

Evidence-based veterinary dermatology: a systematic review of the pharmacotherapy of canine atopic dermatitis

T. OLIVRY^{*,†} R. S. MUELLER[‡]
and THE INTERNATIONAL TASK FORCE ON CANINE ATOPIC DERMATITIS[§]

^{*}Department of Clinical Sciences, North Carolina State University, College of Veterinary Medicine,
4700 Hillsborough Street, Raleigh, NC 27606, USA

[†]Department of Dermatology, School of Medicine, University of North Carolina,
Chapel Hill, North Carolina, USA

[‡]Department of Clinical Sciences, College of Veterinary Medicine & Biomedical Sciences,
Colorado State University, Fort Collins, Colorado, USA

(Received 12 February 2003; accepted 26 February 2003)

Abstract The efficacy of pharmacological interventions used to treat canine atopic dermatitis, excluding fatty acid supplementation and allergen-specific immunotherapy, was evaluated based on the systematic review of prospective clinical trials published between 1980 and 2002. Studies were compared with regard to design characteristics (randomization generation and concealment, masking, intention-to-treat analyses and quality of enrolment of study subjects), benefit (improvement in skin lesions or pruritus scores) and harm (type, severity and frequency of adverse drug events) of the various interventions. Meta-analysis of pooled results was not possible because of heterogeneity of the drugs evaluated. Forty trials enrolling 1607 dogs were identified. There is good evidence for recommending the use of oral glucocorticoids and cyclosporin for the treatment of canine atopic dermatitis, and fair evidence for using topical triamcinolone spray, topical tacrolimus lotion, oral pentoxifylline or oral misoprostol. Insufficient evidence is available for or against recommending the prescription of oral first- and second-generation type-1 histamine receptor antagonists, tricyclic antidepressants, cyproheptadine, aspirin, Chinese herbal therapy, an homeopathic complex remedy, ascorbic acid, AHR-13268, papaverine, immune-modulating antibiotics or tranilast and topical pramoxine or capsaicin. Finally, there is fair evidence against recommending the use of oral aroxylline, leukotriene synthesis inhibitors and cysteinyl leukotriene receptor antagonists.

Keywords: allergic, allergy, atopy, dog, evidence-based medicine, integument, pruritus, skin

INTRODUCTION

Successful treatment of atopic dermatitis (AD) in human individuals requires a multidimensional approach to identify and eliminate exacerbating factors, reduce skin inflammation and relieve itch.¹ Over the decades, dozens of therapeutic interventions have been reported for this disease, but evidence of efficacy is highly variable among drugs used. Investigators at a centre for evidence-based dermatology in the UK recently completed a systematic review of preventive and therapeutic interventions for human AD.² Of a total of 1165 randomized controlled trials (RCTs) identified, 272 studies provided enough data for careful scrutiny of 47 different interventions. The authors concluded that there was reasonable RCT evidence to support recommendation of treatment of AD with oral cyclosporin (CsA), topical glucocorticoids (GC) and ultraviolet (UV) light therapy.² It was also found that there was insufficient evidence to make recommendations for treatment with oral antihistamines, Chinese herbal therapy, homeopathy, evening primrose oil, topical coal tar, emollients and topical doxepin.² Finally, this review established that there was complete absence of

Correspondence: T. Olivry, Department of Clinical Sciences, North Carolina State University, College of Veterinary Medicine, 4700 Hillsborough Street, Raleigh, NC 27606, USA. E-mail: Thierry_Olivry@ncsu.edu

[§]International Task Force on Canine Atopic Dermatitis: Thierry Olivry, NC State University, Raleigh, North Carolina, USA (Chair); Didier N. Carlotti, Cabinet de Dermatologie Vétérinaire, Bordeaux-Mérignac, France; Douglas J. DeBoer, University of Wisconsin-Madison, Madison, Wisconsin, USA; Craig E. Griffin, Animal Dermatology Clinic, San Diego, California, USA; Richard E.W. Halliwell, University of Edinburgh, Edinburgh, UK; Bruce Hammerberg, NC State University, Raleigh, North Carolina, USA; Peter B. Hill, University of Edinburgh, Edinburgh, UK; Andrew Hillier, The Ohio State University, Columbus, Ohio, USA; Toshiro Iwasaki, Tokyo University of Agriculture & Technology, Tokyo, Japan; Hilary A. Jackson, NC State University, Raleigh, North Carolina, USA; Rosanna Marsella, University of Florida, Gainesville, Florida, USA; Ralf S. Mueller, Colorado State University, Fort Collins, Colorado, USA; Timothy Nuttal, University of Liverpool, Liverpool, UK; Pascal Prélud, Centre d'Etude et de Recherche en Immunologie, Paris, France; Edmund J. Rosser, Jr, Michigan State University, East Lansing, Michigan, USA; Candace A. Sousa, Animal Dermatology Clinic, Sacramento, California, USA; Ton Willemse, University of Utrecht, Utrecht, the Netherlands.

RCT evidence for treatment with short bursts of potent vs. longer term weaker topical GC, dilutions of topical GC, oral prednisolone, oral azathioprine, salt baths or miscellaneous bandages.² A second systematic review, published recently, corroborated the evidence of treatment efficacy of patients with AD with moisturizing creams plus topical GC or with topical GC alone.³

The management of canine AD is also multifaceted, and usually combines interventions such as allergen avoidance, allergen-specific immunotherapy, antimicrobial and anti-inflammatory pharmacotherapy.⁴ During the last 20 years, various drugs have been proposed to reduce clinical signs of canine AD. Recent studies by the ACVD Task Force on Canine Atopic Dermatitis provided narrative overviews of the efficacy of the pharmacological interventions reported previously^{5–7} but attempts to systematically review and compare the efficacy between medications were not made. It was felt, therefore, that there was need for an unbiased analysis of the benefit and harm of the multiple medications used for treatment of canine AD.

Accordingly, the main objectives of this systematic review were to identify and critically appraise the evidence of efficacy of pharmacological interventions used for treatment of canine AD. Whenever applicable, this systematic review was reported following the recommendations of the QUOROM statement.⁸

METHODS

Search strategy

In order to retrieve all clinical trials enrolling canine patients with AD, a wide electronic search was carried out using the MEDLINE database. A broad query was done with the following user string: (*dog OR dogs OR canine*) and (*atop* OR pruritus*) with a limit set from 1980 to 2002. A second focused search was made with the same string limited to the 'therapy' category of the clinical queries using research methodology filters. To increase the retrieval of additional veterinary medical citations, both CAB ABSTRACT and ISI Web of Science databases were queried using the following string: (*atopy or atopic or pruritus*) and (*dog or dogs or canine*). The search was limited to articles published after 1980.

