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A systematic review of the safety of topical therapies for atopic dermatitis

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Summary

Background The safety of topical therapies for atopic dermatitis (AD), a common and morbid disease, has recently been the focus of increased scrutiny, adding confusion as how best to manage these patients.
Objectives The objective of these systematic reviews was to determine the safety of topical therapies for AD.
Methods Databases searched included: OVID Medline, Medline In-Process and Other Non-Indexed Citations, Embase, and the Cochrane Central Register of Controlled Trials. In addition to the articles identified by this search, investigators were also referred to a list of links (most recently updated 25 September 2005) to recent Food and Drug Administration (FDA) studies, reports and meetings regarding the topical calcineurin inhibitors for further potential references. Only fully published papers available in English and data obtained from FDA sites were included. Furthermore, the criteria for inclusion and exclusion for each systematic review were further evaluated at a meeting of all of the content and evidence-based medicine experts participating in this process and alteration of the inclusion criteria was done at that time when it was felt necessary to avoid inclusion of lower-quality data in the review. Qualitative review of the abstracted data was performed and reviewed at a meeting of all of the content and evidence-based medicine experts.
Results While systemic exposure to these topical agents does occur, physiological changes appear to be uncommon and systemic complications rare and have only been found with use of topical corticosteroids.
Conclusions Based on the data that are available the overall safety of AD therapies appears to be good with the only documented systemic side-effects of therapy those occasionally seen with use of topical corticosteroids.

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Atopic dermatitis (AD) is an extremely common disease that adversely impacts the quality of life (QoL) of affected children and adults.[1,2] The pathogenesis of AD is incompletely understood, but involves dysregulation of inflammation and the response to antigens.[1,3] Modern therapy of AD has largely been focused on agents that control perturbations in the inflammatory response, i.e. anti-inflammatory and immunosuppressive compounds. The spectrum of topical therapies used to treat AD ranges from emollients to potent anti-inflammatory and immunomodulating agents including topical corticosteroids (TS), a class of compounds with a broad effect on immune regulatory functions, and topical calcineurin inhibitors (TCI), more

recently developed compounds with a more selective effect on immunoregulation.[4] These topical treatments for AD, while effective in controlling disease activity and maintaining clinical remission, may also occasionally be associated with local adverse reactions including infection.[5,6] Furthermore, use of these potent topical anti-inflammatory and immunomodulating drugs can result in absorption and systemic drug exposure and thus use of TS and TCI has the potential to result in systemic side-effects and/or complications which accompany immunosuppression.[7–11]

In order to address what is known about the safety of topical therapies for AD, as well as to identify areas of unmet need in this field, a series of systematic reviews was conducted.

Materials and methods

The following seven focused clinical questions were formulated following extensive discussions among the authors of this paper who are experts in dermatology, AD and/or evidence-based medicine. These authors identified the following key issues that needed to be addressed when attempting to evaluate the safety of therapies for AD.

1 What is the burden of illness of AD, including the prevalence of AD and the effect AD has on QoL?

2 What is the postulated pathophysiology of AD and what are the mechanism(s) of action of topical therapies for AD?

3 What are the local side-effects of topical therapies for AD?

4 What are the systemic exposures of topical therapies for AD and their effect on growth, the hypothalamic-pituitary-adrenal (HPA) axis and other physiological processes?

5 What is the postulated mechanism for increased risk for neoplasia in those using topical immunosuppressive therapies?

6 What is the background prevalence of neoplasia in the general population, those with atopic disease and those receiving topical therapy for AD?

7 What are the systemic side-effects (infection and neoplasia) of topical therapies for AD?

Each of the above questions was then assigned to one or more experts in that specific field of AD and an expert in performing systematic reviews. Separate and specific systematic reviews were then performed for each of the specific focused questions (Appendix S1 in Supplementary Material).

Before developing the specific and unique search strategy for each of these questions, search boundaries, developed by consensus, were formulated using a defined set of treatments for AD (Table 1). Each of the individual search strategies was then adapted to the specific focused question after consultation with an experienced medical librarian (K.K.), who is an expert in performing searches for systematic reviews. Databases searched included: OVID Medline, Medline In-Process and Other Non-Indexed Citations, Embase, and the Cochrane Central Register of Controlled Trials.

The titles and abstracts of identified articles for each of the specific individual search strategies were then reviewed by the content expert for that question. Articles thought to be relevant were identified and subjected to more intensive review. Articles meeting *a priori* inclusion criteria were then abstracted for information pertinent to the focused question being addressed. A hand search of references from these articles was used to identify other possible articles meeting the inclusion criteria that were missed with the database search.

Table 1 Topical therapies for atopic dermatitis used as search terms for these systematic reviews

Anti-inflammatory agents (including all steroidal and nonsteroidal agents)
Antibacterial agents
Coal tar
Doxepin
Calcineurin or calcineurin inhibitors or tacrolimus or pimecrolimus or Protopic or Elidel or Tsukubaenolide
Cromolyn sodium or cromoglycate disodium or Altoderm
Phosphodiesterase inhibitors
Vitamin B_2 or cyanocobalamin
Immunosuppressive agents or immunomodulators
Adrenal cortex hormones or corticosteroids or hydrocortisone
Dermatological agents or ointments or emollients
Ceramides
Histamine H1 antagonists

In addition to the articles identified by the search, investigators were also referred to the following list of links (most recently updated as of 25 September 2005) to recent Food and Drug Administration (FDA) studies, reports and meetings regarding the TCI for further potential references: Pediatric Advisory Committee briefing information, http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2.htm; background package from Fujisawa Healthcare Inc., http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2_02_02_Protopic%20Fujisawa%20briefing.doc; general information on drugs approved by the FDA, http://www.fda.gov/cder/drug/infopage/protopic/default.htm; FDA memorandum, http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2_01_01_%20Briefing%20Memo.pdf; FDA Elidel label with background study information, http://www.fda.gov/cder/foi/label/2004/21302s005lbl.pdf; nonclinical pharmacology/toxicology data for Protopic, http://www.fda.gov/ohrms/dockets/ac/00/slides/3659s1_04_hill/; FDA Pediatric Advisory Subcommittee Transcripts, http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3999T2.pdf and FDA Advisory Committee information, http://www.fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Committees/Pediatric/021505_immuno/0214-1505_PedsP.htm.

