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How clinically relevant are treatment comparisons of topical calcineurin inhibitor trials for atopic eczema?

Short title: Network geometry of atopic eczema trials

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Atopic eczema

Topical corticosteroids

Calcineurin inhibitors

Randomised clinical trial

Network geometry

Abbreviations:

RCT – randomised controlled trial

GREAT database - Global Resource for EczemA Trials

ABSTRACT

We sought to explore the architecture of trials of calcineurin inhibitors for atopic eczema to document the extent to which comparisons with active treatments such as topical corticosteroids (TCS) might have been included or avoided.

We identified all eligible randomized controlled trials (RCTs) using the Global Resource for EczemA Trials database. Network plots were produced where the nodes represented a treatment type and the lines between the nodes represented the number of trials or participants that were involved in the various treatment comparisons.

A total of 174 RCTs for atopic eczema treatments were identified where pimecrolimus, tacrolimus or topical corticosteroids were compared with another intervention or a vehicle/emollient. Of 39 trials involving pimecrolimus and of 41 trials involving tacrolimus, 8 (20.5%) and 13 (31.7%) respectively made comparisons with topical corticosteroids, and 25 (64.1%) and 15 (36.6%) respectively were vehicle-controlled studies.

The high rate of comparisons with vehicle controls in RCTs assessing the efficacy of pimecrolimus or tacrolimus long after efficacy had been established is a matter of concern. Active comparators (mild TCS for pimecrolimus and moderate to potent TCS for tacrolimus) are best placed to inform how topical calcineurin inhibitors compare to established clinical practice.

INTRODUCTION

Atopic eczema, also known as atopic dermatitis or just eczema (Johansson *et al.*, 2004), affects between 0.9% to 24.6% of children worldwide (Odhiambo *et al.*, 2009) as well as many adults (Emerson *et al.*, 1998; Yu and Silverberg, 2015). Topical corticosteroids have been recommended as the first line anti-inflammatory treatment for atopic eczema for over 50 years (Eichenfield *et al.*, 2014; Rattner, 1955). Although their side effect profiles are well established and are safe when used appropriately, some degree of phobia exists with their use (Charman *et al.*, 2000). Over the last 10 years, the topical calcineurin inhibitors pimecrolimus and tacrolimus have been introduced as an alternative form of anti-inflammatory treatment for atopic eczema and are usually cited as second line treatments in various national guidelines (American Academy of Dermatology; NICE guidelines, 2014; SIGN Guidelines, 2011). These recommendations are based on evidence from several randomised controlled trials (RCTs) that have evaluated the efficacy and effectiveness of pimecrolimus and tacrolimus in the treatment of atopic eczema. However, based on our experience of critically appraising hundreds of atopic eczema RCTs for various systematic reviews, it was our impression that relatively few RCTs seem to compare pimecrolimus or tacrolimus directly with the first line treatment of an appropriate potency topical corticosteroid. In order to explore this impression in more detail we set out to examine the geometry of randomised controlled trials for atopic eczema. Inspired by the work of Maruani et al. (Maruani *et al.*, 2015), we developed a network of all atopic eczema RCTs involving pimecrolimus, tacrolimus or topical corticosteroids in order to see whether there has been an excess of vehicle-controlled studies to what might be expected in relation to active comparator studies.

RESULTS

Characteristics of trials

A total of 174 RCTs for atopic eczema treatments were identified whereby pimecrolimus, tacrolimus or topical corticosteroids were compared with another intervention or a vehicle/emollient. Of these, 91 (52.3%) stated that the trial was either fully or partly funded by industry. Table 1 provides further details on the characteristics of these RCTs.

Network of trials

The network plot of all comparisons between treatments from the 174 RCTs is shown in Figure 1 whereby the size of the node is proportional to the number of trials involving that intervention and the thickness of the line is proportional to the number of trials comparing the two interventions. In total, 24 different interventions were assessed within our network. Eighty five (48.9%) trials involved a comparison with a vehicle or emollient.

A second network plot is given in supplementary material 3 whereby the size of the node is proportional to the total number of patients who received that intervention across all trials and the thickness of the line is proportional to the number of patients who were involved in trials comparing the two interventions.

Several comparisons between interventions were overrepresented in the network. This was reflected in the co-occurrence analysis which yielded a significant observed C-score of 111.6 with a 95% confidence interval of the simulated C-score under the null hypothesis of 109.6 to 111.3 (p-value=0.003). The upper confidence interval value of the simulated C-score is lower than the observed C-score meaning that there exists a higher degree of co-occurrence than in the null hypothesis, the null hypothesis being that the pattern in the choices of treatment comparisons within the network is random.

