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Interventions for atopic dermatitis in dogs: a systematic review of randomized controlled trials

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Conflicts of Interest

From 1997 to 2008, Thierry Olivry has participated in NC State University-approved consulting activities for Novartis Animal Health Switzerland (distributors of ciclosporin, which is reviewed herein), Schering-Plough Animal Health USA, Sogeval USA and Janssen Animal Health, Belgium. From 1997 to 2008, he has obtained research funding from Corixa USA, Heska USA, Nosan Japan, Novartis Animal Health Global, Oligos USA, Searle (distributors of misoprostol discussed herein) USA, Schering-Plough Animal Health USA, Virbac France (distributors of Genesis triamcinolone spray mentioned herein) and Nippon Zenyaku (Zenoaq) Japan.
Ralf Mueller has consulted for Novartis Animal Health Switzerland (distributors of ciclosporin reviewed herein) and Royal Canin France. He has obtained research funding from Bayer Animal Health Germany, Boehringer Ingelheim Denmark, Laboratoire de Dermo-Cosmétique Animale (LDCA) France, Pfizer Animal Health Germany, Procter & Gamble USA, TEVA Animal Health (previously DVM-IVX) USA and Virbac France (European distributors of Histacalmine hydroxyzine–chlorpheniramine combination, and whose US subsidiary distributes Genesis triamcinolone spray; both are reviewed in this paper).
Chris Chesney consulted for Schering-Plough and Pfizer Animal Health UK.
Neil McEwan has obtained research funding from Leo Denmark, Virbac France and Schering-Plough Animal Health UK, and he participated in a trial funded by Phytopharm UK.
Prior to 2004, Aiden Foster acted as consultant to Merial Animal Health UK, Leo Animal Health UK and Pfizer Animal Health UK; for Novartis Animal Health Inc. and Phytopharm plc who manufacture ciclosporin and PO7P respectively. Before 2004, he obtained research funding from Merial, Novartis and the Heska Corporation.
Hywel Williams does not have any conflicts of interest.

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Abstract

The objective of this systematic review, which was performed following the guidelines of the Cochrane collaboration, was to assess the effects of interventions for treatment of atopic dermatitis (AD) in dogs. Citations identified from three databases (MEDLINE, Thomson's Science Citation Index Expanded and CAB Abstracts) and trials published by December 2007 were selected. Proceedings books from the major veterinary dermatology international congresses were hand searched for relevant citations. The authors selected randomized controlled trials (RCTs), published from January 1980 to December 2007, which reported the efficacy of topical or systemic interventions for treatment or prevention of canine AD. Studies had to report assessments of either pruritus or skin lesions, or both. Studies were selected and data extracted by two reviewers, with discrepancies resolved by a third arbitrator. Missing data were requested from study authors of recently published trials. Pooling of results and meta-analyses were performed for studies reporting similar interventions and outcome measures. A total of 49 RCTs were selected, which had enrolled 2126 dogs. This review found some evidence of efficacy of topical tacrolimus (3 RCTs), topical triamcinolone (1), oral glucocorticoids (5), oral ciclosporin (6), subcutaneous recombinant γ-interferon (1) and subcutaneous allergen-specific immunotherapy (3) to decrease pruritus and/or skin lesions of AD in dogs. One high-quality RCT showed that an oral essential fatty acid supplement could reduce prednisolone consumption by approximately half. Additional RCTs of high design quality must be performed to remedy previous flaws and to test interventions for prevention of flares of this disease.

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Background

Atopic dermatitis (AD) is a chronic skin disease that can affect humans and animals such as dogs. The International Task Force on Canine Atopic Dermatitis recently defined this canine disorder as 'a genetically-predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed to environmental allergens'.[1]

The treatment of canine AD usually involves the concurrent use of multiple interventions aimed at different facets of the disease.[2] Where ingestion of food allergens or insect bites appear to worsen signs of AD, measures can be taken to avoid these.[2] When offending environmental allergens are identified, allergen-specific immunotherapy has been used to prevent relapses of

canine AD on future allergen exposure.[3] To reduce the severity of clinical signs, veterinary practitioners have prescribed various drugs with anti-inflammatory or antipruritic effect.[2] Antibacterial or antifungal medications are helpful when concurrent skin infections are diagnosed or when microbial allergens are suspected to be involved in the perpetuation of canine AD.[2]

Numerous drugs are prescribed currently to relieve signs of AD in dogs, and these recommendations are based on results of clinical trials performed with small numbers of dogs or without stringent design. Moreover, many drugs are widely used without ever having been tested in any trial. There are concerns that some drugs could exhibit minimal or no beneficial effects. Additionally, medications could be shown to be effective for short-term treatment, yet could provide insufficient benefit for long-term management of canine AD. Drug administration could result in harmful adverse events that are unreasonable when compared with the benefit provided. Importantly, the issue of benefit must also be weighed against the cost of medication, as in many countries the treatment of pet illnesses is not covered by veterinary medical insurance. Finally, AD being a chronic disease, treatment often must be continued for years and, therefore, it must be cost-effective for owners of affected dogs.

In the past two decades, the drugs most commonly prescribed for the treatment of canine AD have included glucocorticoids,[4] antihistamines,[5] essential fatty acids (EFA)[6] and various nonsteroidal anti-inflammatory drugs.[7] A systematic review was recently performed to examine the evidence of benefit and harm of pharmacological interventions used for the treatment of canine AD.[8] In that review, trials using EFA and immunotherapy were not included. Moreover, that earlier review exhibited several limitations as it included trials with or without participant randomization, and the authors did not examine clinical studies that had not been published in peer-reviewed journals. The process of participant randomization is important to prevent the phenomenon of selection bias.[9] Because clinical trials whose results do not support the efficacy of an intervention often are not published,[10] it is possible that the previous systematic review might have overestimated the treatment effect of some drug classes by not reviewing trials presented at meetings but not published in peer-reviewed journals. To overcome the caveats of the previous publication, it was decided to refine the process of systematic review by applying the stringent criteria established by The Cochrane Collaboration (http://www.cochrane.org). The aim of this study was to assess the effects of interventions for the treatment of AD in dogs.

Materials and methods

Criteria used for selecting studies for this review

Types of studies
Randomized controlled trials.

Types of participants
Studies were included that enrolled dogs with skin lesions or pruritus diagnosed as AD, 'allergic inhalant dermatitis' or 'atopy'. Diagnosis by fulfilment of published diagnostic criteria such as those of Willemse[11] or Prélaud *et al.*[12] was acceptable. In the absence of specific mention of these named criteria, trials were included if the description of the participants' clinical signs suggested the diagnosis of AD based on standard methods in vogue at the time of study performance.[13,14]

Types of interventions
Randomized controlled trials reporting the efficacy of the following interventions were considered for review: (i) topical or systemic pharmacological interventions; (ii) individually administered or diet included fatty acid supplements; (iii) injectable immunomodulators (e.g. allergen-specific immunotherapy); (iv) allergen-avoidance measures (e.g. house dust mite control); and (v) other hygiene and nutritional interventions (e.g. flea control, diet change, bathing regimens, etc.).

The comparator controls could be either placebo (e.g. vehicle) or another compound, known or suspected to be effective in the treatment of canine AD.

In this review, short-term treatment referred to studies lasting less than 8 weeks, and long-term effect referred to trials that lasted longer than this duration. This separation corresponds to the time frame by which drug dosages of anti-inflammatory drugs are normally reduced to avoid adverse events.

Types of outcome measures
Because the principal symptoms and signs of canine AD consist of pruritus and skin lesions, included studies had to report an assessment of the extent and/or intensity of at least one of these signs after a preventive or therapeutic intervention.
(1) *Primary outcome measure*: The proportion of canine participants with at least a good-to-excellent improvement when evaluated on a categorical global assessment scale by either investigators (primary outcome 1a) or dog owners (primary outcome 1b).
(2) *Secondary outcome measures*: (a) The percentage of dogs with complete remission of signs, defined by a reduction of 90% or more from baseline investigator-graded lesional (secondary outcome 1a) or owner-rated pruritus scores (secondary outcome 1b).

(b) The percentage of dogs with a 50% or more reduction from baseline investigator-graded lesional (secondary outcome 2a) or owner-rated pruritus scores (secondary outcome 2b).

In the absence of universally accepted validated scores for evaluating skin and pruritus in dogs with AD, the outcome measures listed above were determined using data obtained with any scoring system used by the study authors. Adverse events following the active intervention or its control were also considered as secondary outcome measures.

Search strategy for identification of studies
(1) *Electronic databases*: Relevant trials were identified from three databases: MEDLINE (from 1966), ISI's (Thomson) Science Citation Index Expanded (from 1945) and CAB Abstracts (from 1975). Searches of these databases were performed on 20 January 2005, 24 January 2005 and 11 February 2005 respectively. Trials published in 2005, 2006 and 2007 were selected, in a prospective fashion, using a weekly disease-specific broad search using the MEDLINE database.
(2) *References from published studies*: References in the bibliographies of all clinical trials were checked for additional trials.
(3) *Unpublished literature*: Unpublished and ongoing trials were identified by posting messages in the veterinary dermatology e-mail lists VETDERM, DIPECVD and DIPDERM (2 February 2005).
(4) *Conference proceedings*: Proceedings booklets from the annual meetings of the American Academy of Veterinary Dermatology & American College of Veterinary Dermatology (now North American Veterinary Dermatology Forum), European Society of Veterinary Dermatology & European College of Veterinary Dermatology as well as the five World Congresses of Veterinary Dermatology were hand searched for relevant citations in February 2005 and December 2007. Electronic mail contacts were made to obtain information on trials presented at the meetings of the Belgian, British, French, German,

Italian, Spanish, Swedish and Asian Veterinary Dermatology Associations.
(5) *Language*: There were no language restrictions when searching for publications.

Methods of the review

(1) *Study selection*: Titles and abstracts identified from searches were examined by two reviewers (R.S.M. and A.P.F.). If the information provided in the title and abstract suggested that the trial was not a randomized controlled trial (RCT) including dogs with AD, then the study was excluded. If the information was not clear, then the full text of the paper or presentation was scrutinized. Any disagreement was resolved by discussion between the reviewers, with a third reviewer (T.O.) acting as arbitrator whenever needed. Excluded trials and reasons for exclusion were recorded.
(2) *Data extraction*: This step was achieved by two reviewers (R.S.M., A.P.F.) who independently entered the information onto a data extraction form. Discrepancies were resolved by discussion and verified by a third reviewer (T.O.). Missing data were obtained from the study authors, whenever possible. The reviewers were not blinded to either names of authors, journal or institutions.
(3) *Assessment of methodological quality*: Quality assessment of trial designs was performed similar to the recent systematic review[8] and the following issues were examined and rated as none', 'adequate', 'unclear' or 'inadequate':

1. method of generation of randomization sequences;
2. method of concealment of allocation to treatment groups;
3. masking of allocation for observers (e.g. clinicians) and participants (e.g. dog owners);
4. whether cases lost to follow-up were included in the intention-to-treat (ITT) analyses; and
5. degree of certainty that the participants were affected with AD as judged by the author's description.

