Article ID: WMC003605 ISSN 2046-1690

The Efficacy of Using Tacrolimus Ointment on Children with Atopic Dermatitis

Corresponding Author:
Ms. Sidrah Mohammad,
Medical Student, University of Liverpool - United Kingdom

Submitting Author:
Mr. Muhammed R Siddiqui,
Registrar, Mayday Hospital, 23 Malvern Road, TN24 8HX - United Kingdom

Article ID: WMC003605

Article Type: Review articles

Submitted on:29-Jul-2012, 02:57:05 PM GMT **Published on:** 30-Jul-2012, 05:58:35 PM GMT

Article URL: http://www.webmedcentral.com/article_view/3605

Subject Categories:DERMATOLOGY

Keywords: Paediatrics, Dermatitis, tacrolimus

How to cite the article: Mohammad S, Siddiqui MR. The Efficacy of Using Tacrolimus Ointment on Children with Atopic Dermatitis . WebmedCentral DERMATOLOGY 2012;3(7):WMC003605

Source(s) of Funding:

None

Competing Interests:

None

The Efficacy of Using Tacrolimus Ointment on Children with Atopic Dermatitis

Author(s): Mohammad S, Siddiqui MR

Abstract

Background: Tacrolimus ointment, an immunosuppressant, is a second line treatment for atopic dermatitis, which is prescribed when corticosteroids have no effect or the adverse effects are very severe. Objective: To carry out a structured review on the efficacy of using tacrolimus ointment on children with atopic dermatitis, by comparing the efficacy of tacrolimus ointment against a vehicle (placebo). Method: Databases such as Medline, Pubmed, and Scopus were searched for published studies on atopic dermatitis and tacrolimus ointment. Key terms used were: dermatitis, eczema, protopic, tacrolimus, and ointment. Also, Google scholar and BMA search engine were searched via free text for literature. Various books from the University of Liverpool library were read for background reading. Results: Three key studies were identified from the search method carried out. All three studies were double-blind, randomised, vehicle controlled trials that used similar methods to assess the efficacy of using tacrolimus ointment on children with atopic dermatitis. Even though different measurement tools were used within each study to assess outcomes, all three studies reported that tacrolimus ointment was significantly more effective than the vehicle control for treatment of atopic dermatitis. Conclusion: Tacrolimus ointment is effective to use on children with atopic dermatitis.

Introduction

In the UK, seven million people are affected by skin conditions [1]. One of these conditions is eczema. In the UK, 1 in 12 adults and 1 in 5 children have eczema [2,3].

For people living with eczema, everyday tasks take on a new meaning. From clothes shopping, showering, to sleeping, extra care needs to be taken to cover up symptoms and avoid triggering flare-ups. Having eczema can be a burden for parents [4] and can lead to "sleep deprivation, lack of concentration, and impaired school-work productivity [5]" in patients. The stigma that comes with this condition can affect an individuals confidence levels and their self perception of their image, especially when in public [5].

Eczema is an inflammation of the skin [6, 7]. The word 'eczema' is derived form the Greek word *ekzein* meaning to boil [8]. The words 'Eczema' and 'dermatitis' are used interchangeably [9, 10]. The table below shows the common symptoms of eczema.

see Illustration 1

The rash is symmetrical but not contagious [6]. The different types of eczema are have been described elsewhere [11, 12, 13, 14, 15, 16].

This review is looking at atopic dermatitis in children.

Atopic dermatitis is one of the more common types of dermatitis that affects approximately 20% of the population [19, 17]. Hanifin and Rajka [18] (1980) first came up with criteria that would define this condition. Over the years, its incidence rate has increased more in developed countries than in undeveloped countries [19, 20].

Atopic Dermatitis initially appears in childhood and in 70% of children it clears completely by the age of 12 [6, 19]. It is called 'atopic', meaning hereditary, as 70% of cases are due to family history. It is also associated with hay fever and asthma [9, 17]. There are approximately 23 outcome measurement tools, but so far only three of these have been validated [21, 22, 23].

See Illustraions 2,3,4

The exact cause of atopic dermatitis is unknown, but there are two main theories of how it is could be caused and are broadly classified into immunological and autonomic imbalance[10,12].

Atopic dermatitis also has an impact on society. In 2001, Emerson et al [24] estimated that "the annual cost of atopic dermatitis in children aged 1±5 years was £47million (£17 million spent on consultations, £13million on prescribing, and £17 million spent by families) [24]."