Table 2 details the number of comparisons that were made between, pimecrolimus, tacrolimus, topical corticosteroids and vehicle/emollient. The most clinically relevant comparators for pimecrolimus are mild and moderate topical corticosteroids (NICE guidelines, 2014). Pimecrolimus was compared to mild topical corticosteroids in 1 trial and to moderate topical corticosteroids in 3 trials (2.6% and 7.7% of all trials in the network that involved pimecrolimus respectively). In contrast, pimecrolimus was compared to a vehicle or emollient in 25 trials which equates to 64.1% of all trials in the network that involved pimecrolimus. Five (20%) of the 25 vehicle-controlled trials involved patients with moderate to severe atopic eczema and 21 (84%) declared that they were funded in full or in part by industry.

For topical tacrolimus, the most clinically relevant comparators are mild and moderate topical corticosteroids for 0.03% strength tacrolimus, and moderate and potent topical corticosteroids for 0.1% strength tacrolimus. Tacrolimus was compared to mild topical corticosteroids in 7 trials (1 involved 0.03% strength tacrolimus, 4 involved 0.1% strength tacrolimus and 2 involved both 0.03% and 0.1%), to moderate topical corticosteroids in 2 trials (both involved 0.1% tacrolimus) and to potent topical corticosteroids in 8 trials (3 involved 0.03% strength tacrolimus, 4 involved 0.1% strength tacrolimus, and 1 did not state the strength of tacrolimus used). Fifteen (36.6%) of all 41 trials involving tacrolimus involved a comparison with a vehicle control. Ten (66.7%) of the 15 vehicle-controlled trials involved patients with moderate to severe atopic eczema and 10 (66.7%) declared that they were funded in full or in part by industry.

DISCUSSION

Main findings

Clinicians need good information in order to make the best treatment choices with their patients in a shared decision-making model. When a new treatment is introduced, clinicians ideally want to know "is this new treatment better in some way than the treatments that I already use?" In the case of topical calcineurin inhibitors, such a practical question requires comparison with existing topical corticosteroids rather than vehicle. Vehicle controlled studies are of course needed early on in the development of new drugs in order to determine treatment efficacy and safety. Before a new drug comes onto the market, efficacy and safety have to be established for licensing purposes, typically through a programme of Phase II studies and subsequent Phase III studies. Pivotal Phase III studies are typically large vehicle-controlled studies initially, followed by studies against active comparators later. One can understand the need for four or maybe five vehicle-controlled trials for topical pimecrolimus and tacrolimus to establish efficacy and safety in different populations such as children vs. adults, Hispanics and Blacks compared to White populations and in a few different countries where treatment pathways might differ.

The network map produced in this study suggests an overkill of vehicle-controlled studies for topical pimecrolimus (25 trials, 64%) and to a lesser extent, topical tacrolimus (15 trials, 36.6%). The scientific and ethical justification for so many vehicle-controlled studies need to be questioned, given that scientific equipoise in favour of the active drug is clear after pivotal studies have been performed. Others have commented that the promulgation of so many vehicle controlled studies may be construed by some as being unnecessary and a form of marketing – so called "seeding trials" (Alexander, 2011; Eheberg *et al.*, 2015; Lexchin, 2013; Rose and Kopp, 2015).

Of the trials involving a comparison between pimecrolimus and vehicle/emollient, tacrolimus and vehicle/emollient, or topical corticosteroids and vehicle/emollient, 84%, 66.7% and

45.7% respectively declared that they were funded either in full or in part by industry. Several studies have demonstrated that RCTs sponsored by industry are more likely to produce results in favour of the product made by that company (Katz *et al.*, 2006; Lexchin *et al.*, 2003). Following on from this, evidence also shows that industry sponsored trials are more likely to compare an intervention against an inactive or "straw man" comparator (Ioannidis and Karassa, 2010; Stamatakis *et al.*, 2013).

The use of network plot for reviewing research priorities

Constructing this network of evidence is a method that can enable researchers and clinicians to have a complete picture of the evidence for pimecrolimus, tacrolimus and topical corticosteroids and alert them to treatment comparisons which have not been directly compared in RCTs. The network has also highlighted areas that currently lack evidence which will hopefully provide a clearer direction for future research into treatments for atopic eczema.

Strengths and limitations

Our study does have some limitations. It is possible that we could have missed some unpublished studies of active comparators that did not show favourable results. We did not assess the severity of atopic eczema in each individual RCT nor did we assess any other patient characteristics, for example, age. We also did not write to all of the companies involved to ask for their reasons why so many vehicle controlled studies were done. It is possible for example that some countries required new additional vehicle studies to be done in their own population despite the large volume of clear evidence of efficacy when compared to vehicle from other countries. It is possible that other new treatments for atopic eczema have or will illustrate a similar profusion of vehicle controlled studies, but there are no clear candidates that have been introduced over the last 20 years. One could argue that

topical corticosteroids have also been overly compared against vehicle preparations and that may be so (46 (36.2%) of 127 involving topical corticosteroids made comparisons with a vehicle control). Although it should be recognised that 27 different types of topical corticosteroids have been included in the corresponding nodes in Figure 1, whereas topical pimecrolimus is just one preparation and topical tacrolimus is just three strengths of the same preparation. Strengths of the study include the comprehensive inclusion of all published clinical trials obtained through the GREAT database covering the entire period in which the two topical calcineurin inhibitors were introduced.