The four volumes of *Advances in Veterinary Dermatology*, which include peer-reviewed original articles presented at previous World Congresses of Veterinary Dermatology, were hand-searched for studies pertinent to this review. Similarly, the bibliographies of all articles and book chapters covering treatment of canine AD or pruritus were scanned for additional relevant citations. Finally, a message was posted on the Vetderm listserv (1 November 2002) to request identification and sharing of clinical trials recently accepted for publication in peer-reviewed journals.

Selection of studies

This systematic analysis was restricted to prospective clinical trials published in peer-reviewed veterinary or

medical journals from 1980 to 2002. There was no limitation based on language of publication. Clinical trials were included only if study participants included at least five dogs with AD, this disease being defined as a 'a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features and associated most commonly with IgE antibodies to environmental allergens'.⁹

Only clinical trials that evaluated pharmacological interventions aimed at the treatment of AD were included in this systematic review. Also, studies needed to report at least one clinical outcome to exclude those that solely described biological changes after pharmacological intervention.

In this review, we chose also to exclude clinical trials investigating the efficacy of fatty acid supplementation and allergen-specific immunotherapy, as an attempt to systematically review¹⁰ and an in-depth overview¹¹ of their respective treatment effects have been published recently.

Data extraction

Clinical trials that satisfied inclusion criteria were reviewed independently by the leading authors (TO and RSM) who assessed quality of study design, participants' characteristics, details of interventions and outcome measures. Data were abstracted in tabular form. Results of the review were compared, and where differences were noted, they were discussed and reconciled.

Quality assessment

Assessment of methodological quality Three parameters were addressed to determine the risk for biased estimates of treatment effect in the included studies:

- 1 *randomization*, method of generation and concealment of allocation to treatment groups;
- 2 *masking*, blinding of observers (e.g. clinicians) and participants (e.g. owners) to the treatment allocation;
- 3 *loss-to-follow-up*, presence of dropouts and withdrawals and *intention-to-treat* (ITT) analyses. The latter term denotes the performance of statistical analyses on all subjects entered in the trial, whether or not they had actually received the intervention and completed the study. ITT analyses are believed to prevent overestimation of treatment efficacy in case of substantial withdrawal of study subjects due to adverse drug events.¹²

These three components were graded in accordance to the recommendations of the Cochrane Skin Group as 'adequate', 'unclear' or 'inadequate'.¹³ When trials were not randomized, 'none' was the qualifier provided for the randomization parameter. When statistical analyses were not performed, a specific mention of this was written.

An overall *grade of evidence quality*, based on the parameters discussed above and the number of subjects

entered in active treatment groups, was provided for each study as follows:

- (A) blinded randomized controlled trial (control with either active drug or placebo);
 - (B) controlled trial lacking either blinding or randomization;
 - (C) open, uncontrolled trial;
 - (D) cohort study, case-control analytic study, descriptive study, case report:
- (1) > 50 subjects per group,
 - (2) 20–50 subjects per group,
 - (3) 10–19 subjects per group,
 - (4) < 10 subjects per group.

Example: the quality of evidence of a blinded RCT enrolling 30 subjects (15 in each group), will be graded A3, that of an open trial of 25 dogs will be C2.

Of note is that such grading scheme could be misleading on rare occasions. Indeed, one could assume that a large blinded RCT (A1) with poorly defined outcome measures would provide evidence of higher quality than that of a well-designed yet smaller nonblinded RCT (B2). Readers are urged to use caution whenever making such assumptions.

Assessment of subject enrolment quality For each of the eligible studies, criteria for inclusion of subjects were reviewed to assess the method of diagnosis of AD in comparison with currently accepted standards.^{14,15} The quality of subject selection was evaluated for each trial as follows.

Well-characterized was the term used when only patients with AD were entered in the study, and sufficient details on the methods of diagnosis of AD (clinical signs, rule-out of concurrent or resembling skin diseases, etc.) were provided to allow comparison with current standards.¹⁵

Poorly-characterized was used when participant selection criteria were vague (e.g. uncharacterized 'allergic pruritus'), and insufficient details of the diagnostic work-up were provided.

Fairly-characterized was used for intermediate situations.

Assessment of outcome measures Whenever possible, the following four outcome measures were calculated from reported study data to compare efficacy between interventions: (i) percentage of reduction from baseline of skin lesion scores; (ii) percentage of reduction from baseline of pruritus scores; (iii) percentage of dogs achieving 50% or greater reduction from baseline of skin lesion scores; (iv) percentage of dogs achieving 50% or greater reduction from baseline of pruritus scores.

A 50% reduction from baseline of pruritus or lesional scores is believed to represent a clinically relevant threshold above which both clinicians and owners are satisfied with treatment effect.¹⁶ This benchmark also mirrors the 'good-to-excellent efficacy' subjective outcome

measure that was employed in most clinical trials reported in the early 1990s.

When published information was insufficient to permit abstraction of the four outcome measures described above, authors of recently published RCTs were contacted with a request to supply individual scores of all study subjects. Missing data were replaced in accordance to the 'last-value-carry forward' rule. For non-RCT studies published more than five years ago for which such specific measures were not provided, author-reported variables were quoted. Finally, all published adverse effects were collated and assessed for evaluation of treatment harm.

Meta-analysis of randomized controlled trials

Because there were few trials investigating the same intervention, results were not presented fully in many articles, enrolment of study subjects was heterogeneous, and only few RCTs overall were available, meta-analysis of pooled results was not considered appropriate.

Reporting of qualitative results

Pharmacological interventions were grouped in different sections based on similar mechanisms of drug action. Study design, patient enrolment quality, nature of interventions and main outcome measures were summarized in narrative and/or tabular forms.

