus: Pharmacology and therapeutic uses in dermatology. *International Journal of Dermatology* 2000;**39**:721-7. Ref ID: 171	No RCT

Appendix 11 – Publication mapped to studies reported

	Studies comparing tacrolimus against placebo	
Study Identification	**Reference**	**Report study**
68	Ruzicka et al . A short term trial of tacrolimus ointment for atopic dermatitis.NEJM 1997; 337:816-21	
53	Paller et al. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in paediatric patients. J Am Acad Dermatol 2001;44:S47-57	
55	Hanifin et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: Part 1, efficacy J Am Acad Dermatol 2001; 44 S28-38	
54	Soter et al.Tacrolimus ointment for the treatment of atopic dermatitis in adult patients:Part II, safety. J Am Acad Dermatol 2001; 44:S39-46	Same patients of study No.55 assessing a different outcome
15	Drake et al . The impact of tacrolimus ointment on health-related quality of life of adults and pediatric patients with atopic dermatitis	Report of a different outcome of same patients from studies 55 and 53
116	Fleischer et al. Tacrolimus ointment for the treatment of atopic dermatitis is not associated with an increase in cutaneous infections J Am Acad Dermatol 2002; 47: 562- 70)	Report of a different outcome of same patients from studies 55 and 53
245	Kang et al. Tacrolimus ointment for adults with moderate to severe AD: a dose escalation study. J Invest Dermatol, 1998, 110 (4): abst 681 (abstract No. 1253)	
247	Hanifin, JM Use of tacrolimus ointment in 3- 6 year olds with atopic dermatitis: dose –escalation study.(Abstract No. 1245) J Invest Dermatol 110, 4 abst 680	
232	Boguniewicz et al. A □enereal□d, vehicle- controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children J Allergy and Clin Immuno 1998; 102: 637- 44l	
250	Ohtsuki et al. Tacrolimus ointment is eefective and safe in Japanese atopic dermatitis children. Ann Dermatol Venereol 2002; 129:1S418 (abstract Po 242)	
263	FK506 ointment group. A late phase 2 study to determine the concentration of FK506. Nishinihon J of Dermatology 1997; 59: 427-35 (in Japanese)	
262	FK506 ointment study group. A late phase 2 study to determine the concentration of FK506. Nishinihon J of Dermatology, 1998; 60:685-98 (in Japanese)	

	Studies comparing tacrolimus against corticosteroids	
Study Identification	**Reference**	**Report study**
14	**Reitamo et al Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. J Allergy Clin Immunol 2002 ;109 : 539-546**	
242	**Rustin et al. Tacrolimus ointment shows greater efficacy than corticosteroids in the short term treatment of atopic dermatitis in children. J of European Academy of Dermatol and venereal. 2002. 16 (Suppl 1) :136 (abstract No. P2-42)**	**Abstract published of same data from study No. 14**
253	**Rustin M. Tacrolimus ointment (Protopic) shows superior efficacy and comparable safety in a short- term comparison vs corticosteroids in children with AD Ann Dermatol Venereol 2002; 129: 1S421 (abstact No. Po255)**	**Abstract published of same data from study No. 14**
254	Ruzicka et al Efficacy and safety of tacrolimus ointment (PROTOPIC) vs midpotent to potent corticosteroids in adults with moderate to severe AD. Ann Dermatol Venereol 2002; 129: 1S421 (abstract No. Po256)	
246	Gutgesell,C et al. Double-blind hydrocortisone-controlled tacrolimus ointment for atopic dermatitis. J Invest Dermatol 110(4) : abst 681 (abstract No. 1255)	
24	Reitamo et al Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with AD. J allergy Clin Immunol 2002;109: 547-55	
243	**Bos J, Reitamo S et al. Tacrolimus ointment twice a day is more effective than once daily application of standard corticosteroid therapy in children with atopic dermatitis. J European Acad of Dermatol and enereal. 2002 (Suppl.1): 137 (abstract P2-43)**	**Complete article in press (BJD)**
256	**Bos J, Reitamo S et al. Tacrolimus ointment (PROTOPIC) 0.03% twice daily as the therapy of choice in young pediatric patients (2-6 y) with moiderate to severe AD Ann Dermatol Venereol 2002; 129: 1S408 (abstract No. Po192)**	**Partial report of same data of study No. 243**
258	FK506 ointment study group. Phase 3 comparative study of FK506 ointment versus betamethasone. Nishinihon J of Dermatol 1997; 59:870-879 (in Japanese)	
264	**FK506 ointment study group. Phase 3 comparative study of FK506 ointment versus alclometasone. Acta Dermatol 1997; 92:277-88**	
265	**Nakagawa H et al. Comparative study of FK506 (tacrolimus) ointment vs alclometasone dipropionate ointment in atopic dermatitis (face and neck lesions) J Invest Dermatol 1998; 110 (4): Abst 683 (abstract No. 1266)**	**Not confirmed. Same data reported on study No. 264?**
285	Reitamo, S. 0.1% tacrolimus ointment is significant more efficacious than a steroid regimen in adults with moderate to severe atopic dermatitis. First EADV International Spring Symposium 27 feb.-1 March 2003 St Julian's, Malta, Abstract PP1- 28	

Appendix 12 – Main characteristics of studied populations

Main characteristics of study population in trials comparing tacrolimus against placebo

Study ID	Dg criteria	Severity of AD (% moderate/ severe) Tacrol. 0.03% Tacrol. 0.1% vehicle	Age Mean (SD) Tacrol. 0.03% Tacrol. 0.1% vehicle	Sex (% M/F) Tacrol. 0.03% acrol. 0.1% vehicle
55 Hanifin et al[28]	-Hanifin and Rajka -Rajka and Langeland	43.8/ 56.2 41.1/ 58.9 46.2/ 53.8	37.9 (± 13.8) 39.3 (±14.5) 38.5 (± 14)	45/ 55 40.7 /59.3 4.8/ 55.2
54 Soter et al[30]	-Hanifin and Rajka -Rajka and Langeland	43.8/ 56.2 41.1/ 58.9 46.2/ 53.8	37.9 (± 13.8) 39.3 (±14.5) 38.5 (± 14)	45/ 55 40.7 /59.3 4.8/ 55.2
68 Ruzicka et al[34]	Rajka and Langeland	100% moderate to severe	30 (± 12) 28 (± 12) 29 (± 11)	48/ 52 41 / 59 48/ 52
245Kang et al[35]	No specified	100% Moderate to severe. At least 76% of total body surface affected	Adults. Age not specified	Not specified
263FK506 oint group[49]	Not clearly stated	63/ 37 56/ 43 68/ 32	60.6 (± 10.4) 56 (± 9.2) 58.7 (± 12.5)	59/ 41 61 / 39 47/ 53
53 Paller et al[27]	-Hanifin and Rajka -Rajka and Langeland	38.5/ 61.5 36.4/ 63.6 40.5/ 59.5	2-6 y : 63.2% 58.5% 62.1% 7-15y : 36.8% 41.5% 37.9%	47/ 53 48.3/ 51.7 5.7/ 54.3
247 hanifin JMI [26]			60.6 (± 10.4) 56 (± 9.2) 58.7 (± 12.5)	59/ 41 61 / 39 47/ 53
232 Boguniewicz et al[36]	Hanifin and Rajka	88/ 12 86/ 14 73/ 27	10.2 (± 2.2) 10.8(± 2.7) 10.4 (± 2.9)	42/ 58 43 / 57 41/ 59
250 Ohtsuki et al[44]	No specified	100% moderate to severe	Paediatric patients. Age no specified	Not specified
15 Drake et al[29]	Rajka and Langeland	2-4 y: 66% severe 5-15y 50% severe >15 y 50% severe	2-4 y 16% 5-15y 20% >15 y 64%	50/50 50/50 50/50
116 Fleischer et l[33]	Hanifin and Rajka	Children: 38.5/61.5 36.4/63.3 45.7/54.3 Adults : 43.8/56.2 41.4/58.9 46.2/53.8	2-6 y : 63.2% 58.5% 62.1% 7-15y : 36.8% 41.5% 37.9% adults:38(±14.7) 39.3 (±14.5) 38.5 (±14)	Children: 47/53 48.3/51.7 45.7/54.3 Adults: 44.8/55.2 40.7/59.3 44.8/55.2