Implications for clinical practice and future research

Clinicians and clinical scientists need to become more involved in designing and participating in drug trials when new drugs are introduced and should ask how many vehicle controlled studies have been done and how many more are really needed and for what purpose. Four or five placebo/vehicle studies might be enough even for a global market. Such an ideal might be difficult to realise given that clinical investigators are typically paid well for recruiting patients into such studies. Regulatory bodies might do more to encourage more active comparisons for Phase III studies, using appropriate existing competitor products at the correct dose and frequency. Ethical committees should also question how many vehicle controlled studies have been done before granting permission for more such studies. Most important of all, the public can be made more aware of the difference between vehicle controlled and active comparator trials so that they too can make a judgement of when enough is enough when comparing a new active topical drug against vehicle, especially for those who have moderate to severe disease.

In addition to suggesting a rebalance towards more active rather than placebo or vehicle-controlled studies, greater emphasis should be made on the choice of outcomes such as the

core outcome set currently being developed by the Harmonising Outcomes in Eczema initiative so that studies can be compared directly against each other in systematic review meta-analyses (Schmitt *et al.,* 2015). In addition to efficacy outcomes, safety outcomes should also be recorded and reported. For example, the main rationale for bringing topical calcineurin inhibitors onto the market was concern about possible side effects of topical corticosteroids such as skin thinning. Yet clinically significant skin thinning has rarely been reported in such trials. In the largest clinical trial of topical pimecrolimus compared against mild to moderate topical corticosteroids over a long period, the frequency of clinical skin thinning was just one out of 1213 children for those using long-term topical corticosteroids compared with zero out of 1205 in the topical pimecrolimus group i.e. no real difference at all (Sigurgeirsson *et al.,* 2015). Yet extracting such key information from the trialists took three attempts by different correspondents, and the key data remains buried in the online correspondence section of the journal.

There is no doubt that the Pharmaceutical industry is needed and that it has been responsible for some key innovations in dermatology, including the topical calcineurin inhibitors for treating atopic eczema at sensitive sites and for preventing flares (Schmitt *et al.,* 2011). Active rather than passive engagement in drug development from a whole range of constituencies is what is now needed for new drug developments in dermatology.

MATERIALS AND METHODS

GREAT database

The Global Resource for EczemA Trials (GREAT) database contains records of all RCTs and systematic reviews of treatments for atopic eczema published since the inception of the MEDLINE (1966) and EMBASE (1980) (Centre of Evidence Based Dermatology). The search strategy used to populate the GREAT database is given in Supplementary Material 1.

Searches are also carried out using the Cochrane Library and the Cochrane Skin Group specialised register of trials from inception, therefore the GREAT database also contains many records that are not in MEDLINE or EMBASE as a result of handsearching and other searches done by the Cochrane Skin Group. Further information on the GREAT database can be found at: http://www.greatdatabase.org.uk.

Selection criteria

The GREAT database was searched to identify all RCTs for atopic eczema up until 4th December 2014 that incorporated at least one treatment arm involving pimecrolimus, tacrolimus or topical corticosteroids as an intervention. Any RCTs that only involved intra-drug comparisons, for example different doses of the same drug, were excluded as we felt it unlikely that these dose finding studies would have deliberately avoided a lower or standard dose.

Categorisation of interventions

All doses and regimens of pimecrolimus were grouped together. Tacrolimus was categorised in strengths 0.03%, 0.1% and 0.3%. Where the strength of tacrolimus was not stated or participants were allowed to use multiple different strengths within the trial, these were classified as “any tacrolimus”. Topical corticosteroids were grouped according to potency (mild, moderate, potent or very potent) using the British National Formulary (Joint Formulary Committee). Where trials allowed for any potency of topical corticosteroid to be used as an intervention, these were categorised in a separate group called “any topical corticosteroid”. Interventions involving combined therapies were grouped. For example, all interventions of topical corticosteroids plus an antimicrobial were grouped together. Where topical corticosteroids were combined with another therapy, the potency was ignored for the purpose of categorisation. Emollients and vehicles were grouped together as a topical intervention

without the active principle. Further details of all the intervention categories are given in Supplementary Material 2.