A recommendation of use of these drugs for treatment of canine AD will be proposed following careful scrutiny of the evidence of efficacy and harm of the interventions reported in the various sections. The strength of recommendation qualifier was modified from the 1996 report of the US Preventive Services Task Force as either *good or fair evidence for use of the medication*, *insufficient evidence for/against use of the medication* or *fair or good evidence against use of the medication*.¹⁷ The basis for such recommendation statements will be as follows:

- 1 When more than one study, including at least one blinded RCT, supports the high efficacy of the drug tested, there is 'good' evidence 'for' recommending the use of this medication.
- 2 When at least one blinded RCT provides support of medium to high efficacy of the drug investigated, there will be 'fair' evidence 'for' recommending the use of that drug.
- 3 When blinded RCTs are not available, or when multiple studies yield controversial evidence of treatment effect, it will be concluded that there is 'insufficient' evidence 'for/against' recommending prescription of the medication tested.
- 4 When at least one blinded RCT provides evidence of lack of efficacy, or efficacy associated with common harmful events, there is 'fair' evidence 'against' recommending the use of this medication.
- 5 When more than one study, including at least one blinded RCT, supports the lack of efficacy of the drug tested, or supports any efficacy but with unacceptable side effects, there is 'good'

evidence 'against' recommending the use of the drug evaluated.

RESULTS

As of 1 November 2002, our search strategy identified almost 600 citations, of which a total of 40 clinical trials met our three major inclusion criteria: (i) prospective original experiment, (ii) nonfatty acid nonimmunotherapy pharmacological intervention with clinical outcome measure, and (iii) enrolment of at least five dogs with AD. There were 36 articles written in English, 3 in French and 1 in Japanese. Relevant studies were not found in any other language. The 40 trials reported data on 1607 patients (1247 diagnosed with AD) and 41 different pharmacological interventions. There were 19 blinded RCTs (quality of evidence: grade A), 6 controlled trials lacking either blinding or randomization (grade B), and 15 open, uncontrolled studies (grade C).

Treatment with placebo

Seventeen studies, including twelve blinded RCTs, evaluated the efficacy of various interventions compared with their appropriate placebo.^{16,18–33} Together, these trials had enrolled 517 dogs, 346 of them diagnosed with AD. Length of treatment varied from 1 week¹⁹ to 8 weeks.²⁷

Of eight trials that included evaluation of investigator-graded skin lesion scores before and after treatment with placebo, three reported improvements in values^{16,22,29} three recorded no changes^{25,26,30} and two reported worsening of scores (some of these data were obtained from the authors).^{27,33} The median percentage improvement from baseline of lesion scores was 0% (95% confidence interval [CI]: –9 to 17%; negative integers denote worsening).

Similarly, improvement, no change or worsening of owner-assessed pruritus scores after placebo administration were observed in six,^{16,22,29,30,32,33} three^{21,25,26} and one²⁷ of ten trials, respectively. The median percentage improvement from baseline of pruritus scores was 10% (95% CI: –6 to 18%).

A median of 0% (95% CI: 0 to 21%) of dogs exhibited a $\geq 50\%$ reduction in skin lesion scores during treatment with placebo (eight studies). In contrast, 9% (95% CI: 4 to 16%) of subjects achieved a similar clinically relevant benchmark in pruritus scores after the administration of placebo (16 studies).

One trial evaluated the effects of AD seasonality on the study main outcome variables.¹⁶ Treatment with placebo was associated with a high percentage reduction in skin lesion (59%) and pruritus (66%) scores in dogs with seasonal AD. In dogs with nonseasonal disease, however, the placebo effect was comparatively lower (21% and –1% change in lesion and pruritus scores, respectively).

Treatment with glucocorticoids

Topical glucocorticoids At this time, there is only one company-sponsored trial documenting the efficacy of

topical GC formulations for treatment of clinical signs of skin allergy in dogs.²⁹ One hundred and three dogs with pruritic inflammatory skin disease of known or suspected allergic origin completed this 1-month multicentre blinded RCT (quality of evidence: A1). Of these subjects, 83 were diagnosed with AD, but the criteria for diagnosis of this disease were not specified clearly. Lesional skin was sprayed with either placebo (51 dogs) or 0.015% triamcinolone acetonide solution (TTS Solution, Sparhawk Laboratories, Lenexa, KS, USA) (52 patients) twice daily for 1 week, then once daily for 1 week, then every other day for 2 weeks. Intention-to-treat analyses (i.e. all patients enrolled are kept for statistical analyses whether or not they had dropped-out of the study) were not reported for this trial.

At the end of treatment, veterinarian-assessed overall, erythema, eruption and pruritus scores were significantly lower in the active group than in dogs treated with placebo. Similarly, owner-graded scores for eruption also were lower in dogs receiving the active drug. The median percentage reduction from baseline of clinician-assessed overall scores and owner-graded pruritus score were both 67%. Sixty-nine per cent of dogs improved $\geq 50\%$ in either clinician overall or owner pruritus scores during the trial (data obtained from the leading author). The odds ratio for treatment success (defined by the authors as improvement in two of six point clinician-assessed overall scores) was 6.9 times greater for the active medication than placebo (95% CI: 2.8–16.7).

Investigator-assessed adverse drug effects were seen in 5/52 dogs (10%) and consisted of polyuria, polydipsia or polyphagia (two dogs), increased scaling or shedding (two dogs) and gastrointestinal signs (one dog). In the GC group, the frequency of adverse effects was lower than that reported for the placebo group.

Oral glucocorticoids In spite of the widespread practice usage of oral GC formulations to treat skin lesions of canine AD, only six trials have reported their beneficial effect. In fact, most of the evidence for efficacy of oral GC derives from trials in which these drugs were used as standard-of-care controls for comparison with other interventions.^{19,34–36} Two articles described results from an open and uncontrolled study,^{37,38} and the remaining four articles provided evidence of efficacy using blinded RCT designs.^{19,34–36} Only in the last two trials were ITT analyses conducted.^{35,36} One of the open studies was sponsored by the drug manufacturer.³⁸

These six clinical trials enrolled 476 subjects, and 293 (62%) of them had been diagnosed with AD. The three earliest studies also included patients with other allergic skin diseases^{19,37,38} or nonseasonal idiopathic pruritus (see Table 1 for details).¹⁹ Of the 293 dogs with AD, 141 (48%) were treated with oral GC. Of the 141 dogs with AD entered in the trials, 41 (29%) were treated with oral prednisone,^{19,34} 24 (17%) with prednisolone^{35,37} and 76 (54%) with methylprednisolone.^{36,38} There were no trials comparing the efficacy of oral GC with placebo; two trials evaluated the