No cure is yet known, but there are many treatments available depending on the severity of the condition. For children with atopic eczema, the following treatments have been recommended by the National Institute of Clinical Excellence [25].

see Illustration 5,6

Initially, for all severities of eczema, emollients are first recommended which cost the NHS approximately £16million per year [26]. Starting at a mild strength,

corticosteroids are prescribed as a first line medical treatment. If neither emollients nor corticosteroids are effective, then topical calcineurin inhibitors are prescribed. This review is looking at the efficacy of the topical inhibitor, tacrolimus ointment (commercially known as PROTOPIC®) [27].

"In 1999, tacrolimus ointment was approved for the treatment of atopic dermatitis in Japan. It was then introduced to the United States in 2000, and Europe in 2001 [28]." Tacrolimus is primarily an immunosuppressant which was used initially in kidney and liver transplants to avoid rejection of the organ by the body [29]. It is now used externally on the skin as a second line treatment for atopic dermatitis when people do not respond well to steroids [30]. The main side effects of the use of protopic are skin burning on application and pruritus (itching) [30]. Tacrolimus ointment has been shown to inhibit T-lymphocyte activation, but its pharmacology in atopic dermatitis is yet unknown [30]. This review will assess the efficacy of tacrolimus ointment on children with atopic dermatitis.

Methods

Background reading was carried out on the topic using Google Scholar and BMA search engine via free text, as well as through various books from the University of Liverpool library. The National Institute of Clinical Excellence (NICE) website [25] was accessed for the current guidelines on the treatment of atopic dermatitis in children. In addition, the guidelines for the use of tacrolimus ointment were read on the manufacturers website [27] as well as the package leaflet [31] issued with the ointment. To acknowledge what patients with eczema go through, personal experiences were viewed through Patient UK [32], National Eczema Society [2], National Eczema Association [33], Medinfo [34], and people who had or still have some form of the condition were approached. Databases such as Medline, Pubmed, and Scopus were searched for published studies on atopic dermatitis and tacrolimus ointment. Key terms used were: dermatitis, eczema, protopic, tacrolimus, and ointment. Searches were focused using mesh terms and relevant searches combined using Boolean operators [35]. Table 6 outlines the search terms and databases used.

see illustration 7

*cannot limit to full text

Abstracts of these studies were read. The following criteria were applied to each study.

see illustration 8

The studies identified were then cross referenced and journals were electronically searched. The identified studies were then critically appraised to assess their reliability and validity using criteria adapted from Crombie [36] and CASP website [37].

Abstracts of the 29 potentially relevant studies were read, and studies which did not fit the inclusion criteria were excluded. Threee studies were reviewed [38, 39, 40]. Through cross referencing and searching journals electronically no further relevant studies were identified.

see Illustration 9,10

Results

The table below shows the results of critically appraising the studies.

See Illustrations 11,12

All studies were double-blind randomised controlled trials. Each study was ethically approved by institutional review boards at each centre and consent gained from guardians of the patients. Studies 2 and 3 justified the sample size they used whilst study 1 did not. Within the studies, the treatment and vehicle groups were similar at baseline, and the reasons why participants discontinued the trials were reported. Intention-to-treat analysis was only mentioned in study 2, and is therefore unknown if studies 1 and 3 used this method of analysis or not. The results from the studies are reliable as they agree with each other, and the outcomes are relevant to clinical practice, regarding the use of tacrolimus ointment for atopic dermatitis on children.

The studies carried out similar trials where patients were treated with tacrolimus ointment or a vehicle.

see Illustration 13,14,15

see Illustrations 16,17,18

Studies 1 and 2 used the same age group and excluded participants with >30%BSA, whereas study 3 included participant with up to 100%BSA but excluded 2-6 year olds. Each study used the same diagnostic criteria and excluded children who had conditions that would affect the use of protopic.

The primary outcome for each study was the overall improvement of eczema, decided by the clinician comparing pre and post treatment of %BSA affected. The secondary outcome was the safety of using tacrolimus ointment.

see illustration 19,20,21

Each study found tacrolimus ointment to be

significantly more effective than the vehicle control, but as stated in study 1, no significant difference was found between the different concentrations of tacrolimus ointment used.

see Illustrations 22,23

Each study reported a greater improvement in extent and severity of atopic dermatitis (by means of an EASI score which was calculated pre and post treatment) in the treatment groups compared to the vehicle group. To assess the safety of the treatment, adverse events were recorded. In addition, studies 1 and 3 took blood samples from participants to measure safety of the ointment. In 90% of blood samples taken by study 1, no measurable tacrolimus concentration in the blood was observed concluding that it is safe to use. Similar results were reported in study 3. On the whole, the main adverse effects recorded by each study were skin burning and pruritus which were due to application of the ointment. These declined quickly after the first few days of the trial. Table 14 shows the EASI and pruritus results from each study.

see illustrations 24,25

Study 3 carried out a follow up of 47% (82/173) of its patients, who reported feeling 'much better' at the end of treatment, for time of recurrence of atopic dermatitis. They reported that 79% (65/82) had recurrence of their atopic dermatitis when treatment had been stopped.