Trial networks

A network of all comparisons between treatments from the RCTs identified in our search was developed. Two network plots were produced whereby the nodes represented the interventions and the lines linking the nodes represented a comparison between the two interventions being linked. In the first plot, the size of the node was proportional to the number of trials involving that intervention and the thickness of the line was proportional to the number of trials comparing two interventions. In the second plot, the size of the node was proportional to the total number of patients who received that intervention across all trials. Similarly, the thickness of the line was proportional to the number of patients involved in trials comparing the two interventions.

Trials involving more than two treatment arms of different therapeutic classes were allowed to contribute to the network more than once. For example, a three arm trial comparing pimecrolimus, tacrolimus and vehicle contributed to the lines linking pimecrolimus and tacrolimus; pimecrolimus and vehicle; and tacrolimus and vehicle.

Co-occurrence

In order to determine whether some head-to-head comparisons of specific interventions were avoided or preferred the degree of co-occurrence was assessed using the C-score statistic (Stone and Roberts, 1990). The C-score is estimated by first examining each particular pair of treatments within the network. The number of times each of the two treatments appear in the network is noted along with the number of times the two treatments are directly compared.

This gives an idea of how many times the two treatments could have been compared, given their relative frequencies. The C-score statistic is obtained by averaging over all possible pairs of treatments in the network. Therefore, the C-score reflects the tendency for treatment comparisons not to occur in the network. A larger C-score corresponds to a larger degree of co-occurrence in the network, meaning that there is more likely to be a selective pattern in the choices of treatment comparisons within the network (Salanti *et al.*, 2008).

In order to assess the statistical significance of the C-score statistic a permutations procedure is applied which asks the underlying question: Given the number of studies in our network each comparing two treatments, and given the number of times each of those treatments appear in the network, what are the chances of observing the estimated C-score statistic? This procedure produces a 95% confidence interval and a p-value for the estimated C-score under the null hypothesis that there is no selective pattern in the network. A significant p-value (<0.05) indicates that the estimated C-score is unlikely to be due to chance and that there are selective patterns in the choices of treatment comparisons in the network.

Analyses were carried out using R software version 3.1.0 with the package EcoSimR and the NodeXL add-in with Excel.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Characteristics of RCTs	**N = 174 RCTs**
Trials involving:	
Pimecrolimus	39 (22.4%)
Tacrolimus 0.03%	20 (11.5%)
Tacrolimus 0.01%	22 (12.6%)
Tacrolimus 0.3%	2 (1.1%)
Tacrolimus (strength not stated or multiple strengths used)	5 (2.9%)
Mild topical corticosteroids	61 (35.1%)
Moderate topical corticosteroids	26 (14.9%)
Potent topical corticosteroids	65 (37.4%)
Very potent topical corticosteroids	2 (1.1%)
Sample size: median (inter-quartile range)	71 (30, 200.5)
Trials involving:	
Children <18 years old only	67 (38.5%)
Adults ≥18 years old only	55 (31.6%)
Children and adults	47 (27.0%)
Not stated	5 (2.9%)
Design of the trial:	
Parallel	71 (40.8%)
Within person / split body	44 (25.3%)
Crossover	5 (2.9%)
Unclear / not stated	54 (31.0%)
Study funding:	
Industry funded (either fully or in part)	91 (52.3%)
Non-industry funded (e.g. solely charity or Government funded)	11 (6.3%)
Not stated	72 (41.4%)

Table 1: Characteristics of atopic eczema randomised controlled trials (RCTs) involving pimecrolimus, tacrolimus or topical corticosteroids.