Main characteristics of study population in trials comparing tacrolimus against topical steroids

Study ID	Dg criteria	Severity of AD (% moderate/ severe) Tacrol. 0.03% Tacrol. 0.1% steroid	Age Mean (SD) Tacrol. 0.03% Tacrol. 0.1% steroid	Sex (% M/F) Tacrol. 0.03% Tacrol. 0.1% steroid
24 Reitamo et al[42]	-Hanifin and Rajka -Rajka and Langeland	46.1/ 53.9 50.8/ 49.2 44.6/ 55.4	31.1 (± 11.5) 32.4 (±11.4) 30.8 (± 10.3)	43.5/ 56.5 42.9 / 57.1 46.8/ 53.2
258 FK506 oint. Study group[46]	Hanifin and Rajka -Rajka and Langeland	**----** **51/49** **61/39**	------ 25.9 (±5.7) 26.3 (± 7.6)	-------- 44 / 56 64/ 36
262 Fk 506 oint study group[37]	**Not clear stated**	**61/39** **84/16** **80/20**	58.7 (± 12.5) 60.6 (±10.4) 25.3 (± 6.5)	63/ 37 58 / 42 70/ 30
246Gutgesell et al[39]	**Not specified**	**100% severe**	**Adults 22- 36 y**	**Not specified**
264 FK506 oint.study group[47]	Hanifin and Rajka -Rajka and Langeland	**------ 63/37** **76/24**	------ 25.6 (±7.8) 25.9 (± 8)	-------- 51 / 49 41/ 59
265 Nakagawa et al[38]	**Not specified**	**Face and neck lesions** **Not specification of severity**	**Not specified**	**Not specified**
14 Reitamo et al[41]	-Hanifin and Rajka -Rajka and Langeland	60.8/39.2 54.3/ 45.7 51.4/ 48.6	7.6 (± 3.9) 7.6 (±4.4) 7.2 (± 4)	40.2/ 59.8 51.6 /48.4 51.4/ 48.6
243 Bos et al[48]	-Hanifin and Rajka -Rajka and Langeland	Tacrol. 0.03% UIB: 52.2/47.8 Tacrol. 0.03% BID: 52.9/46.7 Hydrocortisone UIB: 44.9/55.1	Tacrol. 0.03% UIB: 6.7 (±3.9) Tacrol. 0.03% BID: 6.9 (±4.2) Hydrocortisone UIB: 7.2 (±4.1)	Tacrol. 0.03% UIB: 48.3/ 51.7 Tacrol. 0.03% BID: 45.2/ 54.8 Hydrocortisone UIB: 51.7/48.3
285 Reitamo[45]	Not specified	100% moderate to severe	Not specified	Not specified

Appendix 13 – Incidence of Main Adverse Events in Included Trials Comparing Tacrolimus with vehicle

Study ID	Adverse events Application site (Tacrolimus 0.03%)	Adverse events Non Application site	Adverse events Application site (Tacrolimus 0.1%)	Adverse events Non Application site	Adverse events Application site (vehicle)	Adverse events Non Application site
55 Hanifin et al[28]	Reported in Soter et al					
54 Soter et al[30]	Skin burning 96/210 Pruritus 97/210 Skin erythema 52/210	Flu syndrome 49/210 Headache 42/210 Alcohol intolerance7/210	Skin burning 121/209 Pruritus 96 Skin eryt 58/209	Headache 40/209 Flu syndrome 64/212 Alcohol intolerance 14/209	Pruritus : 77/212 Skin b: 55/212 Skin erythema: 24/212	Headache 23/212 Flu syndrome 41/212 Allergic reaction 6.5
68 Ruzicka et al[34]	Burning 20/54 Pruritus 7/54 Eryht 3/54	Exacerbation AD 4/54	Burning 25/54 Pruritus 2/54 Eryht 6/54	Exacerbation AD 4/54	Burning 8/54 Pruritus 4/54 Erythema 3/54	Exacerbation AD 7/54
245Kang et al[35]	Skin burning Pruritus folliculitis		Skin burning Pruritus folliculitis		Skin burning Pruritus folliculitis	
263FK506 oint group[49]	No reported					
53 Paller et al[27]	Skin burning 50/118 Pruritus 47/118	Varicella 6/118 Vesiculobulbar rash 4/118 Sinusitis 4/118	Skin burning 40/118 Pruritus 38/118	Varicella 1/118 Vesiculobulbar rash 1/118 Sinusitis 1/118	Skin burning 34/116 Pruritus 31/116	Sinusitis 9/116
247 Hanifin JMI [26]	No clearly specified					
232 Boguniewicz et al[36]	Skin burning 9/43 Pruritus 11/43 Erythema 0	0	Skin burning 5//49 Pruritus 10/49 Erythema 1/49	0	Skin burning 3/44 Pruritus 7/49 Erythema 2/49	0
250 Ohtsuki et al[44]	No reported					
15 Drake et al[29]	Overall cutaneous infection Ad: 52/210 Ch: 23/117		Overall cutaneous infection Ad: 37/209 Ch: 28/118		Overall cutaneous infection Ad: 38/212 Ch: 24/116	

Adverse Events in Studies Comparing Tacrolimus with Steroids

Study ID	Adverse events Application site (Tacrolimus 0.1%)	Adverse events Non Application site	Adverse events Application site (steroids)	Adverse events Non Application site
24 Reitamo et al [42]	Skin burning 113/187 Pruritus 29/187 Folliculitis 15/187	Flu syndrome 12/ 187 Headache 9/187 Allergic reaction 5/187	Skin burning 24/ 183 Pruritus 18/183 Folliculitis 13/183	Headache 14/183 Flu syndrome 12/183 Allergic reaction 12/ 183
258 FK506 oint. Study group[46]	No reported			
262 Fk 506 oint study group[37]	No reported			
246Gutgesell et al[39]	Skin burning in 2/7		0	
264 FK506 oint.study group[47]	No reported			
265 Nakagawa et al[38]	No reported			
14 Reitamo et al[31]	Skin burning 38 /186 Pruritus 21/186 Folliculitis 8/ 186	Flu syndrome 14/ 186 Rhinitis 6/ 186 Diarrhea 5/ 186 Fever 1/ 186	Skin burning 13 /185 Pruritus 14/ 185 Folliculitis 5/ 185	Flu syndrome 16/ 185 Fever 8/ 185 Rhinitis 4/ 185
243 Bos et al[48]	Tacrol. 0.03% UID Skin burning 48/207 Pruritus 38/207 Tacrol. 0.03% BID Skin burning 50/210 Pruritus 45/210	Tacrol. 0.03% UID Flu syndrome 6/ 207 skin erythema 6/207 fever 5/207 Tacrol. 0.03% BID Flu syndrome 12/210 skin erythema 6/210 fever 5/210	Skin burning 30/207 Pruritus 33/207	Flu syndrome 11/207 skin erythema 2/207 fever 4/207
285 Reitamo[45]	Mild to moderate skin burning more often than steroids		Mild to moderate skin burning more often than steroids.	