To further compare the quality of included trials, additional parameters were recorded. Such parameters included any available data on comparison of groups at baseline and compliance with the prescribed intervention.

All data were recorded in tabular form, and a description of the quality of each trial was given based on the global analysis of the components above. In general, three parameters were evaluated: (i) the methods of generation and concealment of allocation; (ii) the blinding of outcome assessment; and (iii) the handling of withdrawals and dropouts – with ITT analyses if at all possible. Trials for which these parameters were adequate were classified as high quality. Those that did not mention details on any of these parameters were rated as poor quality. Trials of intermediate qualities were unclear for one or two of these parameters.
(4) *Analysis*: Pooling of results and meta-analyses were performed for studies reporting similar interventions and outcome measures using the RevMan 5 analysis software (Review Manager (RevMan). Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) by one of the reviewers (T.O.). Analysis of dichotomous outcomes was determined using the Mantel-Haenszel (M-H) test and reported as relative risks (RR) with 95% confidence intervals (CI). Such reporting was only done for primary outcome measures, comparisons between active interventions and placebo and/or for trials enrolling more than 100 participants.

As we anticipated finding clinical heterogeneity between studies that assessed similar interventions because of the variable inclusion criteria for study participants (e.g. 'well-characterized' AD or presumed 'allergy', or the restriction of participants with a more or less severe phenotype), we used a random effects model for individual or pooled related studies.

Whenever possible, outcome measures were compared between subgroups of study participants affected with AD and those with the diagnosis of 'presumed AD' or 'pruritus of allergic origin'. Where feasible, data for short-term and long-term treatment with an intervention were analysed separately.

Results

Description of studies

Altogether, the general searches identified 645 citations, from which 595 were not felt to be appropriate because of lack of relevance to this review, insufficient details on diagnoses of study subjects, or lack of randomization or control group (Figure 1). Fifty RCTs were selected (Table 1); one study was withdrawn later because of insufficient information available for review.[15]
(1) *Disease definitions*: In all, these 49 RCTs enrolled 2126 dogs of which 2001 had been diagnosed with AD based on standards in use at the time of publication or presentation. In two trials, subjects enrolled included dogs with AD and other diagnoses[16,17] and data from dogs with AD were extracted whenever possible. In two studies from the same group,[18,19] diagnoses were not specified but there was reasonable suspicion that AD was the diagnosis in most of these dogs. Thirty-one RCTs (Table 1) included solely dogs in which hypersensitivities to common environmental allergens were documented by intradermal testing or allergen-specific IgE serology. In only 14 studies (Table 1) was the seasonality of allergic signs specified, all of them reporting that dogs with non-seasonal AD had been selected.
(2) *Number of study subjects*: Altogether, RCTs had enrolled between eight[20] and 268 dogs[21] with a mean of 43 and a median of 30 dogs. There were 29 trials with more than 25 subjects, 12 with more than 50 patients and four with 100 or more dogs (Table 1). In general, trials with a crossover design had enrolled fewer patients than those with parallel testing of interventions. The earlier trials (1984–2001) usually had enrolled fewer dogs (average: 29) than those published since 2000 (average: 55). Before 2002, there had only been two RCTs with more than 50 subjects,[22,23] while there were 14 of them after that time (Table 1).
(3) *Signalment of study subjects*: Enrolled dogs usually belonged to multiple breeds and to both genders (neutered or intact). The ages of subjects were only specified in 30 studies, and when mentioned, it varied greatly from post-pubescent to elderly patients.
(4) *Types of interventions*: The 49 RCTs tested the efficacy of multiple interventions that can be grouped based

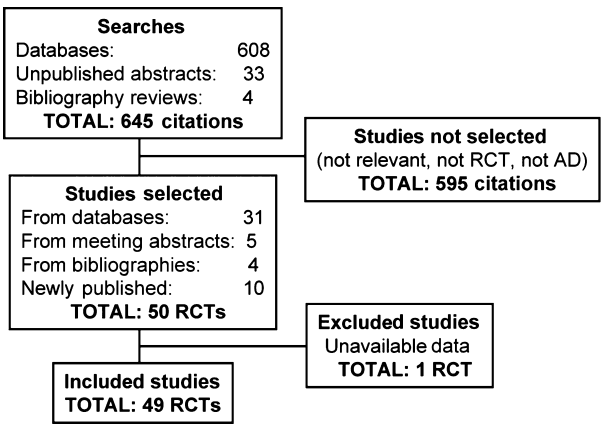


Figure 1. Search summary.

Table 1. Characteristics of included studies

Study ID	Ref. no.	Methods	Participants	Interventions	Outcomes
Willemse (1984)	22	Parallel, 6–54 weeks	51 dogs with IDT+ AD; 1.2–8.7 years	Allergen-specific immunotherapy or placebo	Proportion of dogs with >51% improvement from baseline in clinical score
Paradis (1991)	35	Crossover, 9 weeks	30 dogs including 21 with nonseasonal IDT+ AD; 2–9 years	Astemizole, clemastine, doxepin, trimeprazine, trimeprazine+prednisone, prednisone or placebo	Proportion of dogs with 'good-to-excellent' antipruritus effect assessed
Bond (1992a)	50	Parallel, 8 weeks	25 dogs with nonseasonal AD; 2–11 years	Essential fatty acid combination or placebo (olive oil)	Overall assessment of change in clinical signs and owner's assessment of pruritus
Bond (1992b)	51	Parallel, 16 weeks	37 dogs with nonseasonal AD; ages unclear	Essential fatty acid combinations	Change in lesion and overall impression scores
DeBoer (1992)	63	Crossover, 4 weeks	31 dogs with IDT+ or RAST+ AD; 3–7 years	AHR-13268 or placebo	Change in lesion scores and subjective assessment
Scarff (1992)	52	Crossover, 21 weeks	35 dogs with nonseasonal IDT+ AD; ages unclear	Evening primrose oil or placebo (olive oil)	Change in lesion and overall severity scores
Scoff (1992a)	41	Crossover, 3 weeks + optional 4 weeks if effective	10 dogs with IDT+ AD, 6 dogs with probable AD (IDT not done); 2–9 years	Cyproheptadine or placebo	Proportion of dogs with 'good-to-excellent' antipruritus effect assessed by owner
Scott (1992b)	53	Crossover, 8 weeks+ optional 4 weeks if effective	14 dogs with IDT+ AD, 6 dogs with probable AD (IDT not done); 10 months to 7 years	Essential fatty acid combinations	Proportion of dogs with 'good-to-excellent' antipruritus effect assessed
Bond (1993)	54	Parallel, 16 weeks	28 dogs with nonseasonal IDT+ AD; ages unclear	Essential fatty acid combinations	Change in lesion and overall severity scores
DeBoer (1994)	45	Crossover, 4 weeks	31 dogs with IDT+ or RAST+ AD; 2–10 years	5-lipoxygenase inhibitor (WY-20295) or placebo	Change in lesion scores and subjective judgement
Logas (1994)	16	Crossover, 15 weeks	6 dogs with IDT+ AD, 8 dogs with flea allergy, 2 with idiopathic pruritus; ages unclear	Essential fatty acids (fish oil) or placebo (corn oil)	Change in lesion scores
Paterson (1994)	42	Crossover, 10 weeks	30 dogs with IDT+ AD; 1.5–11 years	Hydroxyzine, cyproheptadine, chlorpheniramine, clemastine, promethazine, trimeorazine	Owner's assessment of pruritus
Scoff (1994)	43	Crossover, 3 weeks+ optional 4 weeks if effective	18 dogs with IDT+ AD; ages unclear	Terfenadine or placebo	Proportion of dogs with 'good-to-excellent' antipruritus effect assessed by owner
Paterson (1995)	55	Crossover, 32 weeks	32 dogs with IDT+ AD; 0.5–8 years; dogs with advanced chronic disease were excluded	Antihistamines with essential fatty acid combination or placebo	Change in pruritus and lesion scores
Sture (1995)	56	Crossover, 21 weeks for first phase	30 dogs with IDT+ AD; ages unclear	Essential fatty acid combination or placebo (olive oil)	Change in lesion and overall severity scores
Paradis (1996)	44	Crossover, 7 weeks	17 dogs with confirmed or presumed AD; ages unclear	Loratadine or placebo	Pruritus relief
Ferrer (1999)	36	Parallel, 4 weeks	40 dogs with IDT+ AD;1–10 years	Arofylline, prednisone at two dosages or combination or arofylline and prednisone	Change in pruritus and lesion scores
Harvey (1999)	32	Parallel, 8 weeks	21 dogs with AD; ages unclear	Essential fatty acid combination or placebo (olive oil)	Change in pruritus, lesions and overall scores

Table 1. (*Continued*)