Overall, the results of all three studies agree with each other, and come to the same conclusion that tacrolimus ointment is significantly more effective than a vehicle control for the treatment of atopic dermatitis on children.

Discussion

All three studies were randomised, vehicle controlled trials, with an aim to assess the effectiveness and safety of using tacrolimus ointment as a treatment on children with atopic dermatitis. All studies were multicentre studies conducted in the US. This method of recruitment represents a wide population and limits selection bias of participants. However, studies 2 [39] and 3 [40] only included participants with a maximum of 30% body surface area affected with atopic dermatitis therefore the children used in these studies will not be representative of all children with atopic dermatitis. A strength of study 1 [38] is that it eliminated this participant selection bias by not setting a maximum percentage of body surface area affected as entry criteria. The main difference between the methods of each study was the concentration(s) of tacrolimus ointment used. Studies 1 and 3, which directly compared different concentrations of tacrolimus ointment and vehicle, found no overall statistical difference in efficacy between the different ointment concentrations used. However in study 3, evaluations of the head and neck region suggest that the higher concentrations (0.1% and 0.3%) may be more effective than 0.03% concentration. This suggests that the lower concentrations (0.03%) of tacrolimus ointment are as effective as the higher concentrations. A drawback of study 1 is that there is no mention of a power calculation, therefore it is not known if the sample size used was large enough to represent the population being studied. Nevertheless, studies 2 and 3 justified the sample size used by the means of a power calculation, both at a power of 80% and a 2-sided 0.05 significance level, with study 3 estimating double the percentage success rate estimated by study 2. (Study 2; vehicle 25% and treatment 40% success, study 3; vehicle 50% and treatment 80% success). It is important to have the correct sample size so that it is representative of the population being studied. Central computer generated randomisation was used in studies 2 and 3 to randomly allocate patients to treatment and vehicle groups. This method eliminated selection bias as all patients had an equal chance of being placed in either of the intervention groups. In addition, study 3 also used block randomisation. This reduced the chance of all participants from one centre being placed in the same intervention group. Study 1 suggests that patients were randomly allocated to groups but it does not elaborate on how this randomisation took place which could lead to bias depending on the method used. Despite this, study 1 stratified the patients into age groups before randomisation. This eliminated age as a confounding factor. In comparison, studies 2 and 3 carried out no stratification. After randomisation, in each study the groups were balanced in terms of gender, race and number, which made them comparable at baseline. The same treatment method was used within each study; the ointment given was applied twice daily to the affected areas of the body. Treatment bias was eliminated as all patients, caregivers, investigators and clinical staff were blinded in each study. However, it is mentioned in study 3 that the department of pharmaceutical sciences who prepared the study medication was not blinded. This would introduce bias if their staff had come into contact with patients during the study or if the company had analysed the results. All three studies reported that clinical improvement was noticeable for treated patients within the first two weeks. Study 3 stated that differences between the treatment and