Only fully published papers available in English and data from the above websites were included in the systematic reviews. Furthermore, the criteria for inclusion and exclusion for each systematic review were further evaluated at a meeting of all of the content and evidence-based medicine experts participating in this process. An alteration of the inclusion criteria was done at that time when, by consensus, it was felt necessary to avoid inclusion of lower-quality data in the review.

Results

Question 1. What is the burden of illness of atopic dermatitis?

Although this specific question was addressed through the systematic review performed, the results do not specifically deal with safety of therapy for AD and are therefore not further presented.

Question 2. What is the pathophysiology of atopic dermatitis and mechanism of action of therapies for atopic dermatitis?

Following the initial search and review of papers it became evident that a formal systematic review process could not address this complex question. As such the results of this search are not presented and will not be further discussed.

Question 3. What are the local side-effects of topical therapy for atopic dermatitis?

The search strategy identified 586 papers, of which 166 were considered potentially relevant. Further analysis of these papers identified 61 studies meeting initial inclusion criteria (randomized controlled trials with more than 50 subjects, unique case reports of potential relevance, summaries or reviews of prior studies or adverse event experiences). Additional information was obtained from data available from package inserts, data summaries and regulatory filings with the FDA. Skin malignancy is addressed in this section of the review, rather than in the sections on systemic side-effects or neoplasia risk.

Coal tar

Topical coal tar has been most extensively studied in patients with psoriasis, and many different formulations and doses have been used. Based on the limited data available, the local side-effect profile has not been well characterized by today's standards. However, there has been no demonstrated increase in incidence of skin cancer when compared with a reference population.[12–16] There were no prospective vehicle-controlled trials of sufficient duration in patients with AD to provide a definitive answer to the question of whether local side-effects or skin neoplasia are increased with the use of coal tar.

Doxepin

Studies investigating the local effects of topical doxepin have demonstrated local side-effects (stinging and burning) both in patients receiving active drug and in those receiving a control vehicle; however, the use of doxepin does result in significantly more sedation (15·5–28% vs. 2–2·5%) that is generally mild and transient.[17,18] Allergic contact dermatitis secondary to the use of topical doxepin has been reported and is well known; however, the specific incidence of this outcome cannot be established with certainty based on the available data.[19–22] The incidence of cutaneous malignancy with the use of doxepin cannot be absolutely established, but it has not been reported in doxepin users.

Antibiotics and antiseptics

The literature is lacking with respect to robust studies in this category. Of particular note, however, is a comprehensive review of consolidated patch test findings performed in the U.K. where the results in over 8500 atopic patients were compared with those in over 33 000 nonatopic patients between 1995 and 1999. The incidence of local adverse events related to topical antibiotic and antiseptic use appears to increase with the use of neomycin sulphate and bufemac, but not bacitracin, in those aged over 40 years and with certain preservatives (formaldehyde, sorbic and benzoic acid, parabens) and fragrance.[23] The incidence of local side-effects and cutaneous malignancy with use of these agents cannot be established given the available data.[23,24]

Corticosteroids

Local adverse effects of TS are known, but are poorly characterized with respect to true incidence, given that evidence from studies performed to modern-day standards is lacking for many products. In controlled trials, secondary infection, skin atrophy, striae, burning, itching, folliculitis, acne-like eruptions and telangiectasia appear to be related to the use of TS, and also appear to be potency dependent.[25–31]

Cases of allergic contact dermatitis with topical corticosteroid use have been reported and are well documented.[32–36] Glaucoma is a reported finding known to be associated with steroid use but the incidence is not well defined. Similarly, while an association between systemic use of steroids and posterior subcapsular cataract has been extensively documented, an analysis of the literature from 1996 to 2001 yielded only seven cases in patients receiving TS.[37] Thus, there is a possible, but unsubstantiated, risk of cataracts associated with the use of TS. Skin carcinogenicity related to the use of TS has been a concern given known immunosuppressive effects for this class of agents, but there are no definitive data to establish that there is an increased risk. The approval process for newer formulations of TS frequently required longer-term animal carcinogenicity studies, and these studies have been unremarkable to date.[38]

In summary, there are few prospective vehicle-controlled trials of sufficient duration in patients with AD to provide a definitive answer to the question as to the incidence of local reactions to TS. With respect to cutaneous carcinogenicity, the clinical data to date do not substantiate an increased risk of cutaneous neoplasms in patients treated with TS. Limited animal carcinogenicity studies also do not support an increased risk for these topical agents. The topic merits further investiga-

tion before a clear evidence-based answer can be fully substantiated.

Calcineurin inhibitors

There are numerous well-designed clinical trials establishing the incidence of local side-effects with use of TCI in AD.[8,39–55] Trials using either tacrolimus or pimecrolimus generally demonstrate no significant differences when compared with a vehicle control in the incidence of local side-effects. Overall local side-effects commonly noted with these agents include local cutaneous effects (e.g. erythema, pruritus and irritation) as detailed in Tables 2 and 3. These tables summarize the local adverse event findings from the clinical studies submitted to the FDA to support the drug approval for pimecrolimus and tacrolimus, respectively. The findings also suggest that skin infections tend to be more numerous in patients receiving TCI, although this finding is not usually statistically significant.[42–46,48,53,56,57] Although the data do not establish a drug-related causal effect, the trend should not be dismissed and clinicians should keep the potential association in mind when using these agents. In general, there seems to be a greater predilection towards virally mediated infections as detailed in Tables 2 and 3. In a recently published study comparing control patients with AD vs. those treated with tacrolimus ointment, a significant increase in infection risk was not demonstrated; however, similar trends are noted and virally mediated infections appear to predominate (Table 4).[54] The topic merits further investigation before a clear evidence-based answer to this question can be fully substantiated.

Preclinical studies in animal models described in the package inserts for tacrolimus and pimecrolimus have demonstrated an increased risk of cutaneous malignancy with the use of topical TCI; however, the clinical relevance of these findings is unclear. In patients treated with pimecrolimus and tacrolimus a small number of cutaneous tumours has been reported to the FDA as of 30 March 2005. As of December 2004, the FDA had received 10 postmarketing reports of cases of cancer and a cancer-related adverse event following use of pimecrolimus. Four of the 10 cases occurred in children, three of these in children < 6 years of age, and the other six cases occurred in adults. Six cases described cutaneous tumours and four described lymphomas. As of the same time point (December 2004), the FDA had received 19 postmarketing reports of cases of cancer and a cancer-related adverse event following use of tacrolimus. Three of the 19 cases occurred in children up to 16 years of age, and 16 cases occurred in adults. Nine cases described lymphomas and 10 described cutaneous tumours, of which seven occurred at the site of tacrolimus application, and included cases of squamous cell carcinoma (SCC), cutaneous sarcoma, malignant melanoma and other tumour types.[58] These reports are not corrected for the number of patients exposed to each agent nor can the incidence of cutaneous malignancy be calculated, as the denominator of the number of patients exposed is unknown.