Table 1. Trials reporting treatment with oral glucocorticoids

Citation (Reference)	Paradis, 1991 (19)	Reddy, 1994 (37)	Guaguère, 1996 (38)	Ferrer, 1999 (34)		Olivry, 2002 (35)	Steffan, 2003 (36)
Quality of Evidence	B2	C1	C1	A3		A3	A1
Randomization (Allocation Generation)	unclear	none	none	adequate		adequate	adequate
Randomization (Allocation Concealment)	unclear	none	none	adequate		adequate	adequate
Masking of Outcome Assessor	adequate	inadequate	inadequate	adequate		adequate	adequate
Intention-to-Treat Analyses	no statistical analyses	no statistical analyses	no statistical analyses	inadequate		adequate	adequate
Quality of Inclusion of Study Subjects	fairly-characterized	poorly-characterized	fairly-characterized	well-characterized		well-characterized	well-characterized
# Dogs Entered in Trial (Total)	30	120	80	40		30	176
# Dogs Entered in Trial (AD only)	21	9	17	40		30	176
# Dogs with AD Treated with GC	21	9	17	10	10	15	59
Length of Trial (Length GC Treatment) (wks)	9 (1) + 2 to verify sustained efficacy	not specified	3 (3)	4 (4)		6 (6)	16 (16)
Pharmacological Intervention	prednisone 0.2–0.4 mg kg ⁻¹ BID	prednisolone 0.5 mg kg ⁻¹ BID, then QD then BID EOD	methylprednisolone 0.4–0.8 mg kg ⁻¹ QD then EOD	prednisone 0.25 mg kg ⁻¹ BID 0.5 mg kg ⁻¹ BID then QD, EOD		prednisolone 0.5 mg kg ⁻¹ QD	methylprednisolone 0.5–1.0 mg kg ⁻¹ QD, then EOD, then dosage tapered by 50 and 75% 45%
Mean/Median % Reduction in Lesional Scores	NA	NA	NA	67%*	83%*	69%	
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA	58%*	67%*	81%	33%
% Dogs with ≥ 50% Reduction in Lesional Scores	NA	NA	NA	70%*	60%*	86%	58%
% Dogs with ≥ 50% Reduction in Pruritus Scores	57%	NA	NA	60%*	60%*	71%	42%
Other Outcome Measures		'good-to-excellent' response in 100% of dogs with atopy	86% 'very good results' (> 75% improvement) assessed by clinician	*data calculated using 'last-value- carry-forward' rule		NA	60–63% 'good-to-excellent' global assessment of efficacy by owner and clinician

Abbreviations: BID: twice daily; EOD: every-other-day, QD: once daily; NA: not available.

treatment effect of prednisolone or methylprednisolone to that of CsA.^{35,36}

In the three trials that only reported clinical outcome measures as overall assessments of efficacy, satisfactory control of clinical signs (pruritus and/or lesions) was described in 57–100% of study subjects.^{19,37,38} At the end of three RCTs^{34–36} the mean/median reduction in lesional scores varied from 45 to 83%, and that of pruritus scores from 33 to 81%. The clinically relevant efficacy benchmark ($\geq 50\%$ reduction of lesional scores) was reached by 58–86% of GC-treated dogs. Similarly, the 50% pruritus reduction threshold was achieved by 42–71% of study subjects. Of note is that the relatively low efficacy of methylprednisolone in the last trial could be explained by the administration of reduced dosages of GC every other day for a duration (16 weeks) longer than that of the other studies.³⁶ The efficacy of oral GC was found to be comparable with that of CsA.^{35,36}

In the six trials reviewed herein, at least one adverse drug event was recorded in 30^{19,34} to 80%³⁶ of study subjects. Side effects of GC therapy included varying degrees of polyuria, polydipsia, polyphagia and weight gain (10–25% of subjects), intermittent digestive clinical signs (vomiting, loose stools) (7–25% of dogs) or development of skin infections (34% of patients). In the open trial, all side effects disappeared at the end of the treatment period.³⁸ In one study, adverse effects of oral methylprednisolone were described as being of mild severity.³⁶

Treatment with calcineurin inhibitors

Oral cyclosporine Our literature search identified four clinical trials investigating the efficacy of CsA for treatment of canine AD.^{16,35,36,39} All studies were funded, partially or completely, by the drug manufacturer. One study described results from a small open trial of 2 weeks' duration,³⁹ whereas the three others were larger blinded RCTs.^{16,35,36} Intention-to-treat analyses were available for all trials.

Together, these four trials had enrolled 311 dogs with AD diagnosed by standard methods. Of 311 dogs, 207 (67%) were treated with CsA proemulsion concentrate (Neoral, Novartis Pharma; Atopica, Novartis Animal Health, Basel, Switzerland), whereas the remaining dogs were treated with either placebo,¹⁶ prednisolone³⁵ or methylprednisolone (Table 2).³⁶

All four trials reported that CsA administered at 5.0 mg kg⁻¹ day⁻¹ led to a decrease in the clinical signs of AD. The mean or median reduction from baseline of investigator-graded lesional scores varied between 52³⁶ and 67%.¹⁶ Similarly, improvement from baseline of owner-assessed pruritus scores fluctuated between 36³⁶ and 100%.³⁹ Satisfactory control of lesions and pruritus (i.e. $\geq 50\%$ reduction of scores during the trial) was achieved in 66³⁶ to 79%³⁹ and 40³⁶ to 86%³⁹ of study subjects, respectively. Of note is that the relative lower improvement in the most recent trial³⁶ could be explained by the decreasing frequency of CsA administration over the study period.

When compared with other interventions, CsA was found to be equally as effective as prednisolone³⁵ and methylprednisolone³⁶ used at standard anti-inflammatory dosages (see GC section). Finally, induction of treatment with the lowest dosage of CsA (2.5 mg kg⁻¹ day⁻¹) was found to be no more effective than placebo.¹⁶ At 5.0 mg kg⁻¹ day⁻¹, CsA administration led to significantly greater reduction in lesion and pruritus scores than the intake of its vehicle.¹⁶

Adverse drug events were reported in 14³⁹ to 81% of study subjects.³⁶ They were categorized as mild to moderate in most patients^{16,36} and consisted most commonly of intermittent vomiting (14–42%) and diarrhoea (16–18%).^{16,35,36,39} Skin infections developed in 29% of subjects enrolled in the largest and longest RCT.³⁶ In this trial, the severity of adverse drug events led to interruption of treatment in 6% of CsA-treated dogs.³⁶ Occasional events led to discontinuation of treatment in other trials, but the causation of CsA was not proven unequivocally.³⁵

Topical tacrolimus A recent small RCT evaluated the efficacy and safety of 0.3% tacrolimus lotion in dogs with AD.³² In this double-blinded, randomized placebo-controlled crossover study, eight dogs with well-characterized AD were selected (quality of evidence: A4). Dogs were randomly assigned to be treated with either compounded 0.3% tacrolimus lotion (Prograf, Fujisawa, Deerfield, IL, USA; maximum dosage: 0.3 mg kg⁻¹ day⁻¹) or placebo lotion (vehicle) once daily for 4 weeks. After a 2-week wash out, treatments were reversed. Data were available only for seven dogs because one subject did not complete the trial, and ITT analyses were not performed. There was no power analysis justifying the low count of subjects, and this low number could have altered the analysis of treatment effect.