vehicle groups were significant by the eighth day of the trial. Due to this, even though it was intended to eliminate treatment bias from the study by double-blinding, bias could have been introduced depending on whether investigators were able to distinguish between the groups based on improvement of the condition due to the treatment. Furthermore, the studies do not mention how many clinicians there were who carried out the assessments, as if there were two or more assessors, then inter-observer consistency and therefore reliability of the results needs to be questioned. Even though the studies used different measurement tools, in the end they reached the same outcome; that tacrolimus ointment is effective and safe to use in paediatric patients with atopic dermatitis. In each study, post treatment, the percentage of body surface area affected by atopic dermatitis was lower in the treatment groups compared to the vehicle groups. Out of the validated outcome measurement tools, only EASI [21] which evaluates the extent and severity of atopic dermatitis was used in all studies. Each study reported that the EASI [21] score was significantly lower, at the end of the trial, in the treatment groups compared to the vehicle-controlled groups. This suggests that tacrolimus ointment was more effective in reducing the severity and area affected by eczema than the vehicle ointment. Each study also carried out an Investigators Global Atopic Dermatitis Assessment [21] but used slightly different scales to score the outcomes. According to Schmitt et al [21] this new means of outcome measurement is only partly validated and more research needs to be carried out on its validity. Study 1 had a 71% drop out rate in the vehicle group due to lack of efficacy of treatment. However, all participants who received at least one application of the ointment were included in the analysis so this should not affect the results. For some unknown reason, in their analysis, study 1 included a 15 year old patient who was treated with 0.03% ointment in a similar designed adult study. Thus reducing the reliability and therefore validity of their results. Only study 2 analysed the results with intention-to-treat.
Out of the three studies, study 3 had the lowest overall drop out rate of 10%. During the two week follow up carried out by study 3, 79% of the patients had a recurrence of atopic dermatitis, due to stopping of the treatment. This suggests that tacrolimus ointment may not be effective in the long term, as when it is not used, the eczema flares up again. Questions that would need to be asked are 'for how long is this treatment effective to use?' and 'for what length of time does it need to be applied to stop recurrence of atopic eczema?' Does it need to be used for life to keep the condition under control? Based on these studies, tacrolimus ointment has been shown to be clinically effective and safe for treatment of atopic dermatitis in children 2-16 year olds. However the longest trial was only carried out for 12 weeks (study 1), therefore the long term effectiveness of using tacrolimus ointment for atopic dermatitis cannot be concluded from these studies. Two long term non-comparative studies, one carried out by Kang et al [41] (for 12 months) and the other by Hanifin et al [42] (for four years), provide an insight on the long term effect of the tacrolimus ointment reporting that there is no loss in efficacy and no increase in adverse effects with prolonged use. Finally, all three studies were sponsored by the same pharmaceutical company.
Studies that are company sponsored tend to have positive results [43, 44]. As well as this, within each study, some of the investigators are full time paid employees of either the drug manufacturing company or the company that sponsored the study (see appendix 2).
This could lead to the reliability of the results being questioned. All three studies were carried out in the US therefore the results cannot be generalised in other countries so similar trials need to be conducted in different countries and see if the same results are found. Also the children used in the studies may not be representative of all children with atopic dermatitis.
This is because these children were chosen as they had a level of atopic dermatitis which interested the investigators. Even though there are theories on how tacrolimus ointment works, the exact mechanism is not yet known. By understanding this, it will help understand its efficacy and further treatment of atopic dermatitis. All the studies reviewed concluded that tacrolimus ointment is effective to use. However, the long term efficacy and therefore safety of its use is unknown and long term cohort studies need to be conducted. So far, seven patients have been diagnosed with cancer whilst using this treatment.
Even though there is no proven link between tacrolimus ointment and cancer, the Food and Drug Administration (FDA) have not ruled out the possibility of a potential risk of cancer and as a result, a warning box is displayed on all drug labelling and the potential risk is the first thing patients are told by many clinicians [45]. To further the validity of results, validated measurement tools should be used in future studies to assess the outcomes of the treatment. As only studies in the English language were looked at, this biases the search for studies as negative results are more likely to be published in other languages [46]. As not all research is published, by only looking and published papers, my search was limited to the number of studies available. Searches were also limited to

availability of full text and therefore, all potential available literature was not looked at. Therefore, the search strategy I carried out would bias my review. To improve my search strategy in the future, gray literature and the Current Controlled Trials Database would be looked at, hand searching of journals will be carried out, and experts in the field will be contacted for more information.

Conclusion(s)

The studies reviewed concluded that tacrolimus ointment is effective to use as a treatment for atopic dermatitis on children. Although my question on the efficacy of his treatment has been answered, there are still many unanswered questions; the main one concerning the long term safety of using this ointment. As yet, there have not been any studies conducted - extending the current four year span. In order for the true and complete benefit of tacrolimus ointment to be assessed, a study running for longer than at least five years is required, and the final choice made between the importance of either short term efficiency or long term safety.