Overall, the local side-effect profile with TCI is predominantly local (burn/sting, erythema etc.) with a nonstatistically significant trend that favours an increase in infections, especially virally mediated diseases, vs. vehicle controls. Results

Table 2 Systematic review of the local side-effects of pimecrolimus (adapted from data supplied to the Food and Drug Administration and obtained via Freedom of Information Act summary basis of approval for pimecrolimus, tacrolimus)

	Paediatric patients, vehicle-controlled (6 weeks)		Paediatric patients, open-label (20 weeks) – pimecrolimus [n = 335; n (%)]	Paediatric patients, vehicle-controlled (1 year)		Adult active comparator (1 year) – pimecrolimus [n = 328; n (%)]
	Pimecrolimus [n = 267; n (%)]	Vehicle [n = 136; n (%)]		Pimecrolimus [n = 272; n (%)]	Vehicle [n = 75; n (%)]	
Skin infection NOS	8 (3·0)	9 (5·1)	18 (5·4)	6 (2·2)	3 (4·0)	21 (6·4)
Folliculitis	3 (1·1)	1 (0·7)	3 (0·9)	6 (2·2)	3 (4·0)	20 (6·1)
Skin papilloma	1 (0·4)	0	2 (0·6)	9 (3·3)	< 1	0
Herpes simplex	1 (0·04)	0	4 (1·2)	9 (3·3)	2 (2·7)	13 (4·0)
Herpes simplex dermatitis	0	0	1 (0·3)	4 (1·5)	0	2 (0·6)
Application site burning	28 (10·4)	17 (12·5)	5 (1·5)	23 (8·5)	5 (6·7)	85 (25·9)
Application site reaction NOS	8 (3·0)	7 (5·1)	7 (2·1)	9 (3·3)	2 (2·7)	48 (14·6)
Application site irritation	8 (3·0)	8 (5·9)	3 (0·9)	1 (0·4)	3 (4·0)	21 (6·4)
Application site erythema	1 (0·4)	0	0	6 (2·2)	0	7 (2·1)
Application site pruritus	3 (1·1)	2 (1·5)	2 (0·6)	5 (1·8)	0	18 (5·5)
Urticaria	3 (1·1)	0	1 (0·3)	1 (0·4)	< 1%	3 (0·9)
Acne NOS	0	1 (0·7)	1 (0·3)	4 (1·5)	< 1%	6 (1·8)

NOS, not otherwise specified.

Table 3 Systematic review of the local side-effects of tacrolimus (adapted from data supplied to the Food and Drug Administration and obtained via Freedom of Information Act summary basis of approval for pimecrolimus, tacrolimus)

	12-week adjusted incidence rate (%)[a]					Incidence (%)[b]	
	Adult (15–79 years)			Paediatric (2–15 years)			
	Vehicle (n = 212)	0·03% Tacrolimus ointment (n = 210)	0·1% Tacrolimus ointment (n = 209)	Vehicle (n = 116)	0·03% Tacrolimus ointment (n = 118)	Adult (n = 316)	Paediatric (n = 255)
Skin burning	26	46	58	29	43	47	26
Pruritus	37	46	46	27	41	25	25
Skin erythema	20	25	28	13	12	12	9
Skin infection	11	12	5	14	10	11	11
Eczema herpeticum	0	1	1	0	2	2	0
Herpes simplex	4	4	4	2	0	12	5
Pustular rash	2	3	4	3	2	6	8
Folliculitis	1	6	4	0	2	11	2
Urticaria	3	3	6	1	1	5	5
Maculopapular rash	2	2	2	3	0	4	3
Rash	1	5	2	4	2	2	5
Fungal dermatitis	0	2	1	3	0	2	6
Acne	2	4	7	1	0	2	4
Sunburn	1	2	1	0	0	4	4
Skin disorder	2	2	1	1	4	1	4
Skin tingling	2	3	8	1	2	2	1
Dry skin	7	3	3	0	1	0	1
Skin neoplasm benign	1	1	1	0	0	2	3
Contact dermatitis	1	3	3	3	4	1	1
Eczema	2	2	2	0	0	3	0
Exfoliative dermatitis	3	3	1	0	0	0	2

[a]In 12-week (twice daily), randomized, double-blind, parallel-group, vehicle-controlled phase III studies (in patients with atopic dermatitis; baseline mean body surface area affected = 46%).
[b]In open-label studies (up to 1 year) with 0·1% tacrolimus ointment.

Table 4 Overall incidence (%) of infections and application site reactions of clinical interest with tacrolimus ointment – a 4-year follow-up study (adapted from Hanifin *et al.*[54])

	Age group (years)			
	2–6 (n = 185)	7–15 (n = 206)	≥16 (n = 408)	Total (n = 799)
Application site events				
Pruritus	21·1	19·4	32·1	26·3
Pustular rash	15·7	11·2	4·9	9·0
Skin burning	20·5	18·0	32·8	26·2
Skin erythema	10·8	5·8	16·2	12·3
Skin infection	22·7	22·3	15·2	18·8
Herpes simplex	4·3	6·3	7·1	6·3
Warts[a]	6·5	7·3	1·7	4·3
Varicella zoster[b]	9·2	1·9	1·2	3·3
Molluscum contagiosum[a]	3·2	4·9	0	2·0
Eczema herpeticum	0	0·5	1·2	0·8

[a]More common in children than in adults.
[b]Varicella zoster includes chicken pox and shingles.

from prospective vehicle-controlled trials performed to date demonstrate no increased malignancy risk; however, the studies are not of sufficient duration or exposure to give a definitive answer regarding whether patients with AD treated with TCI are at an increased risk of cutaneous neoplasms. The topic merits further investigation before a clear evidence-based answer can be fully substantiated.

In summary, local adverse events are a feature of many topical therapies for AD, although there are few high-quality data of sufficient duration or depth (other than for TCI and recently approved TS) that allow quantification of the exact incidence, or establish an incidence greater than that of a control vehicle. Finally, there are no reliable data indicating an increased risk of cutaneous neoplasia with any topical therapy for AD, hence this question cannot be adequately addressed based on the existing data.