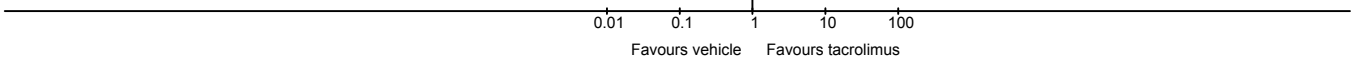
Appendix 14 - Meta-analysis graphs

I.- Meta-analysis of tacrolimus against vehicle.

Tacrolimus 0.03% versus vehicle in adults and children, RR with random- effect model.

Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 05 Tacrolimus 0.03% against placebo
Outcome: 01 Clinical improvement assessed with PGA or other scale as 75% or more improvement from baseline

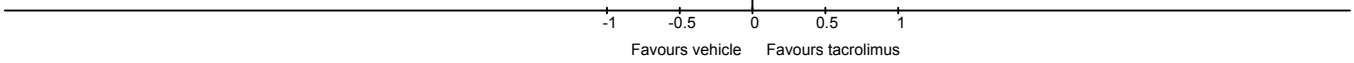
Study or sub-category	Tacrolimus 0.03% n/N	vehicle n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
01 Adults						
263. FK506 oint stud	48/67	31/63		18.42	1.46 [1.09, 1.95]	1997
68. Ruzicka et al	31/54	5/54		11.62	6.20 [2.61, 14.74]	1997
245. Kang S	0/8	0/6			Not estimable	1998
55. Hanifin et al	92/211	30/212		17.67	3.08 [2.14, 4.44]	2001
Subtotal (95% CI)	340	335		47.71	2.80 [1.29, 6.11]	
Total events: 171 (Tacrolimus 0.03%), 66 (vehicle)						
Test for heterogeneity: Chi² = 19.02, df = 2 (P < 0.0001), I² = 89.5%						
Test for overall effect: Z = 2.59 (P = 0.010)						
02 Children						
232. Boguniewicz	30/43	16/42		16.90	1.83 [1.19, 2.82]	1998
247. Hanifin	6/11	1/11		4.32	6.00 [0.86, 41.96]	1998
53. Paller et al	65/117	18/116		16.65	3.58 [2.27, 5.64]	2001
250. Ohtsuki	49/74	9/73		14.42	5.37 [2.85, 10.11]	2002
Subtotal (95% CI)	245	242		52.29	3.33 [1.86, 5.96]	
Total events: 150 (Tacrolimus 0.03%), 44 (vehicle)						
Test for heterogeneity: Chi² = 10.09, df = 3 (P = 0.02), I² = 70.3%						
Test for overall effect: Z = 4.05 (P < 0.0001)						
Total (95% CI)	585	577		100.00	3.05 [1.93, 4.81]	
Total events: 321 (Tacrolimus 0.03%), 110 (vehicle)						
Test for heterogeneity: Chi² = 33.15, df = 6 (P < 0.00001), I² = 81.9%						
Test for overall effect: Z = 4.78 (P < 0.00001)						



2. Tacrolimus 0.03% versus vehicle, RD with random-effect model

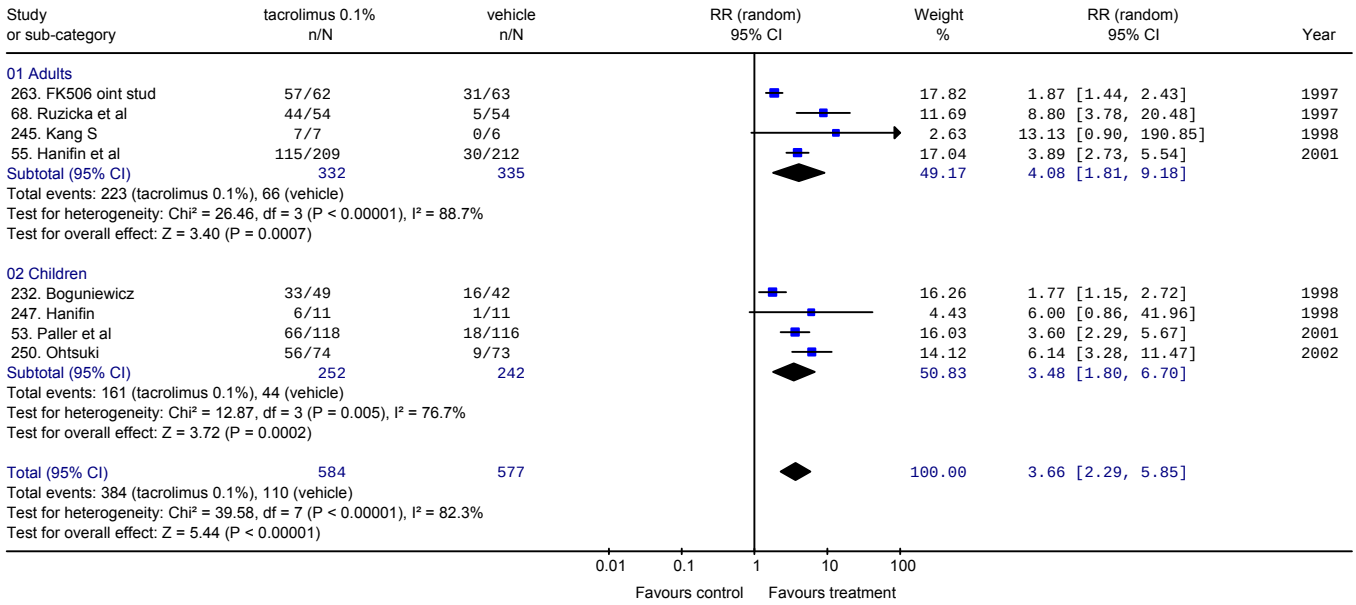
Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 05 Tacrolimus 0.03% against placebo
Outcome: 01 Clinical improvement assessed with PGA or other scale as 75% or more improvement from baseline

Study or sub-category	Tacrolimus 0.03% n/N	vehicle n/N	RD (random) 95% CI	Weight %	RD (random) 95% CI	Year
01 Adults						
263. FK506 oint stud	48/67	31/63		12.83	0.22 [0.06, 0.39]	1997
68. Ruzicka et al	31/54	5/54		13.44	0.48 [0.33, 0.63]	1997
245. Kang S	0/8	0/6		9.12	0.00 [-0.24, 0.24]	1998
55. Hanifin et al	92/211	30/212		17.30	0.29 [0.21, 0.38]	2001
Subtotal (95% CI)	340	335		52.68	0.27 [0.12, 0.42]	
Total events: 171 (Tacrolimus 0.03%), 66 (vehicle)						
Test for heterogeneity: Chi² = 12.19, df = 3 (P = 0.007), I² = 75.4%						
Test for overall effect: Z = 3.54 (P = 0.0004)						
02 Children						
232. Boguniewicz	30/43	16/42		10.94	0.32 [0.12, 0.52]	1998
247. Hanifin	6/11	1/11		6.02	0.45 [0.11, 0.79]	1998
53. Paller et al	65/117	18/116		15.73	0.40 [0.29, 0.51]	2001
250. Ohtsuki	49/74	9/73		14.62	0.54 [0.41, 0.67]	2002
Subtotal (95% CI)	245	242		47.32	0.44 [0.34, 0.53]	
Total events: 150 (Tacrolimus 0.03%), 44 (vehicle)						
Test for heterogeneity: Chi² = 4.14, df = 3 (P = 0.25), I² = 27.6%						
Test for overall effect: Z = 8.86 (P < 0.00001)						
Total (95% CI)	585	577		100.00	0.35 [0.25, 0.45]	
Total events: 321 (Tacrolimus 0.03%), 110 (vehicle)						
Test for heterogeneity: Chi² = 24.03, df = 7 (P = 0.001), I² = 70.9%						
Test for overall effect: Z = 6.81 (P < 0.00001)						