References

1. BBC News. Eczema, 9 Mar 2006. http://news.bbc.co.uk/1/hi/health/medical_notes/4791204.stm (accessed 4 Feb 2008).
2. The National Eczema Society. The National Eczema Society, 11 Sep 2007. http://www.eczema.org/ (accessed 22 Jan 2008).
3. National Institute for Health and Clinical Excellence. NICE guideline to improve management and treatment of children with atopic eczema, 2007. http://www.nice.org.uk/media/C8B/91/2007066AtopicEczemaAPP.pdf (accessed 5 Feb 2008).
4. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB, Manuel JC. The Burden of Atopic Dermatitis: Impact on the Patient, Family, and Society. Pediatric Dermatol. 2005;22(3):192-9.
5. Zuberbier T, Orlow SJ, Paller AS, Taieb A, Allen R, Hernanz-Hermosa JM, et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol. 2006;118(1):226-32.
5. Epstein O, Perkin GD, Cookson J, de Bono DP. Pocket guide to clinical examination. 3rd ed. Spain: Mosby, 2004:40-41.
6. The British Medical Association. The British Medical Association Illustrated Medical Dictionary. UK: Dorling Kindersley Limited, 2002:192-193.
7. Tortora GJ, Derrickson B. Principles of Anatomy and Physiology. 11th ed. USA: John Wiley & Sons, 2006:166.
8. Forbes CD, Jackson WF. A Colour Atlas and Text of Clinical Medicine. England: BPC Hazell Books Ltd, 1993:93-96.
10. Smith PH, Cairns RJ. Dermatology Current Concepts and Practice. 3rd ed. UK: Butterworths, 1981:46-53.
11. World Health Organisation. Environmental hazards trigger childhood allergic disorders, 4 April 2003. http://www.euro.who.int/document/mediacentre/fswhde.pdf (accessed 5 Feb 2008).
12. Fry L. Dermatology an Illustrated Guide. 2nd ed. Great Britain: Cox and Wyman Ltd, 1978:2-20.
13. NHS Direct. Eczema (contact dermatitis), 27 June 2007. http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=585 (accessed 5 Feb 2008).
14. NHS Direct. Eczema (discoid), 20 Nov 2007. http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=611 (accessed 5 Feb 2008).
15. NHS Direct. Eczema (seborrhoeic), 6 Dec 2007. http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=121 (accessed 5 Feb 2008). 16. NHS Direct. Eczema (varicose), 16 Jan 2008. http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=610 (accessed 5 Feb 2008).
17. Oxford. Oxford Concise Medical Dictionary. 7th ed. US: Oxford University PressInc, 2007:228.
18. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980;92:44–47.
19. NHS Direct. Eczema(atopic), 23 Nov 2007. http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=145 (accessed 5 Feb 2008). 20. Leung DYM, Bieber T. Atopic dermatitis. Lancet. 2003;361(9352):151-60.
21. Schmitt J, Langan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. J Allergy Clin Immunol. 2007;120(6):1389-98.
22. Charman C, Williams H. Outcome Measures of Disease Severity in Atopic Eczema. Arch Dermatol. 2000 June 1, 2000;136(6):763-9.
23. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol. 2001;10(1):11-8.
24. Emerson RM, Williams HC, Allen BR. What is the cost of atopic dermatitis in preschool children? Br J Dermatol. 2001;144(3):514-2
25. National Institute for Health and Clinical Excellence. Atopic eczema in children: Management

of atopic eczema in children from birth up to the age of 12 years, December 2007. http://www.nice.org.uk/nicemedia/pdf/CG057NICEguideline.pdf (accessed 6 Feb 2008).
26. BBC News. Eczema baths 'a waste of money', 3 Oct 2007. http://news.bbc.co.uk/1/hi/health/7023804.stm (accessed 22 Jan 2008).
27. Astellas Pharma US. Protopic (tacrolimus) ointment, 2006. http://www.protopic.com/ (accessed 25 Jan 2008).
28. Beck LA. The efficacy and safety of tacrolimus ointment: A clinical review. J Am Acad Dermatol. 2005;53(2):165-70.
29. MedicineNet. What other factors may play a role in atopic dermatitis? 5 April 2005. http://www.medicinenet.com/atopic_dermatitis/page7.htm (accessed 7 Feb 2008).
30. Astellas Pharma US. Protopic (tacrolimus), Aug 2006. http://www.astellas.us/docs/protopic.pdf (accessed 25 Jan 2008).
31. Astella Pharma Us. Package leaflet: information for the user. Nov 2006.
32. Patient UK. Experiences about this topic (Dermatitis And Eczema), 2007. http://experience.patient.co.uk/discussion_list.php?d=138 (accessed 4 Feb 2008).
33. National Eczema Association. Eczema, 2007. http://www.nationaleczema.org/home.html (accessed 5 Feb 2008).
34. MedInfo. Eczema, 5 June 2005. http://www.medinfo.co.uk/conditions/eczema.html (accessed 4 Feb 2008).
35. CSA Illumina. Boolean Operators, 2008. http://www.csa.com/help/Search_Tools/boolean_operators.html (accessed 6 Feb 2008).
36. Crombie IK. The Pocket Guide to Critical Appraisal. London: BMJ Publishing Group, 1996:43-49.
37. Public Health Resource Unit. 10 questions to help you make sense of randomised controlled trials, 2006. http://www.phru.nhs.uk/Doc_Links/rct%20appraisal%20tool.pdf (accessed 6 Feb 2008).
38. Paller A, Eichenfield LF, Leung DYM, Stewart D, Appell M. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. J Am Acad Dermatol. 2001;44(1):47-57.
39. Schachner LA, Lamerson C, Sheehan MP, Boguniewicz M, Mosser J, Raimer S, et al. Tacrolimus Ointment 0.03% Is Safe and Effective for the Treatment of Mild to Moderate Atopic Dermatitis in Pediatric Patients: Results From a Randomized, Double-Blind, Vehicle-Controlled Study. Pediatrics. 2005 September 1, 2005;116(3):334-42.
40. Boguniewicz M, Fiedler VC, Raimer S, Lawrence ID, Leung DYM, Hanifin JM. A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. J Allergy Clin Immunol. 1998;102(4):637-44.
41. Kang S, Lucky AW, Pariser D, Lawrence I, Hanifin JM. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol. 2001;44(1):58-64.
42. Hanifin JM, Leung DY, Paller A, Rico J. Tacrolimus ointment monotherapy is safe and effective for the long-term treatment (more than 3 years) of atopic dermatitis in pediatric patients. J Allergy Clin Immunol. 2003;111(1):130.
43. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003 May 29, 2003;326(7400):1167-70.
44. Research sponsored by drug companies is biased. BMJ. 2003 May 29, 2003;326(7400).
45. The Food and Drug Administration. Protopic and Elidel Presentation. Regulatory Briefing, 14 Jan2005. http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2_01_02_DPDD%20Consult.pdf (accessed 26 Jan 2008).
46. Heres S, Wagenpfeil S, Hamann J, Kissling W, Leucht S. Language bias in neuroscience--is the Tower of Babel located in Germany? Eur Psychiatry. 2004;19(4):230-2.