Question 4. What are the systemic exposures and physiological effects of topical therapies for atopic dermatitis?

The search strategy identified 682 papers and of these, 98 were considered potentially relevant when there was a mention of systemic absorption either by direct plasma level measurements of the compound, indirect product or metabolite, or alteration of the HPA axis. Further analysis identified 44 meeting initial inclusion criteria – primary literature and

quantifiable assessment of systemic absorption. Additional information was obtained from data available from package inserts and regulatory filings with the FDA.

Coal tar

Coal tar applied topically results in measurable systemic exposure to metabolites of the agent (56–380 times increase).[59] The effect of this increased systemic exposure on physiological functions, such as immunosurveillance and neoplasia risk, cannot be established based on the existing data and remains unknown.

Corticosteroids

Use of TS does result in absorption. The degree of absorption and subsequent systemic exposure to TS is based on many factors, such as molecular structure, vehicle, dosage applied, duration of application, use of occlusion, age of the patient, involved body surface area, skin inflammation and inherent metabolic differences among patients. The serum level of cortisol following the administration of topical 1% hydrocortisone cream varied from 47 to 961 nmol L^{-1} when used as a treatment for acute AD and from 18 to 241 nmol L^{-1} when used during convalescence.[60] Topical use of clobetasol resulted in peak serum levels of 0·6–15·8 ng mL^{-1} with associated depression of cortisol activity for 96 h after application.[61] Topical fluticasone 0·05% resulted in serum levels of 59–264 pg mL^{-1}, with two children in a multicentre study demonstrating HPA axis suppression.[62] Other studies measuring the effect of TS on HPA suppression are found in Table 5. The reported impact on growth of use of TS has been varied. Some observational studies have reported an apparent delay in growth and abnormal bone turnover, whereas others have not.[62–67] The effect of TS on cutaneous immunology includes reports of decreased natural killer (NK) cell activity and inhibition of Langerhans cell (LC) activity.[68,69] The effect of TS on systemic immune function and neoplasia risk remains unknown as there are no data available regarding this issue.

Calcineurin inhibitors

Use of TCI also results in absorption and systemic exposure, but less so than that observed with TS. Absorption of TCI, when it occurs, appears to be in part dependent on agent and dose as well as on area treated. Topical tacrolimus 0·1% has exhibited generally low, but varied, absorption with maximum systemic concentrations usually < 5·0 ng mL^{-1} and with most measured levels < 1 ng mL^{-1} in infants, children and adults.[39,42,43,70] Most published data are limited, in that often only mean concentration is reported, not maximum concentration. The highest reported level has been 9·5 ng mL^{-1} in a child and 20 ng mL^{-1} in an adult.[71] Available data suggest that the bioavailability of topical tacrolimus ointment is < 0·5% relative to intravenously administered tacrolimus and < 5% of orally administered tacrolimus in patients with AD[72] (Tables 6 and 7). The effect of tacrolimus on immunity has involved measuring immune response in children receiving pneumoccocal, tetanus and *Haemophilus influenzae* vaccination. No apparent effect on these parameters of immunity was detected.[73] Topical tacrolimus used in an open-label study for 6 months or 1 year did not cause suppression of delayed-type hypersensitivity responses, based upon recall antigen testing, an indirect but very comprehensive measure of cellular immune response.[39]

Pimecrolimus absorption also occurs, although most treated patients have levels that are undetectable (below lower limits of quantification).[8,74,75] When compared with TS, skin concentrations of drug and flux are both less with topical pimecrolimus[76] although occasional patients demonstrate serum concentrations of pimecrolimus as high as 2·6 ng mL^{-1}.[8] Immunologically, topical pimecrolimus induces apoptosis of T cells without affecting LCs.[68] There have been no observed effects on B cell- or T cell-mediated vaccine responses,[77] and in a vehicle-controlled study there was no effect on skin immune response with recall antigen testing.[45] In summary, few patients treated with TCI exhibit measurable systemic exposure to the drug, with more patients having detectable blood levels with tacrolimus than with pimecrolimus. However, the systemic exposure to either compound is limited, transient in nature and far less than that observed with oral use of these compounds.

In summary, all of the therapies for AD can result some systemic exposure to the compound and thus all topical therapies for AD have the potential for systemic-related side-effects or toxicity. The greatest systemic exposure to a topical therapy used for AD occurs with use of coal tar and TS. The best-documented physiological effects of systemic exposure to TS are glucocorticoid related, with effects on the HPA axis and clinical manifestations including adrenal suppression and insufficiency, Cushing's syndrome and growth retardation. Some cases have resulted in serious outcomes, including hospitalization and death.[78] The systemic exposure demonstrated with coal tar or TCI has not been shown to result in any significant systemic physiological effects or toxicity based on the existing data.

Question 5. What is the postulated cause of neoplasia in those treated with topical therapies for atopic dermatitis?

One may consider at least three potential mechanisms by which topical therapies may increase the risk of neoplasia in individuals with AD: (i) direct effects of mutagenesis or genotoxicity, (ii) absorption of drug leading to systemic immunosuppression or effects on local draining lymph nodes and (iii) local cutaneous effects leading to inhibition of immunosurveillance. In addition, there may be contributions from the active ingredient(s), the underlying condition (e.g. AD and associated immune dysregulation and barrier compromise), as well as a combination of any or all of these with the known major carcinogenic effects of ultraviolet radiation. For purposes of this review the focus was on the theoretical mechanisms of increased risk of neoplasia with use of TCI. While

Table 5 Systematic review of the effect of topical steroids on the hypothalamic-pituitary-adrenal (HPA) axis of children