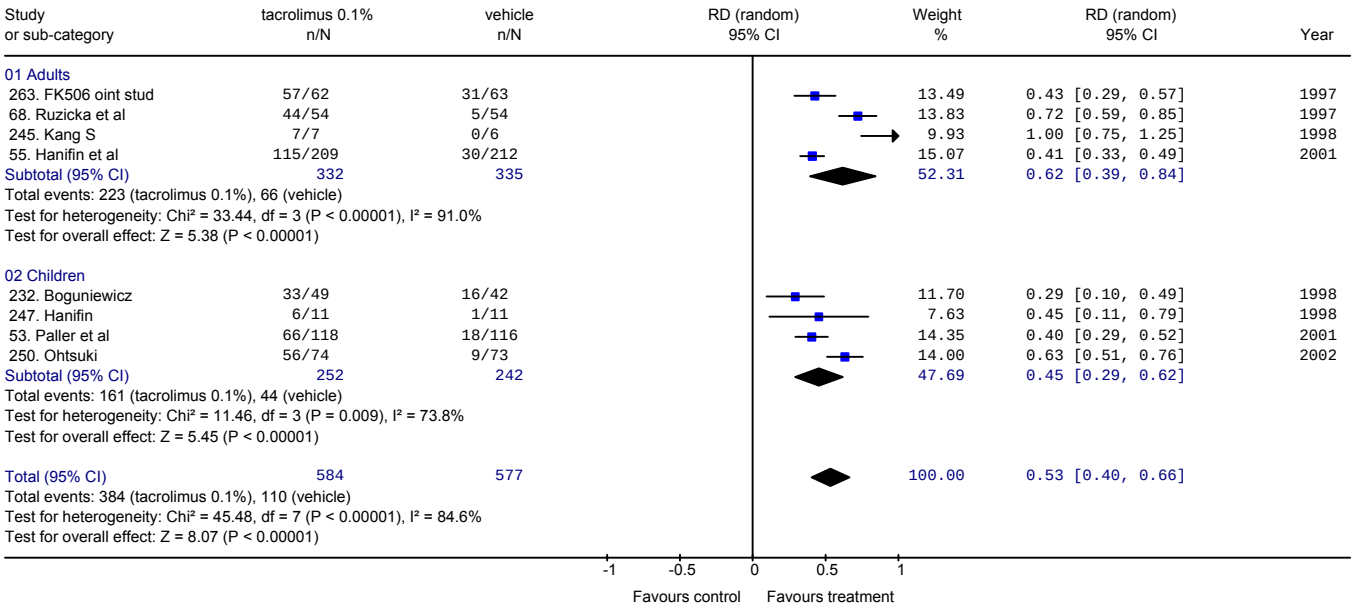
3. Tacrolimus 0.1% against vehicle, RR and random-effect model

Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 02 tacrolimus ointment 0.1% vs vehicle
Outcome: 01 Clinical improvement assessed with PGA or other scale, 75% or more improvement frombaseline



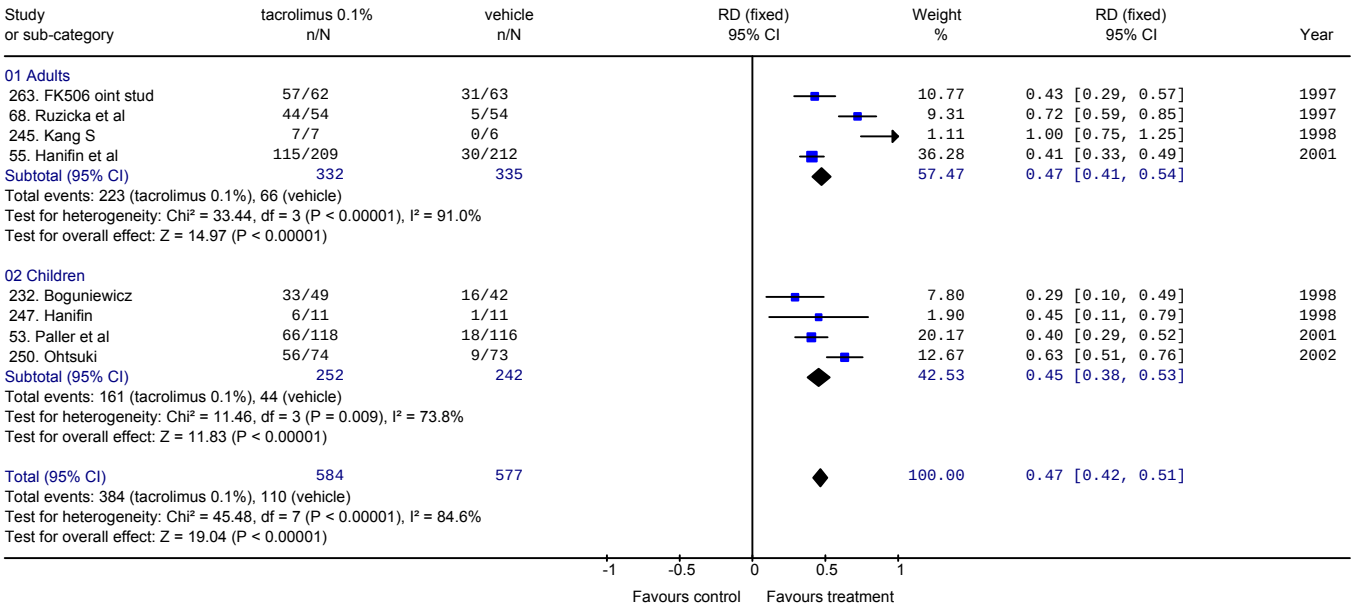
Tacrolimus 0.1% against vehicle, RD with random-effect model

Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 02 tacrolimus ointment 0.1% vs vehicle
Outcome: 01 Clinical improvement assessed with PGA or other scale, 75% or more improvement frombaseline



5. Tacrolimus 0.1% against vehicle, RD with fixed-effect model

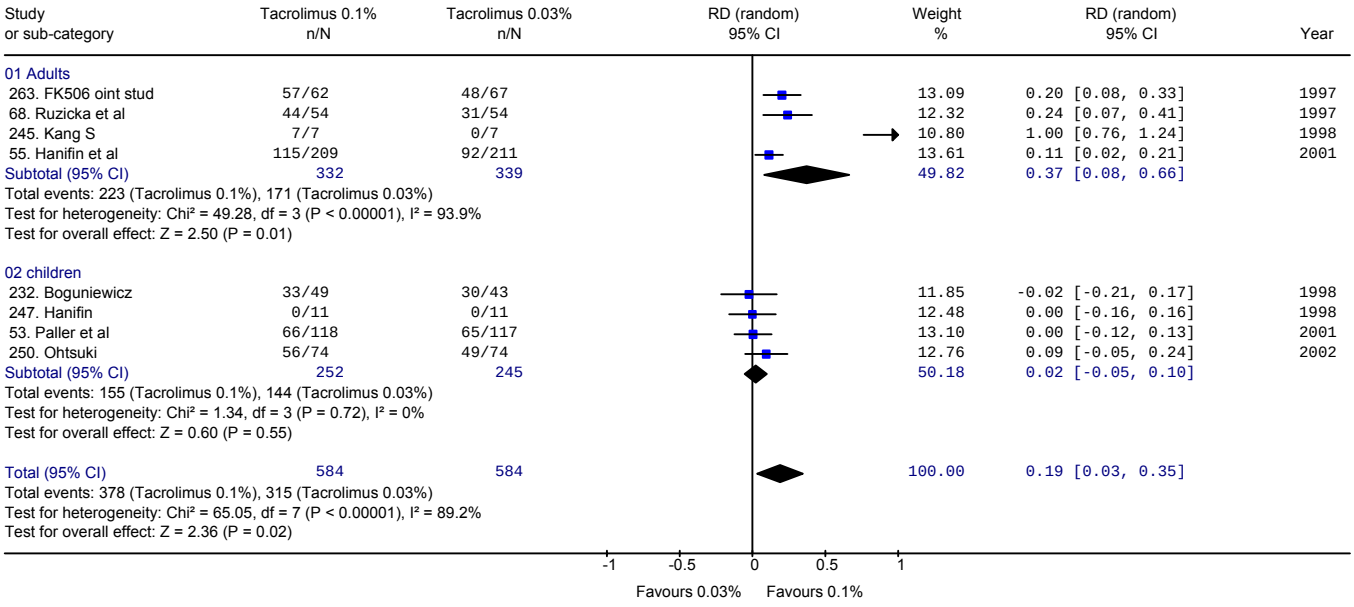
Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 02 tacrolimus ointment 0.1% vs vehicle
Outcome: 01 Clinical improvement assessed with PGA or other scale, 75% or more improvement frombaseline