Number of trials comparing pimecrolimus with:	**N = 39 RCTs[¥]**	**Number industry funded**	**Number non-commercially funded**	**Number unknown funder**
Mild TCS	1 (2.6%)	0 (0%)	0 (0%)	1 (100%)
Moderate TCS	3 (7.7%)	2 (66.7%)	0 (0%)	1 (33.3%)
Potent TCS	4 (10.3%)	2 (66.7%)	1 (33.3%)	1 (33.3%)
Tacrolimus 0.03%	2 (5.1%)	2 (100%)	0 (0%)	0 (0%)
Tacrolimus 0.1%	3 (7.7%)	3 (100%)	0 (0%)	0 (0%)
Any tacrolimus	1 (2.6%)	0 (0%)	0 (0%)	1 (100%)
Vehicle/emollient	25 (64.0%)	21 (84.0%)	0 (0%)	4 (16.0%)
Number of trials comparing tacrolimus 0.03% with:	**N = 20 RCTs*[¥]**	**Number industry funded**	**Number non-commercially funded**	**Number unknown funder**
Mild TCS	3 (15%)	3 (100%)	0 (0%)	0 (0%)
Potent TCS	3 (15%)	2 (66.7%)	0 (0%)	1 (33.3%)
Any TCS	1 (5.9%)	0 (0%)	0 (0%)	1 (100%)
Vehicle/emollient	11 (55%)	8 (72.7%)	0 (0%)	3 (27.3%)
Number of trials comparing tacrolimus 0.1% with:	**N = 22 RCTs*[¥]**	**Number industry funded**	**Number non-commercially funded**	**Number unknown funder**
Mild TCS	6 (27.3%)	5 (83.3%)	0 (0%)	1 (16.7%)
Moderate TCS	2 (10%)	1 (50%)	1 (50%)	0 (0%)
Potent TCS	3 (15%)	3 (100%)	0 (0%)	0 (0%)
Tacrolimus & Potent TCS	1 (5%)	1 (100%)	0 (0%)	0 (0%)
Vehicle/emollient	7 (31.8%)	6 (85.7%)	0 (0%)	1 (14.3%)
Number of trials comparing tacrolimus 0.3% with:	**N = 2 RCTs*[¥]**	**Number industry funded**	**Number non-commercially funded**	**Number unknown funder**
Vehicle/emollient	2 (100%)	2 (100%)	0 (0%)	0 (0%)
Number of trials comparing mild TCS with:	**N = 62 RCTs[¥]**	**Number industry funded**	**Number non-commercially funded**	**Number unknown funder**
Moderate TCS	9 (14.5%)	2 (22.2%)	0 (0%)	7 (77.8%)
Potent TCS	17 (27.4%)	6 (35.3%)	1 (5.9%)	10 (58.8%)
TCS plus another intervention	6 (9.7%)	2 (33.3%)	1 (16.6%)	3 (50%)
Vehicle/emollient	15 (24.2%)	6 (40.0%)	3 (20%)	6 (40.0%)
Other type of intervention	7 (11.3%)	4 (57.1%)	0 (0%)	3 (42.9%)

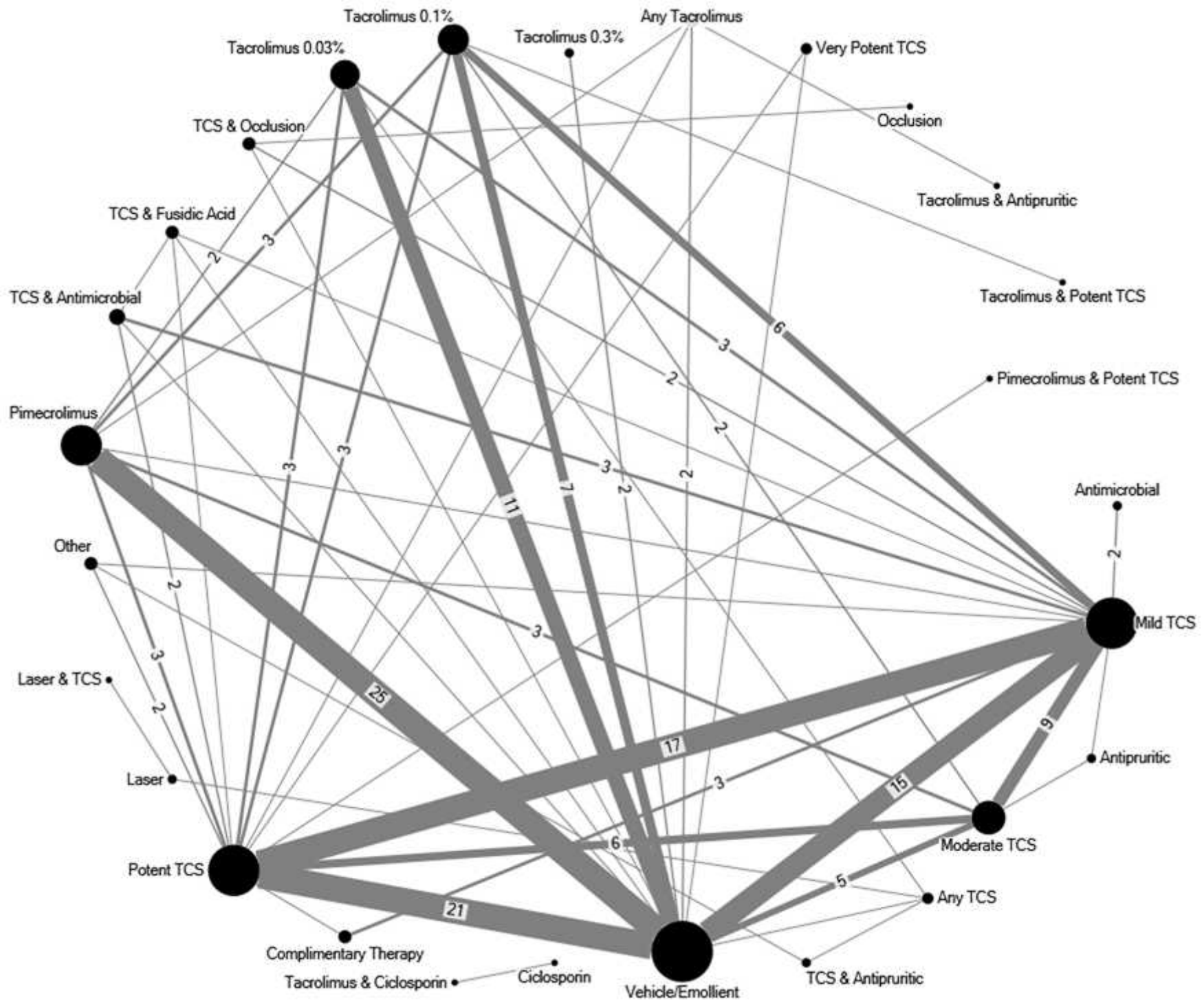
Number of trials comparing moderate TCS with:	**N = 26 RCTs[¥]**	**Number industry funded**	**Number non-commercially funded**	**Number unknown funder**
Potent TCS	6 (23.1%)	0 (0%)	0 (0%)	6 (100%)
Vehicle/emollient	5 (19.2%)	2 (40%)	0 (0%)	3 (60%)
Other type of intervention	1 (3.8%)	0 (0%)	0 (0%)	1 (100%)
Number of trials comparing potent TCS with:	**N = 62 RCTs[¥]**	**Number industry funded**	**Number non-commercially funded**	**Number unknown funder**
Any tacrolimus	1 (1.6%)	0 (0%)	0 (0%)	1 (100%)
Very potent TCS	1 (1.6%)	0 (0%)	0 (0%)	1 (100%)
TCS plus another intervention	3 (4.8%)	0 (0%)	0 (0%)	3 (100%)
Vehicle/emollient	21 (33.9%)	10 (47.6%)	3 (14.3%)	8 (38.1%)
Other type of intervention	3 (4.8%)	1 (33.3%)	1 (33.3%)	1 (33.3%)