Study ID	Ref. no.	Methods	Participants	Interventions	Outcomes
Marsella (2000)	46	Crossover, 10 weeks	10 dogs with IDT+ AD; ages unclear	Pentoxifylline or placebo	Change in pruritus and erythema scores
Crow (2001)	29	Crossover, 9 weeks	9 dogs with IDT+ AD; ages unclear	Zileuton or placebo	Change in pruritus and erythema scores
Ewert (2001)	23	Parallel, 6 weeks	58 dogs with IDT+ AD; ages unclear	Fatty acid copolymer or antihistamine combination	Change in pruritus and lesion scores, global assessment of efficacy
Nagle (2001)	33	Parallel, 8 weeks	50 dogs with IDT+ AD; mean ages: 6 and 5 years	Chinese herbal product or placebo	Change in pruritus and lesion scores
DeBoer (2002)	17	Parallel, 4 weeks	83 dogs with AD+20 dogs with pruritus; 1–14 years	Triamcinolone spray or placebo	Change in lesion and overall impression scores
Marsella (2002a)	20	Crossover, 10 weeks	Eight dogs with IDT+ AD; ages unclear	Tacrolimus solution or placebo	Change in pruritus and erythema scores
Marsella (2002b)	30	Crossover, 16 weeks	12 dogs with IDT+ AD; 1.5–6.5 years	Capsaicin lotion or placebo	Change in pruritus scores
Noli (2002)	57	Parallel, 4 weeks	31 dogs with IDT+ AD; ages unclear	Essential fatty acids (blackcurrant seed oil) or placebo	Change in pruritus and erythema scores
Olivry (2002a)	24	Parallel, 6 weeks	91 dogs with nonseasonal AD; mean ages: 4.8–5.6 years	Ciclosporin (two dosages) or placebo	Change in pruritus and CADESI lesion scores, global assessment of efficacy
Olivry (2002b)	31	Parallel, 6 weeks	30 dogs with nonseasonal AD; mean ages: 3 and 4 years	Ciclosporin or prednisolone	Change in pruritus and CADESI lesion scores
Bensignor (2002)	25	Crossover, 8 weeks	20 dogs with AD; ages unclear	Essential fatty acid-enriched or home-made diet	Change in pruritus and lesion scores
Nesbitt (2003)	18	Parallel, 8 weeks	72 dogs with pruritus consistent with allergic aetiology; mean 4.5–5.8 years	Essential fatty acid-enriched diets with variable fatty acid content	Change in skin and ear pruritus and lesional scores
Olivry (2003b)	26	Parallel, 12 weeks	30 dogs with AD; ages unclear	Ciclosporin with two different dose decreasing regimens	Change in pruritus and CADESI lesion scores
Olivry (2003c)	64	Parallel, 3 weeks	20 dogs with nonseasonal AD; mean ages: 2.0–4.5 years	Misoprostol or placebo	Change in pruritus and CADESI lesion scores
Steffan (2003)	37	parallel, 16 weeks	176 dogs with AD; mean ages: 4.7–5.5 years	Ciclosporin or methylprednisolone	Change in pruritus and CADESI lesion scores, global assessment of efficacy
Dodman (2004)	19	Crossover, 4 weeks	14 dogs with allergic dermatitis; 0.75–10.5 years	Dextromethorphan or placebo	Change in pruritus and lesion scores, global assessment of efficacy
Marsella (2004)	39	Crossover, 10 weeks	14 dogs with IDT+ AD; 2–8.5 years	Tacrolimus ointment or placebo	Change in pruritus and lesion scores
Mueller (2004)	58	Parallel, 10 weeks	30 dogs with nonseasonal IDT+ AD; ages unclear	Essential fatty acid combinations or placebo (mineral oil)	Change in clinical and medication scores
Saevik (2004)	59	Parallel, 12 weeks	60 dogs with nonseasonal IDT or serology-positive AD; mean 3.9–4.5 years	Essential fatty acid combination or placebo (median chain triglyceride oil)	Change in pruritus and lesion scores
Bensignor (2005)	40	Parallel, 6 weeks	20 dogs with nonseasonal AD and pedal lesions; median age of onset: 19 months	Tacrolimus ointment or placebo	Change in lesion scores
Steffan (2005)	21	Parallel for 4 weeks, then open for 16 weeks	268 dogs with nonseasonal IDT+ AD; 1 to >10 years	Ciclosporin or placebo	Change in pruritus and CADESI lesion scores, global assessment of efficacy
Colombo (2005)	47	Parallel, 36 weeks	29 dogs with IDT or ASIgES+ AD; 1–8 years	Allergen-specific immunotherapy at ' standard' and low doses	Change in pruritus and lesion scores
Baddaky (2005)	61	Parallel, 10 weeks with possibility of crossover for 10 weeks	30 dogs with nonseasonal IDT+ AD; mean ages: 3.4–4.5 years	Essential fatty acid-enriched diet or placebo	Change in pruritus and lesion scores

Table 1. (*Continued*)

Study ID	Ref. no.	Methods	Participants	Interventions	Outcomes
Mueller (2005)	48	Parallel, 52 weeks	24 dogs with IDT+AD; 1.5–9 years	Conventional or rush allergen-specific immunotherapy	Change in pruritus, lesion, medication and composite scores
Campbell (2005)	60	Crossover, 24 weeks	23 dogs with AD; ages unclear	Essential fatty acid combination or placebo (olive oil)	Change in pruritus and lesion scores
Rème (2005)	38	Parallel, 6 weeks	61 dogs with IDT+AD; 0.7–8 years	Essential fatty acid combinations and shampoo or prednisolone	Change in pruritus and lesion scores, global assessment of efficacy
Ferguson (2006)	62	Parallel, 12 weeks	120 dogs with IDT or ASIgES+AD; >1.5 years with mean age: 5 years	Chinese herbal extract or placebo	Change in pruritus and CADESI lesion scores, global assessment of efficacy
Iwasaki (2006)	27	Parallel, 8 weeks	92 dogs with moderate/severe AD; mean ages: 5.8 years	Recombinant canine γ-interferon or diphenhydramine spray	Change in pruritus and lesion scores
Thelen (2006)	28	Parallel, 52 weeks	25 dogs with AD; ages unclear	Ciclosporin given with or without a meal	Change in pruritus and CADESI lesion scores
Noli (2007)	34	Parallel, 8 weeks	24 dogs with nonseasonal IDT+AD; 1–12 years	Essential fatty acids or placebo	Change in pruritus and CADESI lesion scores
Ricklin (2007)	49	Parallel, 12 weeks	64 dogs with AD; mean: 2.2 years	*Mycobacterium vaccae* or placebo	Change in pruritus and CADESI lesion scores, global assessment of efficacy

ASIgES, allergen-specific IgE serology; IDT, intradermal testing; RAST, radioactive allergosorbent test; CADESI, Canine AD Extent and Severity Index.

on similarity of mechanism of action. These interventions are:

1. glucocorticoids: topical (1 trial) or oral (5);
2. calcineurin inhibitors: tacrolimus (3) or ciclosporin (6);
3. H1 antihistamines (7);
4. leukotriene inhibitors (2);
5. phosphodiesterase inhibitors (2);
6. allergen-specific immunotherapy and immunomodulators (5);
7. essential fatty acid-enriched diets or supplements (19);
8. herbal preparations (2); and
9. miscellaneous (4).

Because of heterogeneity of study designs, interventions and dosages within medication groups, pooling of data usually was not possible except for two placebo-controlled[21,24] short-term ciclosporin trials.

Methodological quality of included studies

The methodological quality of the 49 included trials is summarized in Table 2. Overall, the quality of trial methodology was rated as poor, intermediate and high in 5, 32 and 12 studies respectively. There was a clear difference in the rating of methodological quality for studies reported before and after 2002. Indeed, out of 22 trials reported from 1984 to 2001, there were two (9%) rated of poor quality and the remainder 20 (91%) of intermediate rating. From 2002 onwards, out of 27 studies, there were 3 (11%) trials of poor quality and 12 (44%) each with intermediate and high grades.

(1) *Randomization and selection bias*: Fifteen of twenty-two studies (68%) published before 2002 did not report the method of randomization, while this was done in 20 of 27 trials (74%) published after that date (Table 2). When reported, the randomization method was adequate in all but one study in which the choice of intervention was made arbitrarily.[22] In all, it is not known how often selection bias occurred, but it is considered to be minimal in studies published after 2002.

(2) *Blinding of outcome assessment and detection bias*: Altogether, the blinding of outcome assessment was the methodological parameter that was employed the most often, having been used since the first trial in 1984.[22] Overall, blinding was considered to be adequate in 40, unclear in five and inadequate in four studies (Table 2).[25–28] In two of the latter trials, a single medication had been used (ciclosporin), but there were two different administration schemes for that particular drug – varying dose reduction regimens[26] or administration with or without a meal.[28] In all, it was considered that detection (i.e. unmasked evaluation) was not a significant source of bias in included trials.

(3) *Handling of losses and attrition bias*: The most common methodological flaw observed was the lack of reporting and inclusion of data from dogs that did not complete the study (Table 2). Until 2002, out of 22 studies, there were only two in which all subjects completed the trials.[29,30] ITT analyses were not reported in any other papers. After the first reports of trials reporting ITT

Table 2. Assessment of study design

Study ID	Ref. no.	Generation of randomization sequence	Blinding	Loss to follow-up	Groups comparable at baseline	Assessment of compliance	Quality
Willemse (1984)	22	Inadequate	Adequate	ITT not performed	Yes	Unclear	Intermediate
Paradis (1991)	35	Unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Bond (1992a)	50	Unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Bond (1992b)	51	Adequate (computer)	Unclear	ITT not performed	Unclear	Unclear	Intermediate
DeBoer (1992)	63	Adequate (computer)	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Scarff (1992)	52	Unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Scott (1992a)	41	Adequate (computer)	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Scott (1992b)	53	Unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Bond (1993)	54	Adequate (computer)	Adequate	ITT not performed	Unclear	Unclear	Intermediate
DeBoer (1994)	45	Unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Logas (1994)	16	Unclear	Adequate	ITT not performed	Yes (crossover)	Adequate	Intermediate
Paterson (1994)	42	Unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Scott (1994)	43	Adequate (computer)	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Paterson (1995)	55	Unclear	Unclear	Unclear	Unclear	Unclear	Poor
Sture (1995)	56	Unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Paradis (1996)	44	Unclear	Unclear	Unclear	Yes (crossover)	Unclear	Poor
Ferrer (1999)	36	Adequate (computer)	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Harvey (1999)	32	Unclear	Adequate	ITT not performed	No, groups had different scores	Adequate	Intermediate
Marsella (2000)	46	Unclear	Adequate	ITT not performed	Yes (crossover)	Unclear	Intermediate
Crow (2001)	29	Unclear	Adequate	All dogs completed the study	Yes (crossover)	Unclear	Intermediate
Ewert (2001)	23	Unclear	Adequate	ITT not performed	Yes	Adequate for fatty acids; unclear for antihistamines	Intermediate
Nagle (2001)	33	Unclear	Adequate	ITT not performed	No, groups had different erythema scores	Adequate	Intermediate
DeBoer (2002)	17	Adequate (computer)	Adequate	ITT not performed	Yes (clinical scores)	Unclear	Intermediate
Marsella (2002a)	20	Adequate (coin toss)	Adequate	ITT not performed	Yes (crossover)	Adequate	Intermediate
Marsella (2002b)	30	Adequate (coin toss)	Adequate	All dogs completed the study	Yes (crossover)	Unclear	High
Noli (2002)	57	Unclear	Unclear	ITT not performed	Unclear	Unclear	Poor
Olivry (2002a)	24	Adequate (computer)	Adequate	ITT performed	Yes	Adequate	High
Olivry (2002b)	31	Adequate (computer)	Adequate	ITT performed	Yes	Unclear	High
Bensignor (2002)	25	Unclear	Inadequate	Unclear	Yes (crossover)	Unclear	Poor
Nesbitt (2003)	18	unclear	Adequate	ITT not performed	Unclear	Unclear	Intermediate
Olivry (2003b)	26	Adequate (computer)	Inadequate	ITT performed	No, groups had different lesion scores	Unclear	Intermediate
Olivry (2003c)	64	Adequate (computer)	Adequate	ITT performed	Yes	Unclear	High
Steffan (2003)	37	Adequate (computer)	Adequate	ITT performed	Yes	Adequate	High
Dodman (2004)	19	Unclear	Unclear	ITT not performed	Yes (crossover)	Unclear	Poor