II.- Tacrolimus 0.03% versus 0.1%

1. Tacrolimus 0.03% versus 0.1% using RD with random-effect model

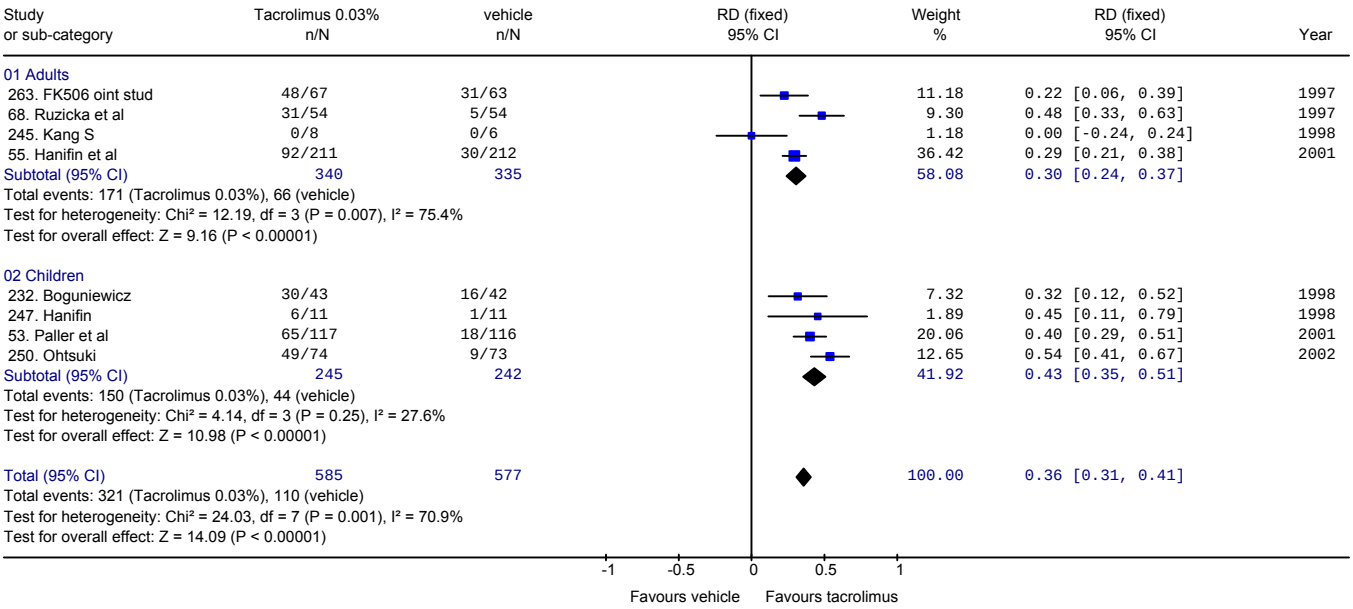
Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 03 Tacrolimus ointment 0.03% against tacrolimus oint. 0.1%
Outcome: 01 Clincal improvement assessed with PGA or other scale, 75% or more improvement fom baseline



2. Tacrolimus 0.03% versus 0.1% using RD with fixed-effect model

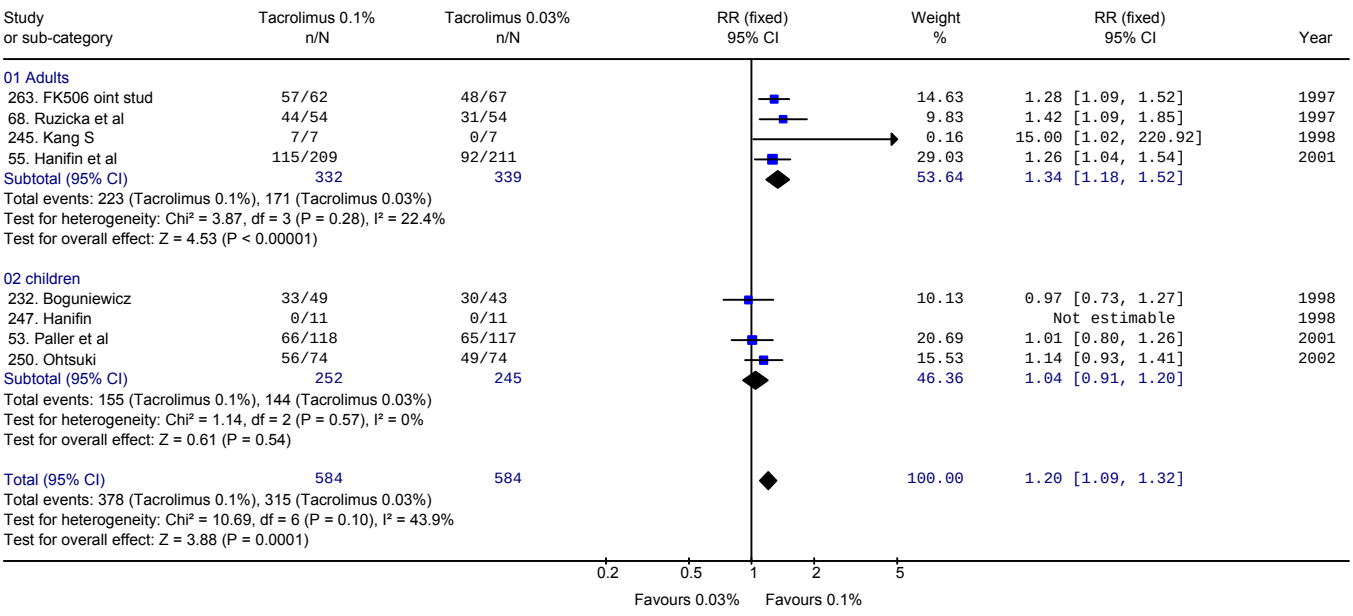
.

Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 05 Tacrolimus 0.03% against placebo
Outcome: 01 Clinical improvement assessed with PGA or other scale as 75% or more improvement from baseline



3. Tacrolimus 0.03% versus 0.1% using RR with fixed effect model

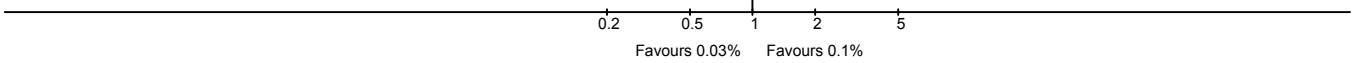
Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 03 Tacrolimus ointment 0.03% against tacrolimus oint. 0.1%
Outcome: 01 Clincal improvement assessed with PGA or other scale, 75% or more improvement fom baseline



4. Tacrolimus 0.03% versus 0.1% using RR with random effect model

Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 03 Tacrolimus ointment 0.03% against tacrolimus oint. 0.1%
Outcome: 01 Clincal improvement assessed with PGA or other scale, 75% or more improvement fom baseline

Study or sub-category	Tacrolimus 0.1% n/N	Tacrolimus 0.03% n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
01 Adults						
263. FK506 oint stud	57/62	48/67		21.29	1.28 [1.09, 1.52]	1997
68. Ruzicka et al	44/54	31/54		13.59	1.42 [1.09, 1.85]	1997
245. Kang S	7/7	0/7		0.21	15.00 [1.02, 220.92]	1998
55. Hanifin et al	115/209	92/211		18.59	1.26 [1.04, 1.54]	2001
Subtotal (95% CI)	332	339		53.68	1.31 [1.14, 1.51]	
Total events: 223 (Tacrolimus 0.1%), 171 (Tacrolimus 0.03%)						
Test for heterogeneity: Chi² = 3.87, df = 3 (P = 0.28), I² = 22.4%						
Test for overall effect: Z = 3.82 (P = 0.0001)						
02 children						
232. Boguniewicz	33/49	30/43		12.71	0.97 [0.73, 1.27]	1998
247. Hanifin	0/11	0/11			Not estimable	1998
53. Paller et al	66/118	65/117		16.00	1.01 [0.80, 1.26]	2001
250. Ohtsuki	56/74	49/74		17.61	1.14 [0.93, 1.41]	2002
Subtotal (95% CI)	252	245		46.32	1.05 [0.92, 1.20]	
Total events: 155 (Tacrolimus 0.1%), 144 (Tacrolimus 0.03%)						
Test for heterogeneity: Chi² = 1.14, df = 2 (P = 0.57), I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)	584	584		100.00	1.19 [1.05, 1.34]	
Total events: 378 (Tacrolimus 0.1%), 315 (Tacrolimus 0.03%)						
Test for heterogeneity: Chi² = 10.69, df = 6 (P = 0.10), I² = 43.9%						
Test for overall effect: Z = 2.69 (P = 0.007)						

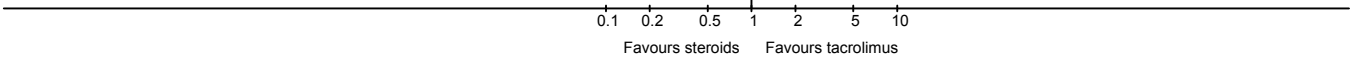


III. Tacrolimus against steroids

1. Tacrolimus against steroids using RR and fixed effect model

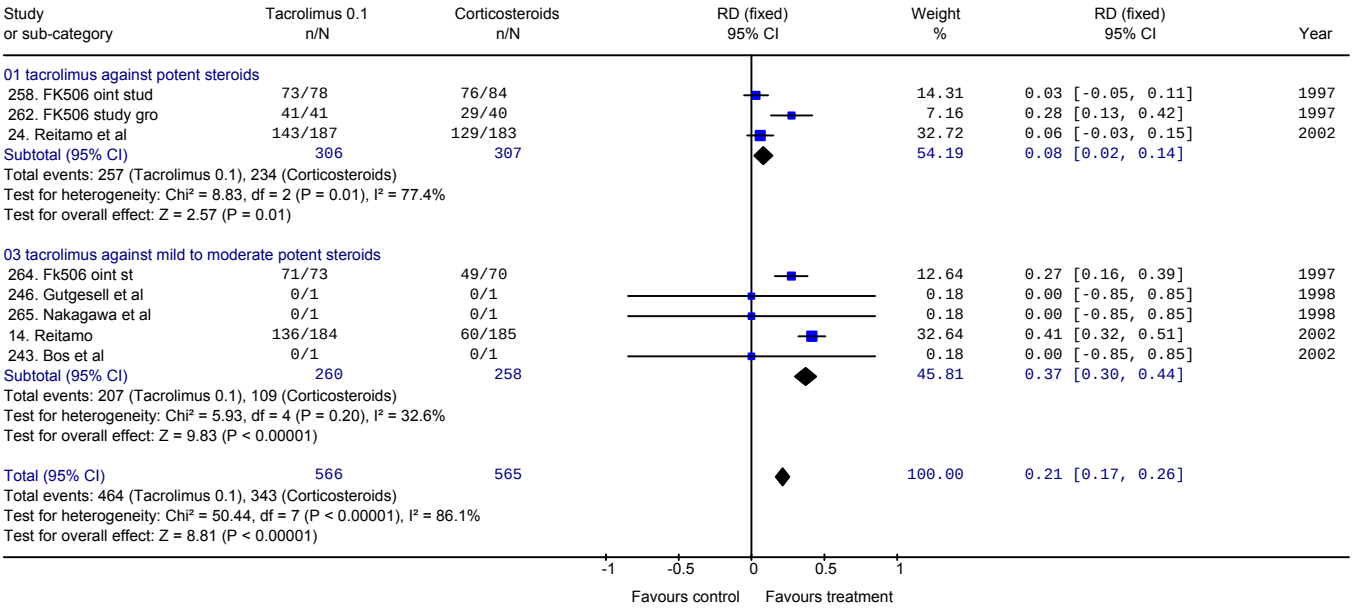
Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 04 tacrolimus oint 0.1% vs topical corticosteroids
Outcome: 01 Clinical improvement assessed with PGA or other scale as 75% or more improvement from baseline

Study or sub-category	Tacrolimus 0.1 n/N	Corticosteroids n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Year
01 tacrolimus against potent steroids						
258. FK506 oint stud	73/78	76/84		16.16	1.03 [0.94, 1.13]	1997
262. FK506 study gro	41/41	29/40		6.48	1.38 [1.14, 1.67]	1997
24. Reitamo et al	143/187	129/183		28.79	1.08 [0.96, 1.23]	2002
Subtotal (95% CI)	306	307		51.44	1.11 [1.02, 1.20]	
Total events: 257 (Tacrolimus 0.1), 234 (Corticosteroids)						
Test for heterogeneity: Chi² = 7.34, df = 2 (P = 0.03), I² = 72.8%						
Test for overall effect: Z = 2.53 (P = 0.01)						
03 tacrolimus against mild to moderate potent steroids						
264. Fk506 oint st	71/73	49/70		11.05	1.39 [1.19, 1.63]	1997
14. Reitamo	136/184	60/185		13.21	2.28 [1.82, 2.85]	2002
243. Bos et al	170/210	109/206		24.30	1.53 [1.32, 1.77]	2002
Subtotal (95% CI)	467	461		48.56	1.70 [1.53, 1.89]	
Total events: 377 (Tacrolimus 0.1), 218 (Corticosteroids)						
Test for heterogeneity: Chi² = 14.87, df = 2 (P = 0.0006), I² = 86.6%						
Test for overall effect: Z = 10.04 (P < 0.00001)						
Total (95% CI)	773	768		100.00	1.40 [1.31, 1.49]	
Total events: 634 (Tacrolimus 0.1), 452 (Corticosteroids)						
Test for heterogeneity: Chi² = 77.99, df = 5 (P < 0.00001), I² = 93.6%						
Test for overall effect: Z = 9.86 (P < 0.00001)						