At the end of the trial, there were no significant differences in owner-assessed pruritus scores within treatment groups (week 4 compared with baseline) or between interventions. After 4 weeks, investigator-graded erythema scores, but not pruritus scores, were significantly lower in dogs treated with tacrolimus compared with those receiving the placebo vehicle. After 4 weeks, and compared with baseline, clinician-assessed pruritus scores were significantly lower in tacrolimus-treated dogs, but not in those receiving placebo. Data obtained from the author yielded median improvements from baseline scores of 0, 33 and 50% for owner-assessed pruritus, and investigator-graded erythema or pruritus, respectively. Thirty-eight per cent of dogs treated with tacrolimus exhibited a $\geq 50\%$ improvement from baseline in erythema scores, whereas 13–50% of subjects achieved the same benchmarks for owner and investigator assessed pruritus, respectively.

At the end of the trial, there were no differences in complete blood counts or chemistry panels between tacrolimus and placebo-treated dogs. Adverse drug events following tacrolimus lotion application were not reported in this study.

Table 2. Trials reporting treatment with the calcineurin-inhibitor cyclosporine

Citation (Reference)	Fontaine, 2001 (39)	Olivry, 2002 (35)	Olivry, 2002 (16)	Steffan, 2003 (36)
Quality of Evidence	C3	A3	A2	A1
Randomization (Allocation Generation)	none	adequate	adequate	adequate
Randomization (Allocation Concealment)	none	adequate	adequate	adequate
Masking of Outcome Assessor	inadequate	adequate	adequate	adequate
Intention-to-Treat Analyses	adequate	adequate	adequate	adequate
Quality of Inclusion of Study Subjects	well-characterized	well-characterized	well-characterized	well-characterized
# Dogs Entered in Trial (Total)	14	30	91	176
# Dogs Entered in Trial (AD only)	14	30	91	176
# Dogs with AD Treated with Active Drug	14	15	30	117
Length of Trial (Length Drug Treatment) (wks)	2 (2)	6 (6)	6 (6)	16 (16)
Pharmacological Intervention	CsA proemulsion concentrate 5.0 mg kg ⁻¹ QD	CsA proemulsion concentrate 5.0 mg kg ⁻¹ QD	CsA proemulsion concentrate 2.5 mg kg ⁻¹ QD 5.0 mg kg ⁻¹ QD	CsA proemulsion concentrate 5.0 mg kg ⁻¹ QD, EOD or TW
Mean/Median % Reduction in Lesional Scores	60%	58%	41%	52%
Mean/Median % Reduction in Pruritus Scores	100%	78%	31%	36%
% Dogs with ≥ 50% Reduction in Lesional Scores	79%	69%	47%	66%
% Dogs with ≥ 50% Reduction in Pruritus Scores	86%	77%	33%	40%
Other Outcome Measures	86% 'good-to-excellent' global assessment by owner	NA	33–40% 'good-to-excellent' global assessment of efficacy by owner and clinician	61% 'good-to-excellent' global assessment of efficacy by owner and clinician
				75–76% 'good-to-excellent' global assessment of efficacy by owner and clinician

Abbreviations: EOD: every-other-day; QD: once daily; TW: twice weekly; NA: not available.

Table 3. Trials reporting treatment with first-generation alkylamine antihistamines

Citation (Reference)	Scott, 1988 (40)	Reddy, 1992 (37)	Paterson, 1994 (43)	Paterson, 1995 (46)
Quality of Evidence	C2	C1	B2	B2
Randomization	none	none	unclear	unclear
(Allocation Generation)				
Randomization	none	none	unclear	unclear
(Allocation Concealment)				
Masking of Outcome Assessor	inadequate	inadequate	unclear	unclear
Intention-to-Treat Analyses	no statistical analyses	no statistical analyses	no statistical analyses	adequate
Quality of Inclusion of	fairly-characterized	poorly-characterized	well-characterized	well-characterized
Study Subjects				
# Dogs Entered in Trial (Total)	45	120	30	32
# Dogs Entered in Trial	19	9	30	32
(AD only)				
# Dogs with AD Treated	19	9	30	32
with Antihistamine				
Length of Trial (Length	6 (1)	not specified	6 (1) + 4 to verify	32 (1) + 4 to verify
Antihistamine Treatment) (wks)			sustained efficacy	sustained efficacy
Pharmacological Intervention	chlorpheniramine	pheniramine maleate	chlorpheniramine	chlorpheniramine
	4 mg TID	2 mg kg ⁻¹ BID	4–8 mg TID	4–8 mg TID
Mean/Median %	NA	NA	NA	NA
Reduction in Lesional Scores				
Mean/Median %	NA	NA	NA	NA
Reduction in Pruritus Scores				
% Dogs with ≥ 50% Reduction	NA	NA	NA	NA
in Lesional Scores				
% Dogs with ≥ 50% Reduction	NA	NA	NA	NA
in Pruritus Scores				
Other Outcome Measures	satisfactory control	44% of dogs with	10% of dogs with	significant
	of pruritus in 9%	atopy had positive	satisfactory (complete)	improvement in
	of dogs as assessed	response none had	pruritus control as	pruritus and erythema
	by the owner	satisfactory response	assessed by owners	scores as assessed by clinician

Abbreviations: BID: twice daily; TID: three times daily; NA: not available.