Table 2. (*Continued*)

Study ID	Ref. no.	Generation of randomization sequence	Blinding	Loss to follow-up	Groups comparable at baseline	Assessment of compliance	Quality
Marsella (2004)	39	Adequate (coin toss)	Adequate	ITT not performed	Yes (crossover)	Adequate	Intermediate
Mueller (2004)	58	Adequate (table)	Adequate	ITT not performed	Yes (clinical scores)	Adequate	Intermediate
Saevik (2004)	59	Adequate (pre-randomization)	Adequate	ITT performed	Yes	Unclear	High
Bensignor (2005)	40	Adequate (coin toss)	Adequate	ITT performed	Yes (lesion scores)	Verbal only	High
Steffan (2005)	21	Adequate (computer)	Adequate (4 weeks)	ITT performed	Yes	Adequate	High
Colombo (2005)	47	Unclear	Adequate	ITT performed	Yes	Adequate	Intermediate
Baddaky (2005)	61	Adequate (computer)	Adequate	ITT not performed	Yes	Adequate	Intermediate
Mueller (2005)	48	Adequate (table)	Adequate	ITT performed	Yes	Unclear	High
Campbell (2005)	60	Unclear	Adequate	Unclear	Unclear	Unclear	Intermediate
Rème (2005)	38	Adequate (computer)	Adequate (clinician)	ITT performed	Unclear	Unclear	High
Ferguson (2006)	62	Adequate (computer)	Adequate	ITT performed	Yes	Adequate	High
Iwasaki (2006)	27	Adequate (table)	Inadequate	ITT performed	Yes	Unclear	Intermediate
Thelen (2006)	28	Adequate (alternating)	Inadequate	ITT performed	Yes	Unclear	Intermediate
Noli (2007)	34	Unclear	Adequate	ITT not performed	No, groups had different ages, gender and lesion scores	Unclear	Intermediate
Ricklin (2007)	49	Adequate (pre-randomization)	Adequate (clinician)	ITT performed	Yes	Unclear	High

ITT, intention-to-treat.

analyses,[24,31] accounting for loss of patients was reported in more than half of the ensuing studies. As a result, attrition bias is likely to have occurred in the 1984–2001 period but less so in later and larger studies.

(4) *Comparison of groups at baseline*: Until 2000, it was the rare trial that compared epidemiologic and disease severity data between groups before the intervention began (Table 2). After 2000, most trials reported such comparisons between groups. In four studies,[26,32–34] disease severity scores were higher in one group compared to another at baseline, but this bore no influence in one trial[26] that evaluated dose-reducing regimens after 4 weeks of ciclosporin administration and scores were not different between groups at that time point. In one study,[34] there were also differences in ages and genders between groups, but there is no evidence at this time that dogs of differing genders and age may respond differently to treatment.

(5) *Use of standardized disease severity scales*: Most studies, especially those published before 2002, employed varying scales to assess the degree of pruritic manifestations and/or skin lesions. There was little consistency in disease severity assessment between studies except for those performed by investigators from the same university. This variation in methodology generally prevents adequate pooling of data among studies. From 2002 onwards, 10 of 27 studies (37%) employed a lesion scale (Canine AD Extent and Severity Index, CADESI version 2) that had some limited validation.[24] All six studies testing the efficacy of ciclosporin used this scoring scheme, and pooling of data was possible for groups receiving ciclosporin or placebo.

(6) *Assessment of compliance*: The assessment of client compliance with the tested intervention was performed and reported adequately in only 12 of 49 studies (24%) (Table 2). Such lack of verification – or reporting – of client compliance may have affected the perception of treatment efficacy in studies where such assessment was not made.

Efficacy of interventions

(1) Topical and oral glucocorticoids:

There was only one RCT that tested the efficacy of a topical glucocorticoid-containing formulation in dogs with AD (Table 3SI: see online version for this and all subsequent tables).[17] In this multicentre trial, 103 dogs (83 with AD) received either a 0.015% triamcinolone solution or placebo spray twice daily for 1 week, once daily for 1 week and every other day for 2 weeks. Sixty-nine per cent of the dogs (36/52) treated with the active intervention exhibited a greater than 50% reduction in lesional and pruritus scores, while these benchmarks were reached, respectively, by only 24% (12/51) and 37% (19/51) of dogs receiving placebo. Whether dogs with AD responded differently than those with pruritus of uncertain origin was not reported. Observed minor adverse events occurred in 10% (5/52) and 18% (9/51) of the dogs treated with triamcinolone and placebo, respectively, with scaling and shedding occurring more often with triamcinolone.

Five RCTs documented the efficacy and safety of oral glucocorticoids for the treatment of 160 dogs, including

151 with AD (94%) (Table 3SI).[31,35–38] In all studies except one,[35] oral glucocorticoids were used for the active control arm of RCTs testing the efficacy of other drugs. Steroid interventions consisted usually of oral prednisone, prednisolone or methylprednisolone given initially at 0.5–1.0 mg/kg per day, in one or two administrations, a dosage that remained permanent[31] or that was decreased after 1 week using either a standard protocol[36,38] or based on outcome.[37] Duration of treatment varied from 1 week[35] to 16 weeks,[37] with only the latter study addressing long-term treatment. In these trials, the number of dogs receiving an oral glucocorticoid intervention varied from 10[36] to 59.[37] The three most recent studies[31,37,38] were of high design quality. Because of the variability in study duration, dosages given and decreasing regimens used, meta-analysis of pooled data was considered not possible.

Efficacy

A good-to-excellent assessment of treatment efficacy was obtained in approximately 20% (7/35)[38] to 61% (36/59) of dogs.[37] In one of these trials,[38] approximately 10% of patients exhibited a 90% or greater improvement in skin lesions or pruritus (3 and 2/26 respectively). A 50% or greater reduction in skin lesion scores was generally observed in 50% (13/26)[38] to 80% (12/15)[31] of dogs, while a similar improvement in pruritus scores was seen in 42% (25/59)[37] to 70% (7/10) of patients.[36] Interestingly, these outcome measures were not different between trials of short duration (1–8 weeks) and the longest study.[37] This lack of difference may be related to the dose-decreasing regimen used in the longest study. The administration of prednisolone provided a higher owner-assessed 'good-to-excellent' response compared to that of placebo [RR: 35.0 (2.2–556.7)] (Figure 2b).[35]

Adverse events

Adverse drug events were reported in 10% (3/30)[35] to 81% (48/59)[37,38] of dogs receiving oral glucocorticoids. When assessed, these events were rated as mild or moderate.[37] Polyuria, polydipsia and/or polyphagia were adverse side effects reported in 10% (3/30)[35,36] to 58% (15/26)[38] of dogs treated with these interventions. Vomiting was seen in ten (5/59) to 15 (3/20) percent of patients,[36,37] weight gain in 12% (7/59)[37] to 38% (10/26) of subjects,[38] while skin infections were reported in up to one-third of the dogs (20/59).[37]

(2) Topical or oral calcineurin inhibitors:

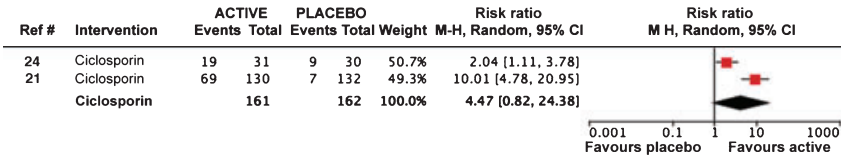
Topical tacrolimus

Three small RCTs (8, 14 and 20 dogs) evaluated whether topical tacrolimus was helpful to relieve signs of AD in dogs (Table 4SI).[20,39,40] The first pilot study tested a compounded 0.3% tacrolimus lotion,[20] while the other two employed the commercially available 0.1% tacrolimus ointment (Protopic; Fujisawa) applied once[39] or twice daily.[40] In all, tacrolimus was applied for 4–6 six weeks to 42 dogs. In one trial,[40] only front feet lesions were treated, and outcome and safety assessments were limited to these areas. Because of the difference in the nature of the interventions and their frequency or mode of administration, the data were not pooled.

Efficacy

Primary outcome measures could not be evaluated from any of these three studies, as a global assessment of efficacy was not assessed by investigators. In the most recent trial,[40] a greater than 90% reduction in lesion scores was not achieved for any feet treated with tacrolimus ointment. The efficacy of the compounded 0.3% tacrolimus lotion appeared to be marginal compared to that of placebo.[20] In contrast, the use of the commercially available 0.1% tacrolimus ointment was followed with a greater reduction in lesional (58–75%) or pruritus scores (42%) compared to placebo (0–25%).[39,40] The magnitude of effect was higher in dogs with localized disease,[39] or when the ointment was applied twice daily[40] compared

(a) **Primary outcome measure 1a: "good-to-excellent" response (clinicians)**



(b) **Primary outcome measure 1b: "good-to-excellent" response (owners)**

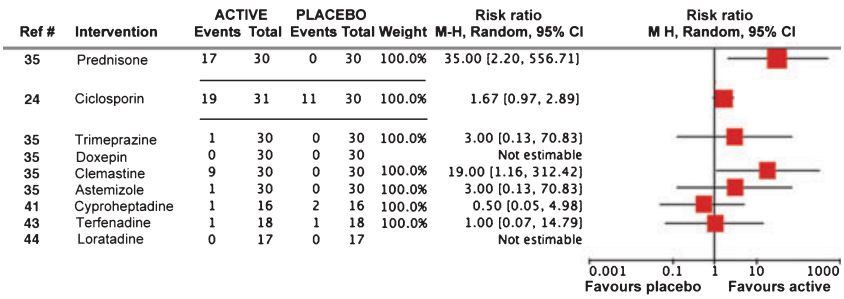


Figure 2. Forest plot of primary outcome measures of placebo-controlled studies. Note: the red boxes represent the relative weight of each RCT when pooled for meta-analysis. The vertical line ('1') represents the level of no effect. The horizontal line for each study represents the confidence interval. If the confidence intervals for individual studies overlap with the vertical line, it demonstrates that, at the given level of confidence, their effect sizes do not differ from no effect. The black lozenge represents the meta-analysed effect of the pooled study. If the lozenge crosses the vertical line, then the overall meta-analysed result cannot be said to differ from no effect at the given level of confidence.

to once daily.[39] The effect on pruritus was not assessed in one trial.[40]

Adverse events

In two trials,[20,39] clinical side effects of tacrolimus application were not seen or listed, and changes in routine blood parameters were not reported to occur. In the last study,[40] the application of tacrolimus ointment to one-fourth of the dogs was followed by immediate or early attempts to lick the medication. This was interpreted subjectively by the owners as a sign of 'irritation'. These reactions occurred during the first days of treatment and they were mild and transient.