	Crespi[228]	Lucky *et al.*[229]	Smitt *et al.*[225]	Patel *et al.*[226]	Hanifin[230]	Ellison *et al.*[11]	Wolkerstorfer *et al.*[227]	Moshang[231]	Friedlander *et al.*[27]	Paller *et al.*[232]
n	39	20	40	14	62	35	31	55	51	94
Age group	Paediatric		1–15 years	3·1–10·7 years	6 months–2 years	0·7–18·7 years	5 months–13 years	4 months–12 years	3 months–6 years	2–12 years
Extent of AD			44–53% BSA	16–90% BSA		Disease severity score 5–8	Severe		Moderate–severe, mean 64% BSA	> 50% BSA
Type of glucocorticoid used	Alclometasone cream	Desonide 0·5%/HC 2·5%	TAC 0·1%, alclometasone cream	1% HC; 9/14 intermittently used moderate–high potency	Mometasone cream/HC cream	Mild, moderate, potent	FP 0·05% dilutions (5%, 10%, 25% and 50%) with wet-wraps	Prednicarbate cream 0·1%	FP cream 0·05%	0·01% fluocinolone in peanut oil
Design; dose	Open; b.i.d.	Open, parallel; b.i.d.	b.i.d., mean 35·2 g weekly	48·7–223·2 mg m^{-2} BSA daily	Matched control	2·6–5·6 g m^{-2} BSA daily	0–2071 μg m^{-2} BSA	Open; b.i.d.	Mean 209·1 g for > 3-year olds, 96·7 g for < 3-year olds	Daily
Duration	3 weeks	4 weeks	3 weeks	3–10 years	3 weeks	0·7–18·7 years	2 weeks	3 weeks	3–4 weeks	4 weeks
Test	Morning cortisol	CST	Plasma cortisol levels	Plasma cortisol levels	CST	Plasma cortisol levels	Plasma cortisol, urine cortisol/creatinine	CST	Plasma cortisol, CST	Plasma cortisol, CST
Conclusion	All normal	All normal	Suppression after 2 weeks, no further after 3	No change basal/peak levels, but peaked earlier	1 abnormal CST: mometasone	No change for mild potency, suppression in 4/4 patients on potent steroids	Suppression of HPA axis with absolute amount of applied FP cream, no relation with urinary ratio	All normal	2/43 children with evolving suppression	No suppression; all normal CST

AD, atopic dermatitis; BSA, involved body surface area; HC, hydrocortisone; TAC, triamcinolone acetonide; FP, fluticasone propionate; b.i.d., twice daily; CST, cotrosyn stimulation test.

Table 6 Systematic review of the systemic absorption of tacrolimus

	Ruzicka *et al.*[233]	Alaiti *et al.*[72]	Reitamo *et al.*[39]	Patel *et al.*[234]	Harper *et al.*[70]	Stiehm *et al.*[73]
n	213	39	314	12	39	23
Age	13–60 years	5–75 years	18–70 years	7–22 months	6–12 years	2–12 years
Extent of AD	Moderate–severe	Moderate–severe	5–60% BSA	Moderate–severe	Moderate–severe	> 10% BSA
Duration of AD	Not known	4–12 months	2–70 years	Not known	Not known	Not known
Strength	0·03%, 0·1% and 0·3% ointment	0·03% ointment	0·1% ointment	0·03% and 0·1% ointment	0·1% ointment	0·03% ointment
Amount	200–1000 cm^2 b.i.d.	0·7–27 mg m^{-2} BSA	b.i.d.	Unknown	0·007–0·016 mg kg^{-1}	b.i.d.
Duration	3 weeks	8 days	6 or 12 months	Unknown	14 days	7 weeks
Test	Blood levels	Blood levels	Blood levels	Blood levels	Blood levels	Blood levels, Abs, vaccine titres, CD3, CD4, CD8, CD19
Blood levels (ng mL^{-1})	Max conc. 1·1 (0·03%), 3·3 (0·1%), 4·9 (0·3%)	Mean max conc. 0·1–3·5	< 1·0 in 74·7% patients, 1–2 in 16·8%, 2–5 in 5·4%, 1 patient > 5	All patients < LoQ in 1st month, no dose effect	< 1 in 92% patients, 17% < LoQ; greatest conc. increase with increasing area treated	Max conc. 1·1, all others < 1·0 at all time points
AUC	Not measured	Increased with larger treatment area, increased in facial use	Not measured	Not known	Group 2 with increase, all groups decreased 14 days later	Not measured

AD, atopic dermatitis; BSA, involved body surface area; b.i.d., twice daily; Abs, antibodies; max, maximum; conc., concentration; LoQ, lower quartile; *AUC*, area under curve.

Table 7 Systematic review of the systemic absorption of pimecrolimus

	Thaci *et al.*[74]	Billich *et al.*[76]	Allen *et al.*[8]	Ling *et al.*[75]
n	13	Rat, pig, human skin	25	49
Age	20–57 years	Human skin: 64, 24 years	4 months–14 years	Mean 36·1–40·5 years
Severity of AD	Hand eczema	N/A	> 10% BSA	Mean 37–49% BSA
Duration of AD	30 weeks–15 years	N/A	Unknown	Unknown
Strength	1% cream	1% w/v	1% cream	1% cream
Amount	b.i.d., dorsal and palmar hand with occlusion	300 μL	Daily to all affected areas, face and neck	Unknown
Duration of treatment	3 weeks	48 h	3 weeks	3 weeks
Test	Blood levels	Franz diffusion, skin strippings	Blood levels	Blood levels
Blood levels (ng mL^{-1})	73·6% < LoQ (0·1), max conc. = 0·91 (day 8), 0·26 (day 22)	Skin conc. of same magnitude vs. steroids, but rate lower; skin conc. same vs. tacrolimus, but rate lower	81% of patients < 1 with > 50% < LoQ (0·5)	95% < LoQ (0·5)
AUC	Max *AUC* 0–12 = 7·6 ng h mL^{-1} (day 8), decreased to 2·91 (day 22)	Not measured	*AUC* 0–12 only possible to calculate in 7 patients	*AUC* 0–24 only possible to calculate in 2 patients

AD, atopic dermatitis; N/A, not applicable; BSA, involved body surface area; b.i.d., twice daily; LoQ, lower quartile; max, maximum; conc., concentration; *AUC*, area under curve.

numerous TS have been available and utilized over decades for the treatment of AD and other inflammatory skin disorders, only the newer TCI have been more rigorously assessed for their carcinogenic capacity. The available scientific data were reviewed and interpreted in the context of the current understanding of the role of the immune system in protecting

against the development and progression of cutaneous malignancy.[79]

In considering the potential direct carcinogenic effects of TCI on keratinocytes, it is possible that the TCI may act as 'initiators' (e.g. mutagens) or 'promoters' (e.g. stimulators of proliferation) of neoplasia. As part of the preclinical development,[80] both tacrolimus and pimecrolimus were assessed for their genotoxicity in bacteria (e.g. Ames test) and mammalian cells, as well as clastogenic (i.e. chromosomal breaking) effects *in vivo*. No assay demonstrated any direct mutagenic or chromosomal-damaging effects attributable to the TCI. Hence, any carcinogenic effects attributable to TCI are much more likely to be the result of indirect activities, e.g. suppression of the host immune system and/or potentiation of the damaging effects of ultraviolet radiation.