Treatment with type-1 histamine receptor antagonists
A total of 693 dogs (454 with AD) were enrolled in 15 clinical trials evaluating the efficacy of type-1 histamine receptor antagonists.^{18,19,23,24,37,40–49} Four studies tested the antipruritic effect of multiple antihistamines used successively.^{19,40,43,46} In two trials, antihistamines were used alone and in combination with FA.^{41,46} One RCT reported the use of a chlorpheniramine–hydroxyzine combination as active control for a fatty acid polymer.⁴⁹ One study evaluated the antipruritic effect of hydroxyzine alone or in combination with terfenadine.⁴⁸ All but 2 of these 15 trials were published before 1996; there were only three blinded RCTs^{23,24,49} and four studies lacked randomization and/or masking.^{18,19,43,46}

First-generation type-1 histamine receptor antagonists
Of the 15 clinical trials, 8 reported the efficacy of first-generation (e.g. sedating) type-1 histamine receptor antagonists of differing classes such as alkylamines (chlorpheniramine,^{40,43,46,49} pheniramine³⁷), ethanolamines (diphenhydramine,⁴⁰ clemastine^{19,41–43,46}), piperidine (hydroxyzine^{40,43,46,49}) or phenothiazines (promethazine,⁴³ triemepazine^{19,43}).

Chlorpheniramine and pheniramine The anti-allergic effect of the alkylamines chlorpheniramine and pheniramine was tested in four open trials enrolling

227 dogs, 90 of them with AD (Table 3).^{37,40,43,46} The duration of treatment with these drugs ranged from 1 to a maximum of 5 weeks. In one trial, the duration of treatment was not specified.³⁷ In another, dogs were treated with various antihistamines for 8 weeks, then fatty acids were added to the most effective medication.⁴⁶ In this trial, only data from the first 8 weeks were reviewed.

In two trials, a satisfactory reduction in pruritus was noted by the owners of ≈ 10% of subjects.^{40,43} In the last study, a significant improvement in investigator-assessed pruritus and erythema was reported during the first 8 weeks of treatment with chlorpheniramine, but the magnitude of improvement could not be estimated from the author's data.⁴⁶ Pheniramine led to satisfactory antipruritic response in none of nine dogs with atopy.³⁷

Adverse drug events of chlorpheniramine were reported in 0⁴³ to 27% of subjects,⁴⁰ but they were not specified in the last study.⁴⁶ Drowsiness was the side effect most commonly observed after treatment with either chlorpheniramine (13% of dogs)⁴⁰ or pheniramine (most dogs).³⁷

Diphenhydramine The antipruritic efficacy of the ethanolamine diphenhydramine was tested in only one open trial (Table 4).⁴⁰ A satisfactory control of pruritus was reported only by owners of 7% of enrolled patients.

Table 4. Trials reporting treatment with first-generation ethanolamine antihistamines

Citation (Reference)	Scott, 1988 (40)	Paradis, 1991 (19)	Paradis, 1991 (41)	Miller, 1993 (42)	Paterson, 1994 (43)	Paterson, 1995 (46)
Quality of Evidence	C2	C2	B2	C1	B2	B2
Randomization (Allocation Generation)	none	none	unclear	none	unclear	unclear
Randomization (Allocation Concealment)	none	none	unclear	none	unclear	unclear
Masking of Outcome Assessor	inadequate	inadequate	adequate	inadequate	unclear	unclear
Intention-to-Treat Analyses	no statistical analyses	no statistical analyses	no statistical analyses	no statistical analyses	no statistical analyses	adequate
Quality of Inclusion of Study Subjects	fairly-characterized	fairly-characterized	fairly-characterized	fairly-characterized	well-characterized	well-characterized
# Dogs Entered in Trial (Total)	45	30	30	72	30	32
# Dogs Entered in Trial (AD only)	19	18	21	72	30	32
# Dogs with AD Treated with Antihistamine	19	18	21	72	30	32
Length of Trial (Length Antihistamine Treatment) (wks)	6 (1)	6 (2)	9 (1) + 2 to verify sustained efficacy	2 (2) + 4 to verify sustained efficacy	6 (1) + 4 to verify sustained efficacy	32 (1) + 4 to verify sustained efficacy
Pharmacological Intervention	diphenhydramine 4 mg TID	clemastine 0.5–1.5 mg BID	clemastine 0.5–1.5 mg BID	clemastine 0.67–2.68 mg BID	clemastine 0.5–1.5 mg BID	clemastine 0.5–1.5 mg BID
Mean/Median % Reduction in Lesional Scores	NA	NA	NA	NA	NA	NA
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA	NA	NA	NA
% Dogs with ≥ 50% Reduction in Lesional Scores	NA	NA	NA	NA	NA	NA
% Dogs with ≥ 50% Reduction in Pruritus Scores	NA	27%	30%	29%	NA	NA
Other Outcome Measures	satisfactory control of pruritus in 7% of dogs as assessed by the owner	NA	NA	NA	10% of dogs with satisfactory (complete) pruritus control assessed by owners	significant improvement in pruritus and erythema scores as assessed by clinician

Abbreviations: BID: twice daily; TID: three times daily; NA: not available.

Adverse effects were seen in 16% of subjects, and these consisted mostly of drowsiness (11%).

Clemastine The efficacy of a second ethanolamine, clemastine, was investigated in five clinical trials: two were open,^{41,42} one was blinded with unclear randomization¹⁹ and the last two had unspecified blinding and randomization (Table 4).^{43,46}

In three studies from the same group, a satisfactory antipruritic efficacy of clemastine was reported by the owners of 27–30% of study subjects,^{19,41,42} whereas such effect was recorded only by 10% of owners in the British trial.⁴³ In the most recent study, a significant improvement in pruritus and erythema was reported by the clinician during the first 8 weeks of treatment, but the magnitude of improvement could not be determined with precision.⁴⁶

In these trials, side effects of clemastine were uncommon and of minimal severity. Drowsiness was reported in two studies.^{42,43}

Hydroxyzine The piperidine hydroxyzine was given to 128 dogs (86 with AD) as part of four trials whose characteristics were described above (Table 5).^{40,43,46,48} A satisfactory antipruritic effect of hydroxyzine was reported by 7–10% of owners.^{40,43} In another trial, a significant improvement in pruritus and erythema values was assessed by the clinician.⁴⁶ Finally, a $\geq 50\%$ reduction in pruritus was observed in one third of dogs given hydroxyzine alone in the most recent study (unpublished data obtained from the author).⁴⁸ Drowsiness was the most common adverse drug effect reported in one study (9% of dogs),⁴⁰ but side effects were either absent or not reported in the other studies.^{43,46,48}

A commercially available combination of 25 mg hydroxyzine and 1 mg of chlorpheniramine (Histacalmine, Virbac, Carros, France) was used as active control for evaluation of a fatty acid formulation in a double-blind RCT of 68 dogs with AD (Table 5).⁴⁹ At the end of antihistamine administration, a $\geq 50\%$ reduction of investigator-assessed lesional scores was found in 6/33 patients (18%). A reduction of more than 2 of 4 pruritus grades was reported by the owners of 10 dogs (30%). The clinical effect of this combination was deemed to be satisfactory by clinicians in eight dogs (24%). Adverse drug events of this antihistamine combination were not reported.