Oral ciclosporin

Altogether, there were six RCTs that reported the efficacy of ciclosporin for the treatment of AD in dogs (Tables 5SI and 6SI).[21,24,26,28,31,37] All were of intermediate or high-quality design, an improvement compared to that of other interventions discussed elsewhere in this review. All trials were designed and/or funded by the drug manufacturer. The number of dogs receiving ciclosporin in these trials totalled 382. There were two trials testing the activity of ciclosporin versus placebo,[21,24] two versus oral glucocorticoids,[31,37] one that examined different ciclosporin dose reduction regimens[26] and one that compared the outcome of clinical signs when ciclosporin was given with or without a meal.[28] One study was designed as a first 4-week-long RCT followed by an open trial, and only the data from the RCT were reviewed herein.[21] Three trials were considered short term as the intervention lasted less than 8 weeks; in these studies, ciclosporin was administered at 5 mg/kg once daily and the dose was not reduced.[21,24,31] The other three trials lasted from 12 to 26 weeks and the dose of ciclosporin was usually decreased after 4 weeks, a halving of skin lesions leading to a 50% decrease in the dose and a 75% reduction in lesions being followed by a similar magnitude of reduction of the dose.[26,28,37] Pooling of data and meta-analyses were considered feasible only for the two placebo-controlled trials[21,24] as they were both short-term, albeit having different durations (6 and 4 weeks respectively). Pooling of data from both glucocorticoid-controlled trials[31,37] was not deemed logical in the light of the marked difference in trial's duration (6 versus 16 weeks) and the absence or presence of dose reduction schemes respectively.

Efficacy

When ciclosporin was given to dogs with AD at 5 mg/kg once daily for 4–6 weeks, both skin lesions and pruritus decreased markedly (Table 5SI). Approximately half to two-thirds of dogs exhibited a greater than 50% reduction in skin lesion or pruritus scores during this period, while 13–27% had a reduction of scores greater than 90%.[21,24,31] At this dose, the efficacy of ciclosporin did not appear different compared to that of prednisolone in the assessment of secondary outcome measures.[31]

Pooling together data from the two placebo-controlled studies,[21,24] the proportion of clinicians who rated the response to ciclosporin as 'good to excellent' was higher, but not significantly, compared to that of placebo [RR: 4.5 (0.8–24.4)] (Figure 2a). The proportion of owners who rated the response of ciclosporin 'good-to-excellent' was higher than that of placebo in one study [RR: 1.7 (1.0–2.9)] (Figure 2b).[24] The administration of ciclosporin at 2.5 mg/kg once daily did not appear to be more effective than that of placebo.[24]

When administered for 3 months or more, ciclosporin appeared to maintain its efficacy in spite of decreasing dosing regimens (Table 6SI). Indeed, in the long term, all outcome measures were of similar magnitude to those evaluated at 4 and 6 weeks when the drug was given once daily at 5 mg/kg. After 8 weeks of administration, ciclosporin was as effective as methylprednisolone [primary outcome 1a: RR: 1.2 (0.9–1.5); primary outcome 1b: RR: 1.2 (1.0–1.6)] (Figure 3a,b).[37] Outcomes of the trial testing two dose reduction schemes (decreasing dosages or increasing dosing intervals)[26] or the administration of the drug with or without food[28] were not significantly different between groups.

Adverse events

Adverse drug events were seen in up to 81% (95/117) of patients receiving ciclosporin.[37] Most commonly reported side effects were vomiting [up to 37% (43/117) of dogs] or diarrhoea/soft stools [up to 18 (21/117) percent].[37] These events were usually reported to be transient, reversible and of mild to moderate severity, and it was only in the rare dog that the drug needed to be

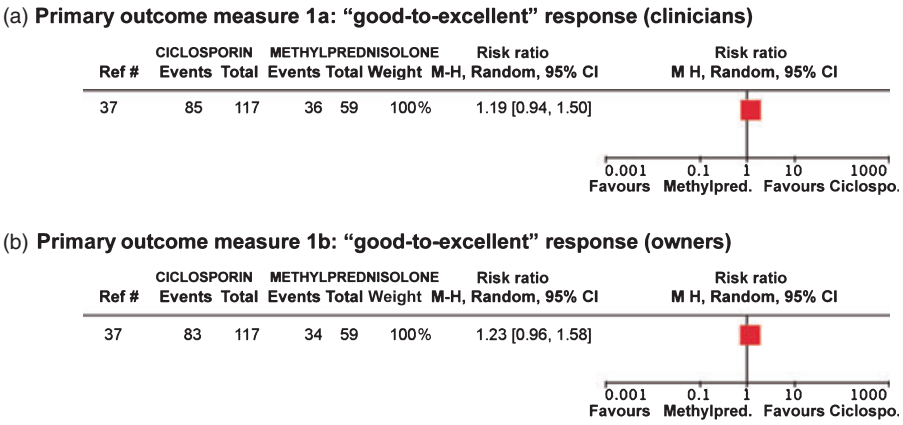


Figure 3. Forest plot of primary outcome measures of the RCT comparing ciclosporin to methylprednisolone.

discontinued because of occurrence of a severe adverse drug event. Consistent and clinically relevant changes in routine blood tests were not seen during the trials.

(3) Topical and oral type 1 antihistamines:
One recent RCT of intermediate design quality reported the efficacy of a topical diphenhydramine spray as control arm for another intervention.[27] Twenty-nine and twenty-six dogs with AD received the antihistamine spray twice daily for 4 and 8 weeks respectively. At study end, a good-to-excellent efficacy to reduce skin lesions or pruritus was reported in 23% (6/26) to 39% (10/26) of treated dogs depending upon the clinical sign or symptom assessed. Adverse drug events were not noted.

Six RCTs tested the effectiveness of oral antihistamines for reduction of clinical signs in dogs with AD (Table 7SI).[23,35,41–44] Design quality was intermediate in all but one of these trials while, in the other,[44] it was assessed as poor. Altogether, 144 dogs received oral antihistamines, 129 (90%) of them diagnosed with AD. The antihistamine interventions lasted between 7 and 14 days, but in three studies,[41–43] antihistamines were re-administered for another 30 days – in case of perceived initial efficacy – so that a repeatable and sustained effect could be verified. Pooling of data from the different placebo-controlled study was considered not possible due to the variation in the type and dose of antihistamines given as well as the variable duration of the trials.

Efficacy
In all, a good-to-excellent antipruritic effect was reported by dog owners in none (doxepin in Ref. 35 loratadine in Ref. 44) to 30% (9/30) of tested patients (clemastine in Ref. 35). Such perception of antipruritic effect was seen in more than 10% of dogs only for clemastine,[35] cyproheptadine[42] and a chlorpheniramine–hydroxyzine combination.[23] A secondary outcome measure was only assessable in the latter study[23] that reported a greater than 50% reduction in lesional scores in 24% (8/33) of dogs. In one RCT,[35] the combination of trimeprazine and prednisone was shown to be more effective than either prednisone or trimeprazine at the same dosages. RR and CI of individual placebo-controlled antihistamine interventions can be found in Figure 2b.

Adverse events
In one study, adverse drug events were not discussed,[44] and another reported no side effects from a chlorpheniramine–hydroxyzine combination.[23] Otherwise, adverse events of oral antihistamines were reported in less than 25% of patients, and they were inconsistent except for somnolence/lethargy reported for first-generation antihistamines.[35,42] Additionally, 4 of 16 dogs (25%) given cyproheptadine exhibited polyphagia, a pharmacodynamic effect of this drug.[41] This clinical sign was reported also in a second trial.[42]

(4) Leukotriene inhibitors:
Two RCTs that included 40 participants evaluated the efficacy of 5-lipoxygenase inhibitors for the treatment of canine AD: one tested an unnamed drug WY-50295[45] and the other one zileuton (Table 8SI).[29] Because of the difference in the nature of the interventions, outcome measure data were not pooled.

Efficacy
In the first study,[45] there were no significant changes in investigator or owner-rated signs during a 1-month treatment with WY-50295 (25 mg/kg twice daily) or placebo. In the second RCT,[29] the administration of zileuton at 2 mg/kg three times daily led to a 50% or greater reduction in erythema scores in three of nine dogs (33%) while this did not occur in any dogs given placebo. A 50% or greater reduction in owner-assessed pruritus scores was achieved by three (33%) and two (22%) of nine dogs given zileuton or placebo respectively.

Adverse events
Adverse drug events were reported in 10% (3/31) of dogs given WY50295, and these consisted of flatulence, sleepiness, weight loss, excitability and urinating in the house.[45] Beyond a mild elevation in the serum activity of alanine aminotransferase, there were no adverse effects following the administration of zileuton for 30 days.[29]

(5) Phosphodiesterase inhibitors:
Two small RCTs (10 dogs per intervention) evaluated the efficacy of oral phosphodiesterase inhibitors in dogs with AD (Table 9SI). One tested arofylline[36] and the other pentoxifylline,[46] and because of differing interventions, efficacy data were not pooled. In both trials, the scale used for outcome measure evaluation was three to five points long thereby limiting the validity of evaluating 50 and 90% reductions in scores obtained with this scale.