Illustrations

Illustration 1

Common symptoms of eczema

Common symptoms of eczema[6, 7].
Itching
Rashes
Redness
Blisters
Dryness of skin
Thickening of the skin

Illustration 2

Validity of outcome measurement tools according to Schmitt et al 21.

Validity of outcome measurement tools according to Schmitt et al [21].	
Outcome Measurement tools	Recommendation
ADAM (Atopic Dermatitis Assessment Measure)	x
ADASI (Atopic Dermatitis Area and Severity Index)	x
ADSI (Atopic Dermatitis Severity Index)	xx
BCSS (Basic Clinical Scoring System)	x
EASI (Eczema Area and Severity Index)	√

Illustration 3

Validity of outcome measurement tools according to Schmitt et al 21.

FSSS (Four Step Severity Score)	xx
IGADA (Investigators' Global Atopic Dermatitis Assessment)	√ x
NESS (Nottingham Eczema Severity Score)	√ x
POEM (Patient-oriented Eczema Measure)	√
SA-EASI (Self-administered Eczema Area and Severity Index)	√ x
SASSAD (Six area, six sign atopic dermatitis)	√ x

Illustration 4

Validity of outcome measurement tools according to Schmitt et al 21.

SCORAD (Severity Scoring of Atopic Dermatitis index)	√
TBSA (Six-area Total Body Severity Assessment)	xx
TISS (Three Item Severity Score)	√ x

Key:

√ Recommended

√ X Acceptable But Not Recommended

X Not Recommended

XX Not Acceptable

Illustration 5

The NICE guidelines 25 for treatment of atopic dermatitis on children.

The NICE guidelines [25] for treatment of atopic dermatitis on children.			
Treatment	Mild atopic eczema	Moderate atopic eczema	Severe atopic eczema
Emollients	√	√	√
Mild potency topical corticosteroids	√	x	x
Moderate potency topical corticosteroids	X	√	x
Potent topical corticosteroids	X	x	√

Illustration 6

The NICE guidelines 25 for treatment of atopic dermatitis on children.

Topical calcineurin inhibitors	X	√	√
Bandages	X	√	√
Phototherapy	X	x	√
Systemic therapy	X	x	√

Key:

√ - Recommended treatment

X - Not recommended treatment

Illustration 7

Database and journal search

Database and journal search.					
Search Number	Mesh terms	Medline	Pubmed	Scopus	LANCET
1	Protopic OR Tacrolimus/	8770	11819	16945	159
2	Eczema/ OR dermatitis, Atopic/	17352	23068	19103	325
3	Safety AND efficacy	48576	51258	99642	1919
4	Ointments/	9589	10370	15767	94
5	1 AND 2 AND 3 AND 4	51	54	33	0
6	Limit 5 to (full text, humans, English language, all child 0-18 years, RCT)	4	13	12*	0

Illustration 8

nclusion/exclusion criteria used.