Trimeprazine and promethazine Trimeprazine and promethazine, two phenothiazine antihistamines, were tested for antipruritic efficacy in 30 dogs (21 with AD) (Table 6).^{19,43} Overall, trimeprazine or promethazine provided satisfactory relief of pruritus in none or one dog only (3%). Trimeprazine in combination with prednisone was deemed effective in 23/30 patients (77%).¹⁹ Somnolence was the sole adverse effect observed in one dog given trimeprazine,¹⁹ whereas this clinical sign was reported as a minor side effect of promethazine administration.⁴³

Second-generation type-1 histamine receptor antagonists Seven clinical trials evaluated the efficacy of second-generation low-sedation type-1 histamine receptor antagonists. Oxatomide was tested in three trials,^{18,44,47} terfenadine in two^{23,45} and the efficacy of astemizole and loratadine was reported in a single study each.^{19,24} Altogether, these trials had entered 275 dogs, including 201 diagnosed with AD.

Oxatomide Oxatomide was the first antihistamine tested in dogs with allergic skin disease,¹⁸ and there are three trials reporting its activity in 180 subjects (135 with AD) (Table 7).^{18,44,47} Reduction of clinical signs was variable, from half of the dogs improving 20–50%,⁴⁴ to 34% of patients exhibiting satisfactory control of pruritus.⁴⁷ Improvement with oxatomide was significantly greater than with placebo.¹⁸ Adverse drug effects were mild, transient, and consisted most commonly of increased appetite.⁴⁷

Terfenadine The antipruritic effect of terfenadine was investigated in three clinical trials, one small blinded RCT²³ and two open studies (Table 8).^{45,48}

In one open study, a $\geq 50\%$ reduction in pruritus was found in 6 of 10 atopic dogs (60%) with terfenadine alone.⁴⁵ A similar benchmark was achieved, in a sustained and repeatable manner, in none of 18 dogs in the RCT given either terfenadine or placebo.²³ The addition of terfenadine to hydroxyzine was deemed to be no more effective than treatment with hydroxyzine alone.⁴⁸ Adverse effects were not described in the open studies^{45,48} and in the RCT, one dog each exhibited hyperactivity, polyphagia, or anorexia, lethargy, ocular discharge and increased pruritus.²³

Astemizole In one of the trials described previously, astemizole was given to 30 dogs (21 with AD) (Table 8).¹⁹ Satisfactory antipruritic efficacy was only reported by the owner of one dog (3%). Adverse drug effects of astemizole were not observed.

Loratadine A small double-blinded RCT evaluated the antipruritic efficacy of loratadine or placebo (5–15 mg once daily for 10 days) in 17 dogs with allergy (Table 8).²⁴ Even though clinical signs improved during the initial treatment period with either loratadine or placebo in some patients, a sustained relief of pruritus was not obtained for any of the study subjects. Adverse drug effects of loratadine were not discussed.

Treatment with phosphodiesterase inhibitors

Three clinical trials, two of them blinded RCTs, tested the efficacy of phosphodiesterase (PDE) inhibitors in dogs with AD (Table 9).^{25,34,50} A total of 63 dogs were enrolled, 58 of them with AD, and 33/63 dogs (52%) were treated with PDE inhibitors. One of the RCTs was funded by the company manufacturing the drug.³⁴

Papaverine administration at 150–300 mg twice daily did not lead to any sustained control of the subjects'

Table 5. Trials reporting treatment with first-generation piperidine antihistamines

Citation (Reference)	Scott, 1988 (40)	Paterson, 1994 (43)	Paterson, 1995 (46)	Umesh, 1998 (48)	Evert, 2001 (49)
Quality of Evidence	C2	B2	B2	C2	A2
Randomization (Allocation Generation)	none	unclear	unclear	none	unclear
Randomization (Allocation Concealment)	none	unclear	unclear	none	unclear
Masking of Outcome Assessor	inadequate	unclear	unclear	inadequate	adequate
Intention-to-Treat Analyses	no statistical analyses	no statistical analyses	adequate	no statistical analyses	unclear
Quality of Inclusion of Study Subjects	fairly-characterized	well-characterized	well-characterized	poorly-characterized	well-characterized
# Dogs Entered in Trial (Total)	45	30	32	21	68
# Dogs Entered in Trial (AD only)	19	30	32	5	68
# Dogs with AD Treated with Antihistamine	19	30	32	7/21	33
Length of Trial (Length Antihistamine Treatment) (wks)	6 (1)	6 (1) + 4 to verify sustained efficacy	32 (1) + 4 to verify sustained efficacy	2 (2)	6 (2)
Pharmacological Intervention	hydroxyzine 2.2 mg kg ⁻¹ TID	hydroxyzine 12.5–20 mg TID	hydroxyzine 12.5–50 mg TID	hydroxyzine 2 mg kg ⁻¹ BID	chlorpheniramine 1–4 mg + hydroxyzine 25–100 mg QD
Mean/Median % Reduction in Lesional Scores	NA	NA	NA	NA	NA
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA	NA	NA
% Dogs with ≥ 50% Reduction in Lesional Scores	NA	NA	NA	NA	18%
% Dogs with ≥ 50% Reduction in Pruritus Scores	NA	NA	NA	33%	30%
Other Outcome Measures	satisfactory control of pruritus in 7% of dogs as assessed by the owner	10% of dogs with satisfactory (complete) pruritus control assessed by owners	significant improvement in pruritus and erythema scores as assessed by clinician	NA	24% of dogs with investigator- assessed satisfactory efficacy at study end

Abbreviations: QD: once daily; BID: twice daily; TID: three times daily; NA: not available.