Table 2: Number of trials comparing topical corticosteroids pimecrolimus, tacrolimus and vehicle/emollient.

*Some trials involved more than one strength of tacrolimus. There were 41 trials in total that involved tacrolimus.

[¥]Not all of the columns for each intervention will add up to the total N shown. This is because comparisons are not repeated down the table. For example, the numbers for pimecrolimus compared with mild TCS are given in the pimecrolimus section and therefore are not repeated under the mild TCS section of the table.

Figure 1: Network of RCTs for atopic eczema involving pimecrolimus, tacrolimus or topical corticosteroids. Nodes represent the interventions – two nodes are linked together with a line if at least one trial compared the two interventions. The size of the node is proportional to the number of trials involving that intervention. Similarly, the thickness of the line is proportional to the number of trials comparing the two interventions. The lines are labelled with the number of comparisons if the number was greater than 1. “Any TCS” represents interventions where participants were allowed to apply any potency of topical corticosteroid. “Any tacrolimus” represents interventions where participants were allowed to apply any strength of tacrolimus or where the study did not state the strength of tacrolimus used.


Tacrolimus 0.1%
Any Tacrolimus
Tacrolimus 0.3%
Tacrolimus 0.03%
Very Potent TCS
Occlusion
TCS & Occlusion
Tacrolimus & Antipruritic
TCS & Fusidic Acid
Tacrolimus & Potent TCS
TCS & Antimicrobial
Pimecrolimus & Potent TCS
Pimecrolimus
Antimicrobial
Other
Mild TCS
Laser & TCS
Antipruritic
Laser
Moderate TCS
Potent TCS
Any TCS
Complimentary Therapy
Tacrolimus & Ciclosporin
Ciclosporin
Vehicle/Emollient
TCS & Antipruritic
Created with NodeXL (http://nodexl.codeplex.com)

Supplementary Material 1 - GREAT Database Search strategy

The MEDLINE and EMBASE databases, the Cochrane Library and the Skin Group Specialised Register were searched from inception, as follows:

MEDLINE (2000 onwards)

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. drug therapy.fs.

6. randomly.ab.

7. trial.ab.

8. groups.ab.

9. 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5

10. (animals not (humans and animals)).sh.

11. 9 not 10

12. exp Dermatitis, Atopic/

13. atopic dermatitis.mp.

14. atopic eczema.mp.

15. exp NEURODERMATITIS/

16. neurodermatits.mp.

17. infantile eczema.mp.

18. childhood eczema.mp.

19. Besniers' Prurigo.mp.

20. exp Eczema/ or eczema.mp.

21. 17 or 12 or 20 or 15 or 14 or 18 or 13 or 16 or 19

22. 11 and 21

EMBASE (2000 onwards)

1. random$.mp.

2. factorial$.mp.

3. (crossover$ or cross-over$).mp.