Efficacy
In the first RCT that lasted 4 weeks,[36] 40 dogs were randomized to receive either arofylline at 1 mg/kg twice daily, prednisolone at 0.5 mg/kg twice daily, prednisolone at 0.25 mg/kg twice daily or a combination of arofylline and low-dosage prednisolone (0.25 mg/kg). Half of the dogs receiving arofylline did not complete the trial. Altogether, more than two-thirds of the dogs that finished the study saw their lesional and pruritus scores decrease by half or more.

Individual scores provided by the author permitted the determination of outcome measures 1a–2b in the second RCT in which dogs were treated with pentoxifylline (10 mg/kg twice daily) or placebo for 4 weeks.[46] Approximately one-third (3/10) of the dogs treated with pentoxifylline, but none of the dogs receiving placebo, had investigator-rated erythema and/or owner-assessed pruritus score reductions of 50% or more.

Adverse events
Fifteen of twenty dogs (75%) receiving arofylline exhibited vomiting, and this sign was the reason for which owners elected to discontinue the trial in seven of these dogs (35%). Lethargy was seen in four dogs receiving this drug. None of the dogs treated with pentoxifylline exhibited study-related side effects.

(6) Allergen-specific immunotherapy and immunomodulators:

Five RCTs examined the efficacy of several immunomodulating regimens in 155 dogs with AD (Table 10SI).[22,27,47–49] The first three studies investigated the treatment effect of various protocols of allergen-specific immunotherapy,[22,47,48] while the two others tested nonspecific immunomodulation with either recombinant canine γ-interferon[27] or a *Mycobacterium vaccae* extract.[49] Study design quality varied from intermediate[22,27,47] to high.[48,49] In all, the trial duration varied from 2 months[27,49] to 54 months.[22] As interventions were markedly different, pooling of data was not possible.

One old RCT compared the long-term efficacy of alum-precipitated allergen-specific immunotherapy to that of placebo in 27 dogs with AD.[22] This long study had a very high level of drop-out rate, thereby affecting outcome assessment. The authors reported superior efficacy of the active intervention over placebo, but the time of outcome assessment was unclear, and separation of lesion and pruritus scores could not be made. In the second study,[47] the investigators compared both 'standard' and 'low-dose' alum precipitated allergen-specific immunotherapy in 27 dogs with AD. When evaluating efficacy using ITT principles, there was a greater than 50% improvement in skin lesions and pruritus in 30–50% of 10–14 dogs, but there was no apparent differences in efficacy between the two treatment protocols. Finally, another trial compared 'standard' and 'rush' aqueous immunotherapy regimens in 24 dogs with AD.[48] Halving of lesional and pruritus scores was reported in 64% to 45% of 11 assessed dogs, respectively, and there were no differences in perceived efficacy and time to improvement between groups.

Altogether, these three trials reported side effects of immunotherapy in a minority of patients, and these consisted either of increased pruritus (3/27 dogs, 11%)[22] or study withdrawal due to discomfort (4/27 dogs, 15%).[47] One study reported no adverse drug events.[48]

One trial tested the efficacy of recombinant canine γ-interferon injections in 75 dogs with AD[27] while the control intervention consisted of an antihistamine spray whose efficacy was discussed above. A good-to-excellent efficacy to control skin lesions or pruritus was observed in 74% (39/53) to 81% (43/53) of dogs receiving γ-interferon compared to approximately one third of the subjects treated with the antihistamine spray. Pain at the site of injection was observed in one dog.

Finally, the last study evaluated the effectiveness of a single injection of a *M. vaccae* extract to reduce signs in 29 dogs with AD.[49] Primary outcome measures could not be determined based on the published information. From data provided by the authors, it was determined that, besides secondary outcome measure 1a, assessed parameters were not significantly different between active and placebo groups. The authors reported, however, that the active intervention was more effective than placebo for dogs with mild to moderate AD (CADESI-02 lower than 60). A painless swelling at the site of injection was reported in 5 of 29 dogs treated with the active extract (17%).

(7) Essential fatty acids:

Our search strategy identified 19 RCTs reporting results of EFA-containing interventions for the treatment of AD in dogs (Tables 11SI and 12SI).[16,18,23,25,32,34,38,50–61] The number of dogs receiving EFA in these trials totalled 527 [438 with AD (83%) and 89 (17%) with pruritus presumed of allergic origin]. In 12 trials,[16,18,23,25,32,34,38,50,53,55,57,60] the duration of EFA administration was considered to be short as the intervention lasted between 2 weeks[53] and 8 weeks.[18,32,34,50,55,57,60] In the remaining seven studies,[51,52,54,56,58,59,61] the duration of EFA supplementation was assessed as 'long' as it varied between 9 weeks[52,56] and 16 weeks.[54] The quality of study design was rated as 'intermediate' in 14 trials;[16,18,23,32,34,50–54,56,58,60,61] it was assessed as 'poor' in three[25,55,57] and 'high' in only two RCTs.[38,59]

Of particular note is that in most trials except for one that tested the efficacy of an oral supplement[59] and three that tested EFA-rich commercial foods,[18,25,61] study dogs ate different diets anticipated to contain substantially variable amounts of EFA. This variability could be an explanation of result heterogeneity, and it prevents a strict evaluation of the efficacy of tested interventions. This heterogeneity is best shown by examining one of the trials in which the basal diets were not standardized but EFA were accounted for by adding those received in the supplements and those of dietary origin.[58] In that particular study, the dosages of total dietary intake of both omega-3 and omega-6 EFA varied markedly within each group. Altogether, as the nature, dosage and duration of the EFA intervention were highly variable in these 19 RCTs, pooling of study results was considered neither feasible nor relevant.

Efficacy

The efficacy of EFA-containing supplements or diets could not be assessed reliably and with certainty in most trials because of poor or intermediate study design quality, variability of dietary EFA intake – due to lack of dietary standardization – as well as nature, dosage and duration of tested interventions (Tables 11SI and 12SI). In most studies, the chosen primary outcome measures of efficacy could not be determined from published data. When secondary outcome measures were reviewed, the efficacy of active EFA intervention did not appear markedly different from that of placebo.[25,32,34,57,58,60]

In one study of high design quality – but with differing basal diets between dogs – the efficacy of an EFA-containing supplement (Megaderm; Virbac, Carros, France) and shampoo (Allermyl; Virbac) was rated as similar to that of prednisolone.[38] The other study of high design quality tested the efficacy of an oral EFA liquid combination (Viacutan; Boehringer Ingelheim Denmark, Copenhagen, Denmark) or placebo for 12 weeks.[59] In this report, the diet was standardized between dogs before and during the trial, a remarkable improvement compared to all other tests of EFA oral supplements. In this RCT, atopic dogs also received oral prednisolone, and the dosage of this corticosteroid was adjusted based on improvement in pruritus in the preceding day. Even though the chosen outcome measures were not assessable from published data, results from the study suggested that this particular

EFA combination led to a significant decrease in prednisolone usage after 8 weeks of supplementation compared to placebo.

Adverse events
Adverse drug events were not discussed in 11 RCTs. In two studies,[32,38] side effects were not seen in dogs receiving EFA oral supplements. A small prevalence (~5%) of gastrointestinal signs (vomiting, loose stools or flatulence) was reported in four studies.[16,53,61] Finally, pain at the site of injections was present in 20% of dogs treated with an EFA copolymer.[23]

(8) Chinese herbal extracts:
There were two RCTs that tested the efficacy and safety of an oral powder containing extracts from three plants (*Rehmannia glutinosa*, *Paeonia lactiflora* and *Gycyrrhiza uralensis*) (Table 13SI). Both preparations were marketed by the same company, but with the first trial[33] in the United States and the second[62] in Europe. In all, 167 dogs with AD were entered in the studies. Designs were of intermediate[33] and high quality.[62] The formulations appeared similar and one of the dosages (200 mg/kg once daily) was identical in the two trials; however, the assessed lesions were different between groups and some data were unavailable for evaluation, consequently pooling of data was not performed.

Efficacy
Only limited data could be used to assess this review's outcome measures. In these two studies, the improvement in skin lesions appeared similar between active and placebo groups with approximately one-fourth to one-fifth of the dogs exhibiting a greater than 50% reduction in scores. A noticeable difference between active and placebo groups in pruritus score reduction was not seen either. In the most recent trial,[62] the authors reported a higher benefit for dogs with more severe skin lesions.

Adverse events
In the first trial,[33] treatment-related adverse drug events were minor, and they consisted mostly of mild diarrhoea (4/24 dogs, 17%). In the second study,[62] 'self-limiting gastrointestinal disorders' such as vomiting, diarrhoea or flatulence were encountered in 10% (placebo) to 42% of dogs (400 mg/kg group), and such events led to cessation of treatment in five dogs (4%).

(9) Miscellaneous interventions:
Four small RCTs (8–29 dogs) reported the efficacy of different interventions, which will be described separately (Table 14SI).

In 1992, DeBoer *et al.* tested the anti-allergic effect of AHR-13268, a benzoic acid derivative with antihistamine, antiserotonine, antileukotriene and mast cell stabilizing action.[63] Trial quality was rated as 'intermediate'. Outcome measures used in this review could not be assessed except for one (2b): the proportion of dogs achieving a 50% or greater reduction in pruritus was three times higher after active (3/29, 10%) compared to placebo (1/29, 3%) interventions. Side effects were inconsistent and did not appear to be different in frequency between active and placebo interventions.

In 2002, Marsella *et al.* evaluated whether a topical capsaicin 0.025% lotion – a substance P antagonist – was superior to placebo in a small crossover RCT of 12 dogs treated for 6 weeks.[30] The quality of study design was evaluated as 'high'. When treated with placebo, none of the dogs reached a 50% or greater reduction in pruritus at the end of this intervention. In contrast, 8% (1/12) and 25% (3/12) of the dogs treated with topical capsaicin achieved 90% and 50% reductions in pruritus respectively. Side effects were not discussed in the published report but pruritus scores worsened during the first week of capsaicin application.

In 2003, a small RCT – rated of high quality – tested the efficacy of the prostaglandin E1 analogue misoprostol or placebo in 20 dogs with AD.[64] None of the dogs achieved 90% reductions in skin lesions after either intervention. One dog treated with misoprostol exhibited a greater than 90% reduction in pruritus. In contrast to placebo treatment for which none of the subjects obtained at least a halving in scores, one-half and one-third of the dogs receiving misoprostol reached this benchmark for skin lesions and pruritus respectively. Only one dog treated with misoprostol exhibited occasional diarrhoea, and tolerability was rated as good by all pet owners.