2. Tacrolimus 0.1% against steroids using RD and fixed effect model

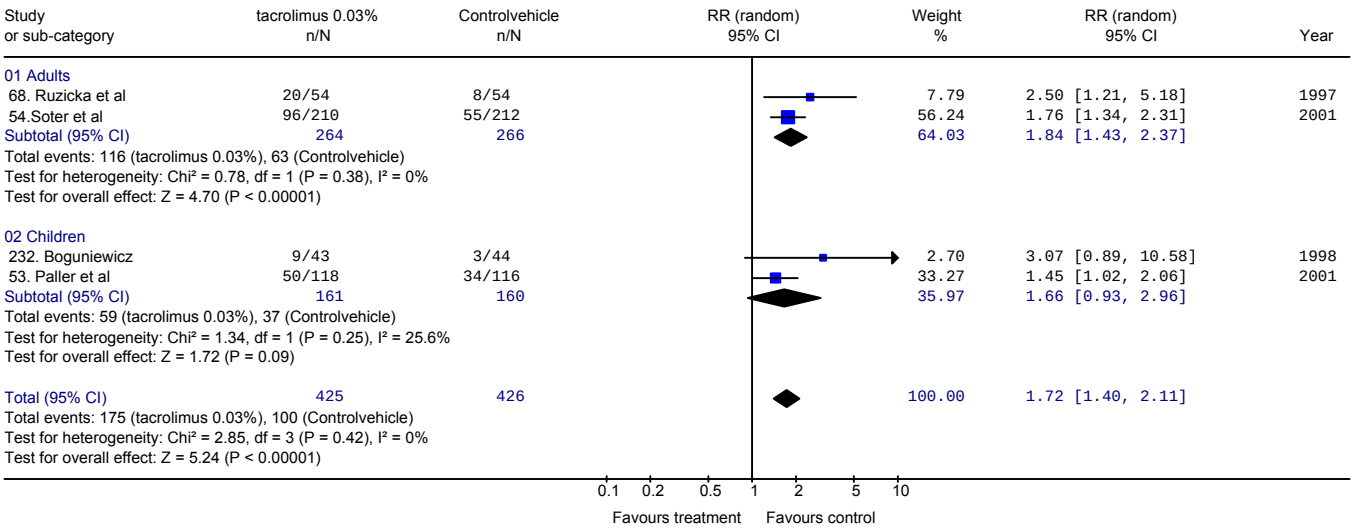
Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 04 tacrolimus oint 0.1% vs topical corticosteroids
Outcome: 01 Clinical improvement assessed with PGA or other scale as 75% or more improvement from baseline



IV. Meta-analysis comparing Incidence of adverse events

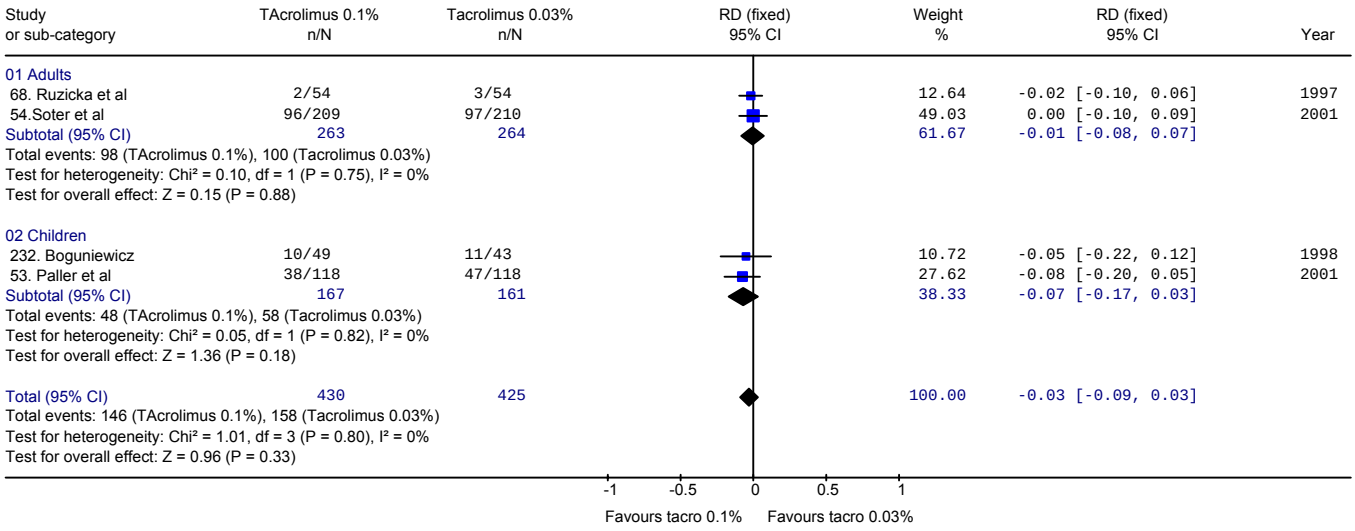
1. Meta-Analysis Comparing Incidence of Skin Burning with Tacrolimus 0.03% and Vehicle in Adults and Children Using RR And Random-Effect Model

Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 05 Tacrolimus 0.03% against placebo
Outcome: 03 Incidence rate of most frequent adverse events: skin burning



2. Meta-Analysis Comparing Incidence of Skin Burning with Tacrolimus 0.03% and 0.1% in Adults and Children Using RD And Fixed-Effect Model

Review: Systematic review of effectiveness and cost-effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis in adults and children 2 y and over
Comparison: 03 Tacrolimus ointment 0.03% against tacrolimus oint. 0.1%
Outcome: 03 Incidence rate of most frequent adverse event: pruritus



Appendix 15 - List of excluded studies of Economic Evaluation Assessment with reason for exclusion