Rodent models of carcinogenicity were reviewed and include assays with TCI given systemically, intradermally or topically. Protocols varied from long-term, drug-only studies to assessment of effects of TCI on photocarcinogenicity and two-stage chemical carcinogenicity protocols. High-dose dermal doses of tacrolimus and pimecrolimus were both associated with lymphoma, consistent with a systemic immunosuppressive effect.[80] Similarly, there was an association with lymphomas for orally administered pimecrolimus at markedly high levels, e.g. > 250 times the maximum recommended human dose. There was no discernible effect on development of cutaneous tumours for orally or dermally administered tacrolimus or pimecrolimus. An observation was made of benign thyroid adenomas only in a 2-year rat study with low-dose oral pimecrolimus. This effect was not observed in the high-dose pimecrolimus experiments. In summary, lymphomas were observed in drug-only murine protocols that would be expected to result in substantially higher systemic levels of TCI than achieved with topical use as is done in AD, and no skin neoplasia was observed under these conditions.

Topical administration of tacrolimus ointment and pimecrolimus cream has also been assayed in animal models for their effects on cutaneous photocarcinogenesis.[80] An increased rate of tumour formation was attributable to topical tacrolimus, but not to topical pimecrolimus (curiously, an increased rate of tumour formation was seen with the cream vehicle of the pimecrolimus formulation). Given the thinness of murine epidermis relative to human epidermis, with any increase in photocarcinogenesis one must consider the possibility of drug absorption and systemic immunosuppression, as opposed to local immune effects. No attempt was made in these experiments to distinguish local from systemic effects of the TCI.

The results of mouse two-stage chemical carcinogenesis studies are shown in Table 8. In this experimental system, mouse skin is painted once with a chemical mutagen (e.g. 'initiator' 7,12-dimethylbenz[α]anthracene), and repeatedly thereafter with a cell activator and stimulator of proliferation (e.g. 'promoter' 12-O-tetradecanoylphorbol-13-acetate). In one study, when tacrolimus was applied 2 h after each application of the promoter, papillomas were significantly increased.[81] Analysis of the draining lymph node lymphocytes revealed a substantial alteration in T-cell counts, consistent with a systemic immunosuppression or immunosuppression in the draining lymph nodes. However, in several other studies, when either tacrolimus or ciclosporin was applied topically *before* the promoter, there was a protective effect of the TCI against tumorigenesis.[82–84] The apparently paradoxical effect[85] of TCI protecting against neoplasia may be explained by the fact that a role for T cells in promoting carcinogenesis has been identified in experimental cancer models,[85–87] including two-stage chemical carcinogenesis.[88] Thus, the effects that TCI may have on promotion of cutaneous neoplasia remain to be fully elucidated.

In renal transplant recipients who continually take oral calcineurin inhibitors as part of a systemic immunosuppressive regimen to prevent graft rejection, there is a clear increase in

Table 8 Mouse chemical carcinogenesis studies with topical calcineurin inhibitors

Author	Model	Result	Comments
Niwa *et al.*[81]	2-stage chemical carcinogenesis (DMBA/TPA) ± topical tacrolimus (daily, 2 h after TPA)	Increased papillomas and carcinomas	Marked increase in tumorigenesis; associated with marked decrease in CD4/CD8 ratio of draining lymph nodes; c/w systemic immunosuppression
Jiang *et al.*[82]	2-stage chemical carcinogenesis (DMBA/TPA) ± topical tacrolimus (2 times weekly, 15 min before TPA)	Decreased papillomas	Marked decrease in tumorigenesis; no mechanism sought; c/w topical anti-inflammatory effects as protective
Yamamoto *et al.*[83]	2-stage chemical carcinogenesis (DMBA/dithranol) ± topical ciclosporin (2 times weekly, 15 min before dithranol)	Decreased papillomas	Marked decrease in chemical carcinogenesis; no mechanism sought; c/w topical anti-inflammatory effects as protective
Yokota *et al.*[84]	2-stage chemical carcinogenesis (DMBA/TPA) ± topical (before TPA) vs. oral ciclosporin	Topical: decreased papillomas; oral: increased carcinomas	Marked decrease in tumorigenesis; c/w topical anti-inflammatory effects as protective; c/w systemic (oral) as immunosuppressive

DMBA, 7,12-dimethylbenz[α]anthracene; TPA, 12-O-tetradecanoylphorbol-13-acetate; c/w, consistent with.

cancer risk, including malignancies of the skin.[89] While several of these cancers are virally associated [e.g. Epstein–Barr virus (EBV) and lymphoproliferative lymphomas; human papillomavirus and cutaneous SCC or cervical cancers], others are not (e.g. thyroid, renal and lung carcinoma). Many of these patients have also received systemic corticosteroids, and thus it is difficult to separate the relative contributions of these immunosuppressive medications in downregulation of the antiviral and antitumour response. Nonetheless, systemic absorption is a consideration of potential increased risk of neoplasia in patients treated with TCI. Furthermore, several cases of cutaneous T-cell lymphoma have also been reported to progress or transform with use of oral calcineurin inhibitors.[90–100]

While systemic absorption of TCI may be minimal, local effects on immunosurveillance are possible, and in fact are likely to be responsible for their ability to treat AD effectively. These effects include inhibition of T-cell production of key cytokines, such as interleukin-2 and interferon-γ, presumed to play roles in the antitumour response. One key distinction from corticosteroids is that topical pimecrolimus does not appear adversely to affect the number or function of LCs, the presumed antigen-presenting cells of the epidermis.[68] If LCs are important in initiating antiviral and/or antitumour immune responses, then this would suggest that topical pimecrolimus is less likely to affect this pathway than corticosteroids.

In summary, TCI are not mutagenic or genotoxic (e.g. potential initiators) or stimulators of proliferation (e.g. potential promoters). Therefore, the major theoretical consideration for their role in carcinogenesis is with respect to inhibition of immunosurveillance through systemic absorption or local effects. Furthermore, there is experimental evidence that TCI may inhibit cutaneous carcinogenesis under certain conditions, perhaps through an anti-inflammatory effect on tumour-promoting T cells. The precise effects of individual TCI on the various components (e.g. $\alpha\beta$ and $\gamma\delta$ T cells, LCs and dendritic cells, NK and NK/T cells) of local immunosurveillance, and the contribution of such to risk of neoplasia, if any, remain to be fully elucidated.