Finally, the opioid antagonist dextromethorphan was used to treat repetitive self-induced pruritic manifestations in dogs with chronic allergic skin disease.[19] Overall study design quality was evaluated as poor. It is suspected that most subjects were affected with AD, but criteria for inclusion were insufficiently described. Outcome measures 1 and 2 could not be determined from published results. The authors reported that, after 2 weeks, 'gross dermatology scores' did not differ significantly between interventions, but a higher pruritus improvement was perceived after dextromethorphan compared to placebo. One dog developed lethargy after receiving dextromethorphan, and this improved after discontinuing the drug.

Discussion

This is the first evidence-based systematic review limited to RCTs detailing interventions for the management of canine AD. A total of 49 RCTs were selected, which had enrolled 2126 dogs. This review found some evidence of efficacy of topical tacrolimus, topical triamcinolone, oral glucocorticoids, oral ciclosporin, subcutaneous recombinant γ-interferon and subcutaneous allergen-specific immunotherapy to decrease pruritus and/or skin lesions of AD in dogs. One high-quality RCT showed that an oral EFA supplement reduced prednisolone consumption.
(1) *Limitations*: There are several limitations that affect the impact of the results of this systematic review.

Participants

Variability of diagnosis of AD

In spite of the perceived commonality of AD in dogs, there are no clear guidelines on how to achieve an irrefutable diagnosis. Moreover, the most recent consensus

definition[1] proposes to separate AD, in which evidence of IgE hypersensitivity to environmental allergens is present, from atopic-like dermatitis, a similar-looking disease in which IgE hyper-reactivity cannot be demonstrated. Such distinction was not made in 25% of the trials discussed herein. In contrast, 28 studies had limited their enrolment to dogs with positive intradermal or IgE serological tests to common aeroallergens.

One of the major limitations of this review is that it spanned more than 20 years, from the mid-1980s to 2007. During this period, standards for diagnosing AD have evolved with a trend to become more homogeneous and better defined in the last decade. In addition to this evolution of diagnostic methods over time, there have been cultural and 'ideological' differences as well. As a result, discrepancies are to be expected in the enrolment of dogs in RCTs, especially between older and newer trials. All patients enrolled might exhibit pruritic manifestations, but some of them could have had IgE-mediated atopic disease while others are likely to have suffered from atopic-like dermatitis or resembling diseases. There are also trials that enrolled dogs with AD as well as dogs with 'pruritus of allergic origin', even though criteria for defining the latter were usually lacking. This likely diversity of diagnoses is a logical source of heterogeneity in treatment responses to similar interventions.

Another source of variation in outcome between resembling RCTs is that, even if the diagnosis of AD were to be restricted to a typical clinical and immunological standard, it is likely that the genetic cause of this canine disease is multifactorial, as it is in humans with the homologous condition. In addition to this genetic heterogeneity, there is an expected variability in disease stage (acute, subacute, chronic), degree of severity (mild, moderate, severe), lesion type and distribution (dogs with pruritus but no lesions, dogs with localized manifestations, dogs with generalized disease), flare factors (type of allergens, nonallergenic causes), type and degree of skin infections, environment and nutrition. All of these factors are likely to cause variation in responses to similar interventions, even though it could be argued that this variability is what defines AD itself.

Variability of response between ages or breeds

Finally, dogs enrolled in the various RCTs have been from different breeds and of various ages. It is possible, at least theoretically, that dogs of different breeds might respond variably to the same drugs, as the genetic foundation of AD is likely to vary between breeds. Variations in the type of coat and nature of the surface skin environment are additional potential causes of outcome heterogeneity, especially for topical interventions. It is unknown whether dogs of various ages could respond differently to treatment, but the evolution of the immune system during ageing could be expected to lead to variations in responses to immunological interventions, such as allergen-specific or allergen-independent immunotherapy.

Study design

There is a clear variation in the overall quality of study design between RCTs performed before and after 2002. In general, trials completed before that date were shorter, they enrolled fewer dogs, had less clear criteria for enrolment, provided no or fewer details about randomization, comparison of groups at baseline or patient attrition, nor did they report ITT analyses. As a result, quality of trial methodology was generally poorer before 2002 than after. It is only in 2002 and after that RCTs with overall design quality rated as 'high' were published.

Outcome measures

Another source of heterogeneity is the lack of standardized outcome measures between trials. At first, reported outcome measures were limited to a single subjective assessment of the reduction in pruritus by dog owners. Over time, evaluations of the intensity or extent of individual skin lesions – often grouped in a 'total' score – by an investigator were added. Disease severity scales were generated as needed, without any information on their validity and reliability. After 2002, trials usually reported changes in pruritus categorical or visual analogue scales, lesional scales (often the second version of the CADESI) with or without global assessment of treatment outcome. The scrutiny of each trial during this review confirmed the existing heterogeneity in reporting of outcome measures. This variability led to a difficulty in appropriately assessing treatment effect and comparisons between similar interventions. This obstacle was overcome by obtaining original subject data from study authors of recently performed trials and by recalculating the outcome measures selected for this review. Even though there is no information on the validity of the chosen outcome measures, they were felt to adequately characterize overall treatment effect assessed by investigators and dog owners (primary outcome measures 1a and 1b). Moreover, we reported the percentage of dogs achieving complete (or near complete) or partial remissions in skin lesions and pruritus manifestations (secondary outcome measures 1 and 2). Similar outcome measures have been proposed recently by the International Task Force on Canine AD.[65]

(2) *Validity of reviewed interventions*: In spite of the limitations highlighted above, the search strategy identified RCTs reporting results of both therapeutic and preventive interventions. All major categories of drugs currently employed by veterinarians for the treatment of AD in dogs were reviewed herein (glucocorticoids, calcineurin inhibitors, antihistamines, EFA, immunotherapy). As such, this systematic review provides information likely to be relevant to both general and specialty practitioners and the general public. Most RCTs were self-funded except for two major categories of drugs, EFA and ciclosporin, for whom studies were supported by the drug manufacturers. This observation should not be taken as an indication of inherent conflict of interest as company-sponsored trials, especially when performed in the last decade, enrolled higher number of dogs, lasted longer and they usually had designs of higher quality. Moreover, such trials often employed glucocorticoid or antihistamine comparators, thereby also providing efficacy data for such commonly used interventions. One should keep in mind, however, that company-sponsored trials that do not report positive results are unlikely to be published. A

probable publication bias might be present in this review as all recent studies directly funded by commercial companies had reported favourable results of efficacy of their proprietary interventions.

Unfortunately, in spite of the high number of identified RCTs, pooling of study results was very limited because of the scarcity of trial duplication, variation in dosages for the same interventions and variable timing of outcome measure assessment. Only one meta-analysis was considered relevant: we pooled data for outcome measure 1a of two RCTs comparing the effect of ciclosporin and placebo.[21,24]

Finally, it is worth mentioning that, besides ciclosporin, all interventions discussed herein were about drugs for which pharmacological data are unavailable in the canine species. Indeed, dosages and frequencies of administration generally had been extrapolated from those employed in humans. Rarely did trials employ optimal dose-finding strategies. Unfortunately, as shown for the antihistamine clemastine, pharmacogenetic differences can lead to a drug being bioavailable in humans but not in dogs.[66,67] Therefore, the lack of evidence of any efficacy for a particular intervention could be due, in part or in all, to inappropriate or suboptimal drug dosages.

(3) *Implications for practice*.

Topical and oral glucocorticoids

In spite of topical glucocorticoids being the most commonly used class of drugs for the treatment of AD in humans, only one RCT reported the efficacy of a 0.015% triamcinolone spray (now marketed as Genesis; Virbac US, Fort Worth, TX, USA) for the treatment of pruritus and skin lesions in dogs with AD by the end of 2007. Based on the review of secondary outcome measures, this spray was deemed likely to be more effective than placebo, and over a 1-month trial course, only minor side effects were seen. The findings from this trial, albeit showing efficacy of this class of drug for the treatment of canine AD, cannot be used as a proof that any glucocorticoid topical formulation will always be effective. Indeed, differences in vehicles, glucocorticoid nature or concentrations are all factors that could influence efficacy and safety. Moreover, the short duration of this trial did not provide information on any skin atrophy potential that this formulation might have if it were used repeatedly over long durations.

Secondary outcome measures of five RCTs suggested the efficacy and relative safety of oral glucocorticoids (prednisone, prednisolone or methylprednisolone) for the treatment of AD in dogs. The anti-allergic effect appears to be fairly rapid and homogeneous at dosages that range from 0.5 to 1.0 mg/kg taken in one or two daily doses. Once the efficacy is deemed acceptable, the dose of glucocorticoids is usually reduced to maintain treatment effect. Side effects of these drugs are common, predictable and they appear related to glucocorticoid doses and treatment duration.

Topical and oral calcineurin inhibitors

The analysis of secondary outcome measures of three small RCTs suggested the efficacy of topical tacrolimus for relieving signs of canine AD. The highest efficacy was seen with the commercially available 0.1% tacrolimus ointment (Protopic; Astellas US, Deerfield, IL, USA) applied twice daily onto local skin lesions. Treatment of generalized skin lesions, in addition to being impractical and costly, yields lower benefit. Besides possible application-induced licking, tacrolimus ointment appears to be safe in the short term.

The analysis of secondary outcome measures of six RCTs – including two relatively large ones – suggested the likely efficacy of oral ciclosporin (Atopica, Novartis Animal Health, Basel, Switzerland) for reduction of skin lesions and pruritus in dogs with AD. Induction of treatment is normally started with 5 mg/kg once daily for 4–6 weeks. Upon halving of clinical signs, the dose of ciclosporin is usually reduced by half, either by increasing dosing intervals (i.e. from once daily to every-other-day) or by decreasing the daily dosage (i.e. 5 mg/kg to 2.5 mg/kg). With either of these two dose reduction schemes, the efficacy is usually maintained. With further improvement, the dose of ciclosporin may be reduced again, either by reducing the daily dosage or increasing time between two doses. Food intake at the time of dosing does not appear to bear any effect on treatment efficacy. Side effects are relatively common and usually consist of transient vomiting and diarrhoea. The long-term safety of ciclosporin given at such dosages to dogs with AD has not been established beyond 6 months.