Inclusion/exclusion criteria used.		
Features	Inclusion criteria	Exclusion criteria
Participants	Human	Animals
Age group	Children 0-18 years	Adults/mixed
Publication Type	RCT	Other types e.g. cohort
Publication date	1997-2008	<1997
Type available	Full text	Abstracts
Duration	>2 weeks	< 2 weeks
Language	English	Other
Intervention	Tacrolimus ointment	Not tacrolimus ointment
Comparator	Vehicle (placebo)	Non-comparative. Compared to other treatments/drugs
Outcome	Safety and efficacy	Not safety and not efficacy

Illustration 9

Study number by which each study is referred to in this review.

Study number by which each study is referred to in this review.		
Study Number	Title	Authors
Study 1[38]	A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in paediatric patients.	Paller A, Eichenfield LF, Leung DYM, Stewart D, Appell M.
Study 2[39]	Tacrolimus Ointment 0.03% Is Safe and Effective for the Treatment of Mild to Moderate Atopic Dermatitis in Paediatric Patients: Results From a Randomized, Double-Blind, Vehicle-Controlled Study.	Schachner LA, Lamerson C, Sheehan MP, Boguniewicz M, Mosser J, Raimer S, et al.

Illustration 10

Study number by which each study is referred to in this review.

Study 3[40]	A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children.	Boguniewicz M, Fiedler VC, Raimer S, Lawrence ID, Leung DYM, Hanifin JM.

Illustration 11

Results and RCT critical appraisal questions adapted from Crombie11 and CASP website12.

Results and RCT critical appraisal questions adapted from Crombie[11] and CASP website[12].			
Checklist	Study 1[38]	Study 2[39]	Study 3[40]
Aims clearly stated	√	√	√
Appropriate study design used	√	√	√
Sample size justified	x	√	√
Treatments randomly allocated	√	√	√
Groups similar at baseline	√	√	√
Eligibility criteria specified	√	√	√
Outcomes assesses double-blind	√	√	√
Patient withdrawals	√	√	√

Illustration 12

Results and RCT critical appraisal questions adapted from Crombie11 and CASP website12.

Reasons for withdrawal stated	√	√	√
Intention to treat	√/x	√	√/x
Side effects reported	√	√	√
Outcomes relevant	√	√	√
Results agree with other papers	√	√	√
Was the study ethically approved?	√	√	√

Key: (√) yes (x) no (√/x) can not tell

Illustration 13

Study characteristics 38, 39, 40

Study characteristics [38, 39, 40]			
Study characteristics	Study 1	Study 2	Study 3
Study design	RCT	RCT	RCT
Duration	12 weeks	6 weeks	22 days with a 2 week follow up
Sample size	Total: 351 No. in vehicle - 116 No. in 0.03% - 117 No. in 0.1% - 118	Total: 317 No. in vehicle - 159 No. in 0.03% - 158	Total: 180 No. in vehicle - 44 No. in 0.03% - 43 No. in 0.1% - 49 No. in 0.3% - 44

Illustration 14

Study characteristics 38, 39, 40

Ointment concentration used	0.03% and 0.1% Applied twice daily	0.03% Applied twice daily	0.03%, 0.1% and 0.3% Applied twice daily
Control used	Vehicle	Vehicle	Vehicle
Type of eczema	Moderate to severe	Mild to moderate	Moderate to severe
Methods of assessment	Clinical assessment on: Day 1, weeks 1, 2, 3, 6, 9, and week 12/EOS Blood taken: Only from 6 centres at day1, week 1, 3 and12/end of treatment	Day 1, day 4, and weeks 2, 4 and 6/EOS Blood taken: No	Prestudy, day 1, 8, 14, 22/end of treatment, 29, and day 36/termination Blood taken: On day 1, 4, and 22/end of treatment

Illustration 15

Study characteristics 38, 39, 40

No. of patients who dropped out	105	90	18
% drop out (1dp)	29.9	28.4	10
Conclusion	Tacrolimus ointment is safe and effective to use	Tacrolimus ointment is safe and effective to use	Tacrolimus ointment is safe and effective to use

Illustration 16

Patient characteristics 38, 39, 40

Patient characteristics [38, 39, 40]			
Characteristics	Study 1	Study 2	Study 3
Age group	2-15year olds	2-15year olds	7-16year olds
Gender	Male and Female	Male and Female	Male and Female
Body Surface Area (%BSA) affected	10% to 100%	2% to 30%	5% to 30%
Diagnosis of atopic dermatitis made based on	Hanifan and Rajika criteria	Hanifan and Rajika criteria	Hanifan and Rajika criteria