Question 6. What is the prevalence of neoplasia in the population with and without atopic dermatitis?

Manuscripts identified in the initial literature search were excluded from further review if they did not include human subjects, were not in English, were individual case reports, or were published only as abstracts. This yielded 375 manuscripts published in the past 10 years. By an initial title review, 108 appeared to be on topic. Full abstracts of the 108 were reviewed and by this review 50 were thought to be appropriate. The full manuscript for each of these publications was then read. Twelve were noted to be off topic or were rejected because of the above exclusion criteria. An additional seven publications were reviewed based on a review of the reference sections of those publications that were fully reviewed. As a result, 45 publications were evaluated more fully.[101–144]

There is no precise source for determining the rate of malignancy in those who do not have AD. One publication that estimates the rate of malignancy in the U.S.A. estimates that the life-long risk of developing lymphoma for those between birth and 39 years of age is 0·14% for men and 0·09% for women; for those between 40 and 59 years of age is 0·46% for men and 0·31% for women; and for those between 60 and 79 years of age is 0·32% for men and 1·00% for women.[101] Both this review and another noted that the yearly rate of lymphoma had been increasing for several years but has now levelled off.[101,102] Unfortunately, it is impossible to use Surveillance, Epidemiology and End Results data to differentiate lymphoma in those with AD from lymphoma in those who do not have AD, which is important to the study question.

Seven studies specifically evaluated lymphoma and AD (or eczema).[103–109] These studies found odds ratios both above and below 1·0. An estimated random effects meta-estimate of these studies is 0·87 (95% confidence interval, CI: 0·4–11·3), and the wide CI reflects the imprecision of this estimate. Of note, three studies found that exposure to TS or systemic steroids increased the risk of lymphoma.[103–105] The incidence of lymphoma in those with asthma, hay fever or both is not different from that in the general population.[110]

Several studies also evaluated the relationship between AD and other types of malignancies including prostate cancer, lung cancer, leukaemia, pancreatic cancer, brain tumours, skin cancers, cervical cancer and myeloma.[107–127] No association between atopic illness and an increase in a specific malignancy or malignancy in general could be demonstrated.

In summary, it does not appear that AD is likely to be associated with any specific local or systemic malignancy. Further study is needed before any firm conclusion is possible.

Question 7. What are the systemic side-effects of topical therapies for atopic dermatitis?

The literature search yielded 602 titles of which 105 were included, and five additional studies were identified through hand searches.[6,17,18,26–29,39,41–46,48–50,52,54–57,70,77,128–130,145–227] Inclusion criteria included: trials reported as full length, English-language papers, a length of treatment of 2 weeks or longer, and a sample size of 20 or more. Additionally, after the initial search and review were completed, steroid studies were further restricted to those performed since 1990. Case reports, letters, editorials and nonsystematic reviews were excluded.

Corticosteroids were the most frequently studied agent, and there were no reports of solid or haematological malignancy or systemic infections found in any clinical trials (Table 9). It should be noted that because corticosteroids have been prescribed for so many years, doctors may not have felt compelled to submit reports of malignancy. The same can be said for other long-standing agents such as emollients, coal tar etc. Conversely, the lack of reports may indicate that there is no increased risk, or perhaps even a decreased risk with the use of these agents.

Table 9 Systematic review of the systemic side-effects (infection and neoplasia) of topical therapies for atopic dermatitis

Agent	Studies	Patients	Age range	Time on drug	Results
Tacrolimus[a]	15	13 170	2–79 years	2 weeks–49 months	No malignancy; spontaneous reports of 11 lymphomas
+Steroid	4	2438	2–70 years	3 weeks–6 months	No malignancy
Pimecrolimus[b]	5	844	3 months–adult	3 weeks–6 months	No malignancy: spontaneous reports of 13 lymphomas
+Steroid	7	3064	3 months–79 years	3 weeks–2 years	No malignancy
Steroid	39	5325	6 months–88 years	2 weeks–6 months	No malignancy; no systemic infections
+Anti-infective	11	1202	1–84 years	13 days–1 month	No systemic events
Emollients	3	267	18–55 years	2 weeks–3 months	No systemic events
Tar	1	117	Mean 19 years	Mean 30 days	7 malignancies reported (< 17·3 expected): no lymphoma
Doxepin	4	952	12–65 years	1 week	No systemic effects
Anti-infectives	4	171	1–74 years	2–10 weeks	No systemic events
Atopiclair	1	30	> 16 years	1 week	No systemic events
Sodium chromoglycolate	3	196	5 months–18 years	12 weeks	No systemic events
Vitamin B_{12}	1	49	18–70 years	8 weeks	No systemic events
Ciclosporin	1	20	2–29 years	2 weeks	No systemic events
Phosphodiesterase inhibitors	2	117	18–64 years	2–4 weeks	No systemic events

[a]Spontaneous reports of 11 lymphomas outside of clinical trials as of February 2005.
[b]Spontaneous reports of 13 lymphomas outside of clinical trials as of February 2005.

No malignancies have been reported in the published clinical trials for the TCI tacrolimus and pimecrolimus; however, 11 and 13 cases, respectively, of lymphoma were spontaneously reported to the FDA and/or companies manufacturing these products as of 1 March 2005 and data are on file with the FDA, Novartis and Astellas. These spontaneous case reports cannot be completely evaluated, but based on a review of the information that is available, no case of an EBV-positive B-cell lymphoma typical of an immunosuppression-related lymphoma has been reported. Whether these cases represent more than would be expected in the general population of patients with AD is impossible to determine as the exact exposure in terms of patient number (the denominator needed for comparison of population-based incidence rates), dose and duration of treatment is not known.

Based on this systematic review of published clinical trials and other sources of information, there are no data indicating an increased risk of systemic side-effects or complications (systemic infections or cancers) related to the use of the various topical medications in the treatment of AD (Table 9). However, the length of many of the studies evaluating these treatments was only a matter of weeks, and clearly was not long enough to make any definite conclusions. At least with TS, decades of open use in clinical practice with no documented relationship with systemic infections or systemic malignancy provide reasonable confidence that these treatments are unlikely to lead to systemic infections or cancers. TCI have been the most intensely studied of the topical therapies for AD with excellent short-term (weeks) and long-term (years) safety as demonstrated in the highest form of evidence-based randomized controlled trials. The spontaneous reports of lymphoma that have occurred outside of controlled trials cannot be used to conclude that the use of these compounds can result in systemic malignancy. Moreover, the types of malignancies reported are not consistent with those expected to arise with systemic exposure and the subsequent neoplasm development related to immunosuppressant effects. However, the currently available data do not allow one to exclude a risk of malignancy with use of these compounds.