Topical and oral type 1 antihistamines

In spite of such drugs having been used for several decades in dogs with AD, the examination of results of six RCTs did not provide conclusive evidence of efficacy of topical or oral treatment of this disease. Indeed, the reviewed RCTs were not large and of high quality, they were generally of short duration, and there was variable and usually low efficacy among drugs tested compared to that of placebo. A possible explanation for such heterogeneity in efficacy could be inappropriate doses or frequencies of administration, as such parameters usually had been extrapolated from human pharmacological data without additional studies in dogs. Such interspecies difference in pharmacokinetics is best highlighted with the example of clemastine, the antihistamine reported to have one of the highest clinical effectiveness in dogs.[35] Clemastine is now known not to be bioavailable after oral use in the canine species.[67] Overall, side effects of type 1 antihistamines appear to be infrequent and inconsistent: sedation and lethargy are the most common adverse events seen with drugs of the first generation. Cyproheptadine induces polyphagia.[41]

Leukotriene inhibitors

Two small RCTs, both of intermediate methodological quality, provided some proof of low efficacy (less than a third of dogs achieving a 50% in pruritus) of 5-lipoxygenase inhibitors for the treatment of canine AD. Side effects were uncommon, however.

Phosphodiesterase inhibitors

There are two small RCTs of intermediate methodological quality that provided evidence of variable efficacy and side effects of phosphodiesterase inhibitors for the treatment of canine AD. Arofylline effectively reduces pruritus and skin lesions, but it commonly induces unacceptable vomiting. Pentoxifylline exhibits low efficacy as an antiallergic drug; side effects were not seen during the single trial that tested it.

Allergen-specific immunotherapy and immunomodulators

Overall, the review of secondary outcome measures of three small RCTs evaluating the use of allergen-specific immunotherapy suggested a probable beneficial treatment effect and low risk of this category of intervention, but the superiority of a particular regimen ('standard' versus 'low-dose' or 'rush' protocols) could not be determined. Injectable recombinant canine γ-interferon was deemed likely to be effective and safe in a single trial. In another study, an *M. vaccae* extract was found to be possibly efficacious and safe in dogs with mild to moderate AD.

Essential fatty acids

Omega-6 and omega-3 EFA of vegetable or fish origin have been proposed for reducing signs of AD in dogs for more than 20 years. Multiple combinations of EFA are available commercially, either in capsule or liquid forms, and most commercial diets now have enriched their EFA content. Since 1992, 19 RCTs reported the efficacy of EFA interventions in dogs with AD. In spite of this relatively high number of RCTs, the review of secondary outcome measures of four studies failed to show convincing benefit over that of placebo. As a result, it remains unclear whether EFA are of any benefit to relieve signs of AD in dogs. The main causes for such uncertainty are issues of study design (e.g. short duration of trials, lack of diet standardization and variably assessed outcome measures) and the lack of harmonization in nature and dosages of EFA being administered. In one high-quality RCT, however, an EFA supplement led to decreased glucocorticoid usage after 8 weeks. Supplementation with EFA may cause minor digestive signs.

Chinese herbal extracts

From the data available in two RCTs, there was insufficient evidence to examine whether the tested Chinese herbal extracts offered a beneficial effect compared to placebo. Transient digestive adverse drug events were common, especially at higher dosages.

Miscellaneous interventions

There are four small RCTs that tested variable interventions for the treatment of AD in dogs. In all, treatment efficacy of each intervention was negligible or of medium potency. Of the four drugs tested, misoprostol appeared to have the strongest, albeit quite modest treatment effect (e.g. one-third of dogs exhibiting a halving in pruritus).

(4) *Conclusions*.

In summary, veterinary dermatology is in need of performance of RCTs of higher design quality, that employ drugs whose pharmacokinetics and pharmacodynamics have been optimized in dogs, with the number of subjects and controls determined from pilot studies and power analyses, and with designs that have been adapted according to the suspected mechanism of action and perceived potency of the tested intervention. Most importantly, RCTs must reflect the manner in which such intervention is likely to be employed in clinical practice.

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Supporting Information

The initial study protocol is available at: http://www.cochrane.org/reviews/special/68canine_ad_protocol.pdf.

A longer version of this systematic review, which follows closely the guidelines of the Cochrane Collaboration, is available in the online version of this article, which contains an additional section named 'Implications for Research':

Document S1. Interventions for Atopic Dermatitis in Dogs: A Systematic Review of Randomized Controlled Trials.

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Résumé L'objectif de cette revue, effectuée selon les recommandations de la « Cochrane collaboration », était d'évaluer les effets des communications sur le traitement de la dermatite atopique canine (DAC). Les citations retenues à partir de trois bases de données (MEDLINE, Thomson's Science Citation Index Expanded et CAB Abstracts) et les essais publiés jusqu'à décembre 2007 ont été retenus. Les citations pertinentes des proceedings des principaux congrès internationaux de dermatologie vétérinaire ont été recherchées manuellement. Les auteurs ont sélectionnés les études contrôlées randomisées (RCT) publiées de janvier 1980 à décembre 2007, rapportant l'efficacité des traitements ou préventions topiques ou systémiques de la DAC. Les études devaient faire état du prurit et/ou des lésions cutanées. Les études étaient choisies et les données recueillies par deux investigateurs, les points de divergence étant arbitré par un troisième. Les données manquantes étaient demandées aux auteurs des études les plus récentes. Les résultats ont été regroupés et des méta-analyses effectuées sur les publications semblables et leurs effets. Quarante-neufs études ont au total été sélectionnées, ce qui représente 2 126 chiens. Cette revue a mise en évidence l'efficacité du tacrolimus topique (3 RCT), de la triamcinolone topique (1), des glucocorticoïdes oraux (5), de la ciclosporine orale (6), de l'interféron-gamma recombinant sous-cutané (1) et de l'immunothérapie spécifique d'allergène sous-cutanée (3) dans la diminution du prurit et/ou des lésions cutanées des chiens atopiques. Une étude de haute qualité a montré qu'une supplémentation orale en acides gras essentiels pouvait réduire la consommation de prednisolone de moitié.D'autres études contrôlées randomisées de haute qualité doivent être réalisées afin de corriger les erreurs antérieures et de tester les moyens de préventions des poussées de cette maladie.

Resumen El objetivo de esta revisión sistemática, que se realizó siguiendo los parámetros de la colaboración de Cochrane, fue valorar los efectos de diferentes intervenciones en el tratamiento de la dermatitis atópica (AD) en perros. Se buscaron citas en tres diferentes bases de datos (MEDLINE, índice expandido de citas científicas de Thomson, y los resúmenes CAB), así como pruebas clínicas publicadas hasta diciembre del 2007. Se buscaron manualmente citad en los resúmenes de los más importantes congresos de dermatología a nivel internacional. Los autores seleccionaron pruebas clínicas al azar controladas y publicadas desde enero de 1980 a diciembre de 2007, las cuales indicaban la eficacia de las intervenciones tópicas o sistémicas en el tratamiento o la prevención de la dermatitis atópica canina. Los estudios tenían que indicar la valoración del prurito, de las lesiones de la piel o de ambos. Los estudios fueron seleccionados ry los datos extraídos por dos autores. Y las discrepancias se resolvieron por una tercera persona. Los datos que faltaban fueron pedidos a los autores de los estudios en pruebas de reciente publicación. Se desarrolló una compilación de resultados y un meta análisis para los estudios que indicaban intervenciones similares y que mencionaban la valoración de los resultados. Se seccionaron un total de 49 estudios clínicos los cuales agrupaban un total de 2126 perros. Esta revisión encontró evidencia de la eficacia del tratamiento tópico con tacrolimus (3 estudios), triamcinolona tópica (1 estudio), glucocorticoides por vía oral (5 estudios), ciclosporina oral (6 estudios) interferón gamma recombinante por vía subcutánea (1 estudio) e inmunoterapia especifica de alergeno por vía subcutánea (3 estudios) para disminuir el prurito y/o las lesiones de la piel en perros con dermatitis atópica. Un estudio de alta calidad demostró que ácidos grasos esenciales suplementados por vía oral pueden reducir el consumo de prednisolona aproximadamente a la mitad. Otros estudios adicionales de alta calidad en el diseño se deben realizar para evitar previos defectos y para evaluar las intervenciones para la prevención de recidivas de la enfermedad.

Zusammenfassung Das Ziel dieser systematischen Review, die nach den Richtlinien der Cochrane Collaboration durchgeführt wurde, war es, die Auswirkungen von Interventionen auf die Behandlung von atopischer Dermatitis (AD) bei Hunden zu erheben. Literaturzitate, die durch drei Datenbasen (MEDLINE, Thomsońs Science Citation Index Expanded und CAB Abstracts) gefunden wurden und Studien, die bis Dezember 2007 publiziert worden waren, wurden ausgewählt. Proceedings Bücher von wichtigen internationalen veterinärdermatologischen Kongressen wurden per Hand auf relevante Zitate durchgesehen. Die Autoren wählten randomisierte kontrollierte Studien (RCTs) aus, die zwischen Jänner 1980 und Dezember 2007 publiziert worden waren und die Wirksamkeit von topischer oder systemischer Interventionen auf die Behandlung oder auf die Prävention von caniner AD beschrieben. Die Studien mussten entweder eine Beurteilung von Juckreiz oder von Hautveränderungen, oder beidem, beschreiben. Die Studien wurden von zwei Reviewern ausgewählt und von ihnen wurden die Daten exzerpiert, wobei eventuelle Diskrepanzen durch einen dritten Gutachter bereinigt wurden. Fehlende Daten wurden von Autoren von unlängst publizierten Studien nachgefordert. Eine Zusammenfassung der Ergebnisse und eine Meta-Analyse wurden bei Studien, die ähnliche Interventionen und Ergebnisse berichteten, durchgeführt. Insgesamt wurden 49 RCTs ausgewählt, die zusammen 2126 Hunde beinhalteten. In dieser Review wurden Hinweise auf die Wirksamkeit von Takrolimus (3 RCTs), topisch verwendetem Triamcinolon (1), oralen Glukokortikoiden (5), oralem Cyclosporin (6), subkutanem rekombinanten gamma-Interferon (1) und subkutaner Allergen-spezifischer Immuntherapie (3) bei der Verminderung von Pruritus und/oder den Hautläsionen bei caniner AD gefunden. Eine RCT von hoher Qualität zeigte, dass die Verwendung eines oralen Supplements von essentiellen Fettsäuren den Prednisolon-Konsum um etwa die Hälfte vermindern konnte. Weitere RCTs mit hoher Studienqualität müssen durchgeführt werden, um frühere Fehler auszubessern und um Interventionen zu testen, die ein Aufflammen dieser Krankheit verhindern können.