Illustration 17

Patient characteristics 38, 39, 40

Entry criteria	- Astemizole for 6 weeks - Other drugs for 7 days -Corticosteroids for 4 weeks -Cream, lotions, emollients for 1 day - non-sedating antihistamines for 7 days	- Nonsteroidal immunosuppress-ants - systemic corticosteroids - UV light therapy - concomitant topical medication - cosmetics on treatment sites	Before enrolment stop: - topical corticosteroids for 1 week - systematic corticosteroids for 6 weeks - UV light therapy for 1 month - non-sedating antihistamines

Illustration 18

Patient characteristics 38, 39, 40

Exclusion criteria	- Other skin disorders - infected atopic dermatitis - any disease that would contraindicate use of tacrolimus - any chronic condition not under control - pregnancy or lactation	-other skin disorder in area to be treated - a known hypersensitivity to excipients of the ointment - previous use of tacrolimus ointment - pregnant or nursing	- anti-infective drugs - pregnancy
Therapy restrictions	Treatments mentioned in entry criteria were restricted during the trial until end of treatment	Treatments mentioned in entry criteria were restricted during the trial until end of treatment	Treatments mentioned in entry criteria were restricted during the trial until end of treatment

Illustration 19

Study outcomes 38, 39, 40

Study outcomes [38, 39, 40]			
	Study 1	Study 2	Study 3
Primary outcome	Overall improvement of eczema	Overall improvement of eczema	Overall improvement of eczema
How measured	Physician's global evaluation of clinical response	IGADA rating	Physician's global evaluation of clinical response

Illustration 20

Study outcomes 38, 39, 40

Efficacy - how measured	- Physician's global evaluation of clinical response, - EASI score - % BSAaffected	- EASI scores - %BSAaffected - Patient's assessment of itch	- modified EASI - Head and Neck Total Score - patient rating atopic dermatitis - patients assessment of pruritus
Safety – how measured	- incidence of adverse effects - results of routine lab tests	incidence of adverse effects: - cutaneous - drug-related - application site	

Illustration 21

Study outcomes 38, 39, 40

Statistical tests carried out	- Chi-squared test without continuity corrections - Variance - Cochran-Mantel-Haenszel - Kaplan-Meier analyses	- Cochran-Mantel-Haenszel - covariance - Pearson X^2 test - Fisher's test	- 1-way ANOVA - chi-square test - Kruskal-Wallis test

Illustration 22

showing the overall percentage success rates in each study.[38, 39, 40]

showing the overall percentage success rates in each study.[38, 39, 40]				
Study Number	Definition of success rate	Overall % success rate in treatment group(s)	Overall % success rate in vehicle group	P value
Study 1	>90% improvement	- 35.9% success rate in 0.03% concentration group - 40.7% success rate in 0.1% concentration group	6.9% success rate	P < 0.001

Illustration 23

showing the overall percentage success rates in each study.38, 39, 40

Study 2	% of patients clear or almost clear	50.6% success rate	25.8% success rate	P < 0.0001
Study 3	>75% improvement	- 69% success rate in 0.03% group - 67% success rate in 0.1% group - 70% success rate in 0.3% group	38% success rate	P=0.005 for 0.03% group P=0.007 for 0.1% group P=0.004 for0.3% group

Illustration 24

EASI and Pruritus results.14, 38, 39, 40

EASI and Pruritus results.[14, 38, 39, 40]			
Study Number	Improvement in EASI score for treatment group(s) [Expressed as a percentage (%)]	Improvement in EASI score for vehicle control group [Expressed as a percentage (%)]	Pruritus score at end of treatment
1	Greater improvement in treatment groups compared to vehicle group. (Individual scores not stated)	Greater improvement in treatment groups compared to vehicle group. (Individual scores not stated)	Greater improvement in treatment groups compared to vehicle group. (Individual scores not stated)

Illustration 25

EASI and Pruritus results.14, 38, 39, 40

2	54.8	20.8	0.03% group – 2.1 Vehicle group – 3.7 (on a scale of 0 – 10, where: 0 = no itch and 10 = worst itch)
3	0.03% group - 72 0.1% group - 77 0.3% group - 81	26	Treatment groups: 74% - 89% Vehicle group – 61% (p = 0.027) (expressed as percentage improvement from pre to post treatment)

Disclaimer