4. placebo$.mp. or PLACEBO/

5. (doubl$ adj blind$).mp.

6. (singl$ adj blind$).mp.

7. (assign$ or allocat$).mp.

8. volunteer$.mp. or VOLUNTEER/

9. Crossover Procedure/

10. Double Blind Procedure/

11. Randomized Controlled Trial/

12. Single Blind Procedure/

13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14. exp Dermatitis, Atopic/

15. atopic dermatitis.mp.

16. atopic eczema.mp.

17. exp NEURODERMATITIS/

18. neurodermatitis.mp.

19. infantile eczema.mp.

20. childhood eczema.mp.

21. (besnier$ and prurigo).mp.

22. eczema.mp. or exp Eczema/

23. 21 or 17 or 20 or 15 or 14 or 22 or 18 or 16 or 19

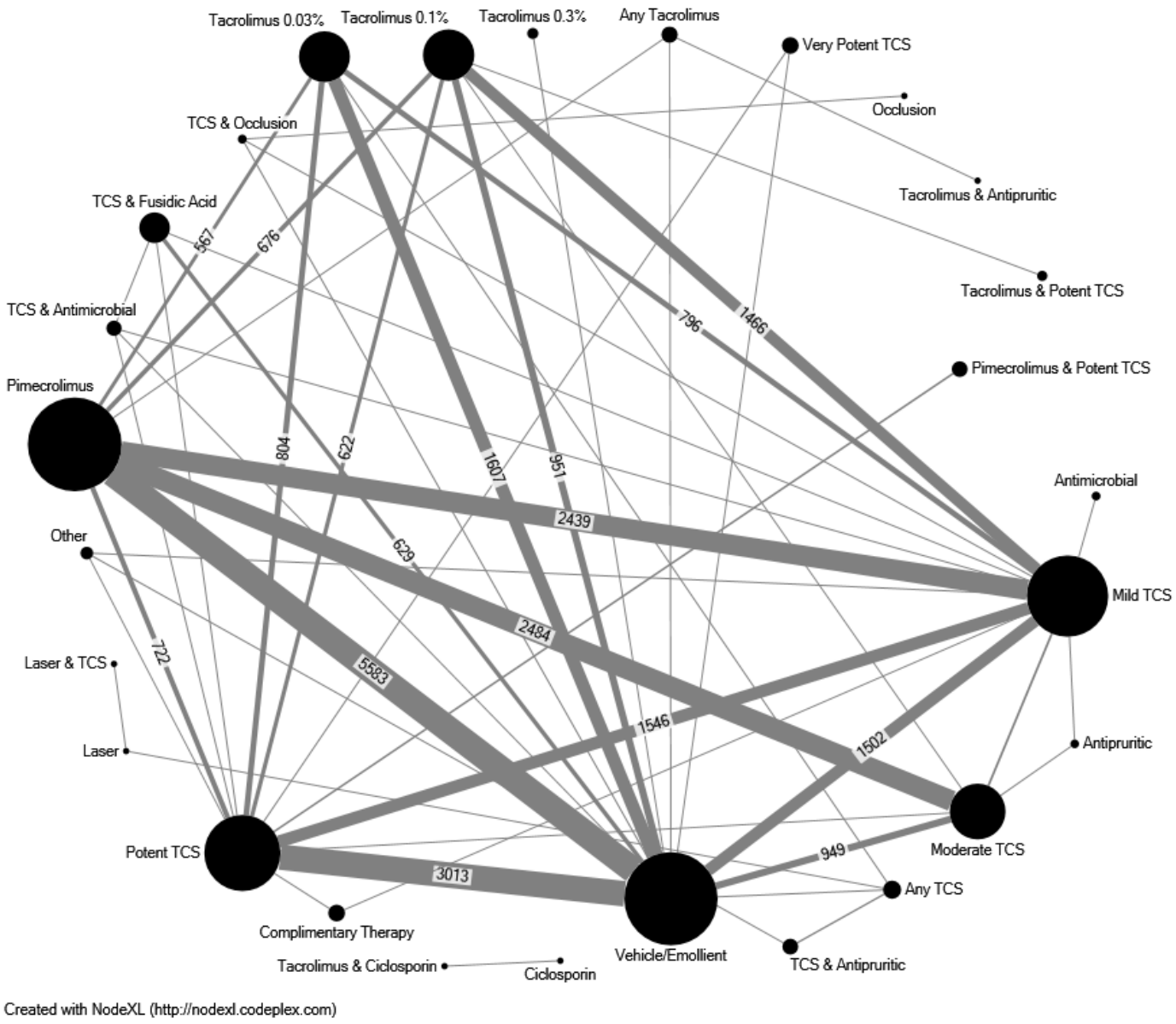
24. 23 and 13

From 2000 onwards, the CINHAL, AMED and LILACS databases have also been searched using the same terms for eczema and appropriate terms to identify RCTS.