Discussion

AD is a common illness, yet, surprisingly, there are few quality data derived from prospective, population-based cohorts as to its exact prevalence in the U.S. and other populations. The best estimate based on the limited data available suggests an approximately 15% lifetime prevalence of the disease. The burden of illness of AD must be substantial given the prevalence of the disease and the impact this disease has on the QoL of the patient and his/her family. The pathophysiology of AD is similarly incompletely understood but probably involves intrinsic or acquired abnormalities of the epidermal barrier as well as defects in the regulation of immune and inflammatory function. Whether genetic vs. environmental factors predominate in the phenotypic expression of AD remains unknown. Further identification of the pathophysiological mechanisms of AD is critical to the development of novel and targeted therapies for this disorder.

The mechanism(s) of action of current topical therapies for AD include those with little effect on immunosuppression (emollients, doxepin etc.), broad effects (TS) and narrower effects (TCI) and hypothetically these therapies could result in systemic immunosuppression if drug dose and penetration lead to significant absorption. Absorption with TS and TCI does occur but varies widely depending on a variety of factors including, but not limited to, disease state, dosage form and the unique physiology of each patient. Local side-effects from these agents are generally greater with TS than have been demonstrated with TCI.

Most of the topical agents used in the treatment of AD do not have systemic side-effects. There are systemic laboratory alterations described with topical use of potent TS; however, the clinical relevance of these laboratory changes remains unknown. Evidence of systemic immunosuppression resulting from topical application of calcineurin inhibitors has not been documented. Systemic therapy with oral calcineurin inhibitors does cause immunosuppression and has been accompanied by the development of either cutaneous malignancies (SCC) or EBV-related B-cell lymphomas as seen in chronically immunosuppressed transplant patients. An increased rate of EBV-related B-cell lymphomas and/or cutaneous SCC would be expected in patients with AD treated with TCI if sufficient absorption of these agents altered immunosurveillance. However, neither B-cell lymphomas, as described in patients immunosuppressed by oral calcineurin inhibitors, nor an increase in epithelial malignancies with TCI have been established. Spontaneous cases of such tumours within this population have been reported, but these reports are few in number and appear to be within the occurrence rate expected in 'normal' populations. In summary, topical anti-inflammatory agents do not appear to promote local cutaneous neoplasms, but the available data are limited and do not exclude the possibility of this outcome. Given the enormous exposure of the population with AD to these agents, the potential risk of malignancy must be low given that significant findings would have been observed, particularly for TS that have been widely used for about half a century. In contrast, topical TCI have been available for only about 5 years, and therefore the clinical experience in understanding the potential for lymphoma is much more limited. Clearly, investigation with longer-term trials is required to delineate further this potential risk.

What is known with regard to the safety of topical therapies for AD? (i) The prevalence of AD varies but is estimated to be approximately 15% over the lifetime of an individual. (ii) QoL is adversely affected by AD. (iii) The pathophysiology of AD is multifactorial and involves abnormalities in barrier function and regulation of the inflammatory response. (iv) The local side-effects of topical AD therapy are predominantly a local cutaneous effect (erythema, itch, burn etc.), and infections are infrequent and are usually mild. (v) The systemic exposure to TS and TCI is limited. The only well-documented systemic side-effect of these agents is the effect of TS on the HPA axis. (vi) The postulated mechanism of neoplasia in patients treated with topical immunosuppressants is likely to be an effect on immunosurveillance as genotoxicity and mutagenicity do not occur. (vii) The incidence of neoplasia in patients with AD is not increased vs. control patients in clinical trials of any topical agents but large long-term controlled trials are lacking in all.

Areas of uncertainty and unmet needs regarding the safety of topical therapies for AD include the following: (i) the exact point and lifetime prevalence of AD in various age groups and ethnic populations with data that allow comparison among populations; (ii) the magnitude of the effect of AD on an individual's QoL as well as that of the carer(s) when compared with a normative population; (iii) whether improvement in QoL with topical therapy for AD is clinically meaningful; (iv) the exact abnormality in immune regulation and barrier function responsible for the development of AD; (v) the percentage of patients treated with TS and TCI who have significant systemic exposure and an effect on systemic immunological function, and how such patients be determined *a priori* so that alternative therapy can be used; (vi) the incidence of neoplasia in patients with AD treated with TS and TCI when compared with that of the general population.

The areas of uncertainty require resolution that can come only from well-designed clinical trials, and certain issues, such as the risk of immunosuppression-related malignancy associated with use of topical therapies for AD, may never be resolved. At this time, the evidence supports the continued use of all of the currently available topical therapies for AD. The data do not support the use of one therapy over another based on any current evidence of difference in safety profiles among the various topical therapies for AD. Although systemic side-effects have occasionally been noted with TS but not with TCI no direct head-to-head studies evaluating safety of these two treatments have been performed. As such, the choice of therapy for AD should be individualized based on the tolerability and efficacy of each agent. Until data are available that support the consideration of other factors, such as safety, in choosing therapy for AD, individualized tolerability and efficacy should remain the most important factors in choice of treatment for AD.

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Supplementary Material

The following supplementary material is available for this article:

Appendix S1. Search strategies.

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.

1365–2133. 2006. 07538x (This link will take you to the article abstract).

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Conflicts of interest

Fennerty	Consulting fees from Novartis
Peterson	Consulting fees from Novartis
Ellis	Lecture and Consultant fees from Novartis and manufacturers of other therapies for atopic dermatitis
Callen	Consulting fees from Novartis
Paller	Lecture and Consulting fees and research support from Novartis and Astellas
Margolis	Consultant fees from Astellas, research support from Novartis
Eichenfield	Lecture and Consulting fees from Novartis and manufacturers of other therapies for atopic dermatitis, Research support from manufacturers of therapies for atopic dermatitis
Chamblin	Lecture fees from Astellas
Goldfarb	Lecture and Consulting fees and research suport from Novartis and Fujisawa
Piacquadio	Drug development consulting and services for manufacturers of therapies for atopic dermatitis.