Reference	Reason for exclusion
Lim KK, Su WPD, Schroeter AL, Sabers CJ, Abraham RT, Pittelkow MR. Cyclosporine in the treatment of dermatologic disease: An update. *Mayo Clinic Proceedings* 1996;**71** :1182-91.Ref ID: 3	No tacrolimus
Nghiem P. "Topical immunomodulators?": introducing old friends and a new ally, tacrolimus. *Journal of the American Academy of Dermatology* 2001;**44**:111-3.Ref ID: 5	Review
Oranje AP,.De Waard-Van Der Spek FB. Atopic dermatitis: Review 2000 to January 2001. *Current Opinion in Pediatrics* 2002;**14**:410-3. Ref ID: 1	Review
Schiffner R, Schiffner-Rohe J, Landthaler M, Stolz W. Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non-corticosteroids. [Review] [128 refs]. *Pharmacoeconomics* 2003;**21**:159-79. Ref ID: 13	Review
Sillevis Smitt JH. [Constitutional eczema; the possibilities of local treatment]. [Review] [41 refs] [Dutch]. *Nederlands Tijdschrift voor Geneeskunde* 2002;**146**:400-4. Ref ID: 17	Review
Van der Valk PGM. From tar to tacrolimus. The topical treatment of atopic dermatitis in 2003. *Pharmaceutisch Weekblad* 2003;**138**:476-81. Ref ID: 20	Review
Whalley D, Huels J, McKenna SP, Van Assche D. The benefit of pimecrolimus (Elidel, SDZ ASM 981) on parents' quality of life in the treatment of pediatric atopic dermatitis. *Pediatrics* 2002;**110**:1133-6. Ref ID: 15	No tacrolimus
Lamb SR,.Rademaker M. Intravenous immunoglobulin therapy for the treatment of severe atopic dermatitis. *Expert Opinion on Pharmacotherapy* 2001;**2**:67-74.	No tacrolimus
Thumm EJ, Stoss M, Bayerl C, Schurholz T. Randomized trial to study efficacy of a 20% and 10% Hippophae rhamnoides containing creme used by patients with mild to intermediate atopic dermatitis. *Aktuelle Dermatologie* 2000;**26**:285-90. Ref ID: 39	No tacrolimus
Kubota K, Machida I, Tamura K, Take H, Kurabayashi H, Akiba T *et al*. Treatment of refractory cases of atopic dermatitis with acidic hot-spring bathing. *Acta Dermato Venereologica* 1997;**77**:452-4. Ref ID: 40	No tacrolimus
Berth J, J., Finlay, A.-Y., Zaki, I. *et al*. Cyclosporine in severe childhood atopic dermatitis: a multicenter study [see comments]. *Journal of the American Academy of Dermatology* 1996;**34**:1016-21. Ref ID: 41	No tacrolimus
Remy W, Rakoski J, Siebenwirth J, Ulm K, Wiesenauer M. Classical homeopathic treatment in atopic dermatitis. Study protocol. *Allergologie.* 1995;**18**:246-52. Ref ID: 42	No tacrolimus
Salek MS, Finlay AY, Luscombe DK, Allen BR, Berth JJ, Camp RD *et al*. Cyclosporin greatly improves the quality of life of adults with severe atopic dermatitis. A randomized, double-blind, placebo-controlled trial. *British Journal of Dermatology* 1993;**129**:422-30. Ref ID: 43	No tacrolimus
Finlay,.A. Quality of life improvement in cyclosporin treated atopic dermatitis patients - a double blind crossover study.British Association of Dermatologists 71st Annual Meeting, London 1991. Abstract. *British Journal of Dermatology* 1991;**125**:16. Ref ID: 45	No tacrolimus
Czech W, Brautigam M, Weidinger G, Schopf E. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. *Journal of the American Academy of Dermatology* 2000;**42**:653-9. Ref ID: 37	No tacrolimus
Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ *et al*. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *British Journal of Dermatology* 2000;**142**:52-8.	No tacrolimus
Lanz MJ, Eisenlohr C, Llabre MM, Toledo Y, Lanz MA. The effect of low-dose inhaled fluticasone propionate on exhaled nitric oxide in asthmatic patients and comparison with oral zafirlukast.[comment]. *Annals of Allergy, Asthma, & Immunology* 2001;**87**:283-8. Ref ID: 36	No tacrolimus
Case histories in drug discovery and design 2001. *Drug News & Perspectives* 2002;**15**:60-4. Ref ID: 9	Review
Bonifazi E. Antiinflammatory topical drugs in atopic dermatitis. *European Journal of Pediatric Dermatology* 1998;**8**:157-60. Ref ID: 12	Review
Boucher M. Tacrolimus ointment for the treatment of atopic dermatitis. *Issues in Emerging Health Technologies* 2001;1-4. Ref ID: 14	Review
Cheer SM,.Plosker GL. Tacrolimus ointment. A review of its therapeutic potential as a topical therapy in atopic dermatitis. [Review] s]. *American Journal of Clinical Dermatology* 2001;**2**:389-406. Ref ID: 18	Review
Drake L, Prendergast M, Maher R, Breneman D, Korman N, Satoi Y *et al*. The impact of	No economic

tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *Journal of the American Academy of Dermatology* 2001;**44**:S65-S72. Ref ID: 16	study
Galli E, Cicconi R, Rossi P, Casati A, Brunetti E, Mancino G. Atopic dermatitis: Molecular mechanism, clinical aspects and new therapeutical approaches. *Current Molecular Medicine* 2003;**3**:127-38. Ref ID: 7	No economic study
Girolomoni G, Ayala F, Fabbri P, Gelmetti C, Monfrecola G, Paradisi M *et al*. Guidelines for diagnosis and therapy of atopic dermatitis. *Giornale Italiano di Dermatologia e Venereologia, Vol 134(6) (pp 665-669), 1999* 1999. Ref ID: 2	Review
Kemp AS. Cost of illness of atopic dermatitis in children: A societal perspective. *Pharmacoeconomics* 2003;**21**:105-13. Ref ID: 8	Cost-study
Granlund H, Erkko P, Remitz A, Langeland T, Helsing P, Nuutinen M *et al*. Comparison of cyclosporin and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. *Acta Dermato Venereologica* 2001;**81**:22-7. Ref ID: 35	No tacrolimus
Schachner L, Field T, Hernandez RM, Duarte AM, Krasnegor J. Atopic dermatitis symptoms decreased in children following massage therapy. *Pediatric Dermatology* 1998;**15(5)**:390-5. Ref ID: 27	No tacrolimus
Staab D, von Rueden U, Kehrt R, Erhart M, Wenninger K, Kamtsiuris P *et al*. Evaluation of a parental training program for the management of childhood atopic dermatitis. *Pediatric Allergy & Immunology* 2002;**13**:84-90. Ref ID: 28	No tacrolimus
Schoni MH, Nikolaizik WH, Schoni AF. Efficacy trial of bioresonance in children with atopic dermatitis. *International Archives of Allergy & Immunology* 1997;**112**:238-46. Ref ID: 29	No tacrolimus
Marchesi E, Rozzoni M, Pini P, Cainelli T. Comparative study of mometasone furoate and betamethasone dipropionate in the treatment of atopic dermatitis. *G.ITAL.DERMATOL.VENEREOL.* 1994;**129**:IX-XII. Ref ID: 30	No tacrolimus
Chandra RK,.Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. *Annals of Allergy* 1991;**67**:129-32. Ref ID: 31	No tacrolimus
Thaci D, Brautigam M, Kaufmann R, Weidinger G, Paul C, Christophers E. Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. *Dermatology* 2002;**205**:383-8. Ref ID: 32	No tacrolimus
Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S *et al*. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. *BMJ* 2002;**324**:768. Ref ID: 33	No tacrolimus
Chinn DJ, Poyner T, Sibley G. Randomized controlled trial of a single dermatology nurse consultation in primary care on the quality of life of children with atopic eczema. *British Journal of Dermatology* 2002;**146**:432-9. Ref ID: 34	No tacrolimus
Kemp AS. Atopic eczema: its social and financial costs. *Journal of Paediatrics.& Child Health* 1999;**35(3)**:229-31. Ref ID: 21	No tacrolimus
Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema:its impact on the family and financial cost. *Archives of Disease.in Childhood.* 1997;**76(2)**:159-62. Ref ID: 22	No tacrolimus
Gieler U, Hohmann M, Niemeier V, Kupfer J, Stangier U, Ehlers A. Cost evaluation in atopic eczema. *Journal of Dermatological Treatment.* 1999;**10(Suppl 1)**:S15-S20. Ref ID: 23	No tacrolimus
Verboom P, Hakkaart VR, Sturkenboom M, De Zeeuw R, Menke H, Rutten F. The cost of atopic dermatitis in the Netherlands: an international comparison. *British Journal of Dermatology* 2002;**147(4)**:716-24. Ref ID: 24	No tacrolimus
Herd RM, Tidman MJ, Prescott RJ, Hunter JAA. The cost of atopic eczema. *British Journal of Dermatology* 1996;**135(1)**:20-3. Ref ID: 25	No tacrolimus
Emerson RM, Williams HC, Allen BR. What is the cost of atopic dermatitis in preschool children? *British Journal of Dermatology* 2001;**144(3)**:514-22. Ref ID: 26	No tacrolimus
Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ *et al*. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *British Journal of Dermatology* 2000;**142**:52-8. Ref ID: 38	No tacrolimus
Case histories in drug discovery and design 2001. *Drug News & Perspectives* 2002;**15**:60-4. Ref ID: 9	No economic evaluation
Lamb SR,.Rademaker M. Intravenous immunoglobulin therapy for the treatment of severe atopic dermatitis. *Expert Opinion on Pharmacotherapy* 2001;**2**:67-74. Ref ID: 11	No tacrolimus
Lamb SR,.Rademaker M. Pharmacoeconomics of drug therapy for atopic dermatitis. [Review] [43 refs]. *Expert Opinion on Pharmacotherapy* 2002;**3**:249-55. Ref ID: 4	No economic evaluation

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