SUPPLEMENTARY MATERIAL 2 – BREAKDOWN OF INTERVENTION CATEGORIES

Category	Types of Interventions
Pimecrolimus	• All doses of pimecrolimus. *Interventions of pimecrolimus + another therapy are included as a separate category.
Tacrolimus 0.03%	• All doses of tacrolimus 0.03%
Tacrolimus 0.1%	• All doses of tacrolimus 0.1%
Tacrolimus 0.3%	• All doses of tacrolimus 0.3%
Any tacrolimus	• Trials where patients were allowed to receive any strength of tacrolimus or where the strength was not stated. *Interventions of tacrolimus + another therapy are included as a separate category regardless of the strength of tacrolimus used.
Mild potency topical corticosteroids	• Hydrocortisone 0.5, 1 and 2.5% cream/ointment • Flumethasone pivalate (Locorten) 0.03% • Prednicarbate
Moderate potency topical corticosteroids	• Clobetasone butyrate 0.05% (Eumovate®) cream/ointment • Betamethasone 0.025% (Betnovate RD®) cream/ointment • Fludroxycortide tape (Haelan®) • Desonide 0.05% • Fluorocortolone 0.25% • Halometasone 0.05% • Alclometasone dipropionate 0.05% (Modrasone) • Fluprednidene acetate • Fludroxycortide (flurandrenolone) 0.0125% Haelan®
Potent topical corticosteroids	• Betamethasone 0.1% cream / ointment / lotion (Betnovate®) • Betamethasone 0.05% with salicylic acid 3% (Diprosalic®) ointment • Mometasone furoate 0.1% (Elocon®) cream/ointment • Fluticasone propionate cream 0.05% or ointment 0.005% (Cutivate) • Fluocinonide 0.05% cream/ointment • Triamcinolone acetonide 0.1% • Desoximethasone • Methylprednisolone aceponate 0.1% • Fucicort (Fusidic acid and betamethasone 17-valerate) • Diflorasone diacetate 0.05% • Halicinonide • Topical budesonide 0.025% • Beclomethasone
Any topical corticosteroids	• Trials where patients were allowed to receive any potency of TCS. *Potency was grouped for all trials where the intervention was TCS + another therapy
Very potent topical corticosteroids	• Clobetasol propionate 0.05% (Dermovate®) cream/ointment • Diflucortolone 0.3% (Nerisone forte®) oily cream/ointment

Antimicrobial	• Mupirocin ointment (Bactroban) • Tetracycline (TT) ointment • Miconazole cream • Miltefosine solution (Miltex ®) • Sertaconazole cream (Dermofix, Ferrer Co., Spain)
Occlusion	• Coverflex® tubular bandage • Wet wraps (tubifast bandages)
Complimentary therapy	• Kamillosan ® cream (camomile) • Herba Saxifragae cream • Thermal water • Hamamelis
Laser	• UVA/UVB monotherapy • XeCl gas 308nm excimer laser (Talos ® - 10 or 20mm spot size, 200mW per cm, 60ns, 200Hz)
Antipruritic	• Pramoxine hydrochloride lotion • Oral cetirizine • Terfenadine • Topical doxepin
Vehicle / Emollient	• Any trial including an intervention referred to as a "vehicle" • MAS063DP emollient cream • Emollient containing Sunflower Oleodistillate (Stelatopia ®) • Ceramide-hyaluronic acid based emollient foam • Moisturizer containing licochalcone A • Floderm Topical Cream - Drex Pharma • Oil-in-water Emolient containing licochalcone A • Moisturizer containing spent grain wax, Butyrospermum parkii extract, Argania spinosa kernel oil • Emollient (Advabase ®) • Eletone containing high lipid content, utilises specialized Hydrolipid technology • Vaseline • WWT with emollient (petroleum 20% in cetomacrogol cream) • Moisturiser
Other interventions	• Methyl-lipoxin • Montelukast • Coal tar • Cerimide-dominant barrier repair formulation



SUPPLEMENTARY MATERIAL 3

Network of RCTs for atopic eczema involving pimecrolimus, tacrolimus or topical corticosteroids weighted by the number of patients in the trial.

Nodes represent the interventions – two nodes are linked together with a line if at least one trial compared the two interventions. The size of the node is proportional to the number of patients receiving that intervention across all 174 RCTs. Similarly, the thickness of the line is proportional to the number of patients involved in RCTs that compare the two interventions. The lines are labelled with the total sample size if the sample size was greater or equal to 500. “Any TCS” represents interventions where participants were allowed to apply any potency of topical corticosteroid. “Any tacrolimus” represents interventions where participants were allowed to apply any strength of tacrolimus or where the study did not state the strength of tacrolimus used.