Table 6. Trials reporting treatment with first-generation phenothiazine antihistamines

Citation (Reference)	Paradis, 1991 (19)	Paterson, 1994 (43)	
Quality of Evidence	B2	B2	
Randomization (Allocation Generation)	unclear	unclear	
Randomization (Allocation Concealment)	unclear	unclear	
Masking of Outcome Assessor	adequate	unclear	
Intention-to-Treat Analyses	no statistical analyses	no statistical analyses	
Quality of Inclusion of Study Subjects	fairly-characterized	well-characterized	
# Dogs Entered in Trial (Total)	30	30	
# Dogs Entered in Trial (AD only)	21	30	
# Dogs with AD Treated with Antihistamine	21	30	
Length of Trial (Length Antihistamine Treatment) (wks)	9 (1) + 2 to verify sustained efficacy	6 (1) + 4 to verify sustained efficacy	
Pharmacological Intervention	trimeprazine 5–15 mg BID	trimeprazine 5–15 mg BID	promethazine 12.5–25 mg QD
Mean/Median % Reduction in Lesional Scores	NA	NA	NA
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA
% Dogs with $\geq 50\%$ Reduction in Lesional Scores	NA	NA	NA
% Dogs with $\geq 50\%$ Reduction in Pruritus Scores	3%	NA	NA
Other Outcome Measures	NA	3% of dogs with satisfactory (complete) pruritus control assessed by owners	0% of dogs with satisfactory (complete) pruritus control assessed by owners

Abbreviations: QD: once daily; BID: twice daily; NA: not available.

Table 7. Trials reporting treatment with the second-generation antihistamine oxatomide

Citation (Reference)	Yoxall, 1980 (18)	Hayasaki, 1994 (44)	Héripret, 1996 (47)
Quality of Evidence	B2	C2	C1
Randomization	unclear	none	none
Randomization (Allocation Generation)	unclear	none	none
Randomization (Allocation Concealment)	unclear	inadequate	inadequate
Masking of Outcome Assessor	unclear	no statistical analyses	no statistical analyses
Intention-to-Treat Analyses	unclear	poorly-characterized	fairly-characterized
Quality of Inclusion of Study Subjects	fairly-characterized		
# Dogs Entered in Trial (Total)	23	21	136
# Dogs Entered in Trial (AD only)	23	21	91
# Dogs with AD Treated with Antihistamine	23	10	91
Length of Trial (Length Antihistamine Treatment) (wks)	4 (2)	2–13 (2–13)	2–4 (2–4)
Pharmacological Intervention	oxatomide 2 mg kg ⁻¹ day ⁻¹	oxatomide 1 mg kg ⁻¹ day ⁻¹	oxatomide 1–1.5 mg kg ⁻¹ BID
Mean/Median % Reduction in Lesional Scores	NA	NA	NA
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA
% Dogs with $\geq 50\%$ Reduction in Lesional Scores	NA	NA	NA
% Dogs with $\geq 50\%$ Reduction in Pruritus Scores	NA	NA	NA
Other Outcome Measures	mean reduction in clinical score of 12 points (maximum score before treatment was 37 points)	50% of dogs showed 20–50% improvement	34% of dogs with satisfactory improvement in pruritus

Abbreviations: BID: twice daily; NA: not available.

pruritus.⁵⁰ In the pentoxifylline RCT, the median reductions from baseline of clinician-assessed erythema scores, or owner and clinician-graded pruritus values were 0, 33 and 50%, respectively (data obtained

from the authors).²⁵ Three, four and six of ten dogs (30, 40 and 60%) achieved a clinically relevant, i.e. $\geq 50\%$ reduction benchmark of their erythema, and owner- or clinician-evaluated pruritus scores.²⁵ Similarly, in the

Table 8. Trials reporting treatment with second-generation piperidine antihistamines

Citation (Reference)	Scott, 1994 (23)	Umesh, 1995 (45)	Umesh, 1998 (48)	Paradis, 1991 (19)	Paradis, 1996 (24)
Quality of Evidence	A3	C2	C2	B2	A3
Randomization (Allocation Generation)	adequate	none	none	unclear	unclear
Randomization (Allocation Concealment)	adequate	none	none	unclear	unclear
Masking of Outcome Assessor	adequate	inadequate	inadequate	adequate	unclear
Intention-to-Treat Analyses	unclear	no statistical analyses	no statistical analyses	no statistical analyses	no statistical analyses
Quality of Inclusion of Study Subjects	fairly-characterized	poorly-characterized	poorly-characterized	fairly-characterized	poorly-characterized
# Dogs Entered in Trial (Total)	18	30	21	30	17
# Dogs Entered in Trial (AD only)	18	10	5	21	17
# Dogs with AD Treated with Antihistamine	18	10	7/21	21	17
Length of Trial (Length Antihistamine Treatment) (wks)	3 (1.5) + 4 to verify sustained efficacy	1 (1)	2 (2)	9 (1) + 2 to verify sustained efficacy	3 (1.5) + 4 to verify sustained efficacy
Pharmacological Intervention	terfenadine 5 mg kg ⁻¹ BID	terfenadine 30–60 mg BID	terfenadine 60 mg BID + hydroxyzine 2 mg kg ⁻¹ BID	astemizole 2.5–10 mg QD	loratadine 5–15 mg BID
Mean/Median % Reduction in Lesional Scores	NA	NA	NA	NA	NA
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA	NA	NA
% Dogs with ≥ 50% Reduction in Lesional Scores	NA	NA	NA	NA	NA
% Dogs with ≥ 50% Reduction in Pruritus Scores	6% (sustained in 0%)	60%	38%	3%	18% (sustained in 0%)
Other Outcome Measures	NA	NA	NA	NA	NA

Abbreviations: QD: once daily; BID: twice daily; NA: not available.

Table 9. Trials reporting treatment with phosphodiesterase inhibitors

Citation (Reference)	Scott, 1993 (50)	Ferrer, 1999 (34)	Marsella, 2000 (25)
Quality of Evidence	C3	A3	A3
Randomization	none	adequate	unclear
(Allocation Generation)			
Randomization	none	adequate	adequate
(Allocation Concealment)			
Masking of Outcome Assessor	inadequate	adequate	adequate
Intention-to-Treat Analyses	no statistical analyses	inadequate	adequate
Quality of Inclusion of	fairly-characterized	well-characterized	well-characterized
Study Subjects			
# Dogs Entered in Trial (Total)	13	40	10
# Dogs Entered in Trial	8	40	10
(AD only)			
# Dogs with AD Treated	8	10	10
with PDE Inhibitor			
Length of Trial (Length	3 (1.5) + 4 to verify	4 (4)	8 (4)
PDE Inhibitor Treatment) (wks)	sustained efficacy		
Pharmacological Intervention	papaverine	arofylline	pentoxifylline
	150–300 mg BID	1 mg kg ⁻¹ BID	10 mg kg ⁻¹ BID
	NA	50%*	0%
Mean/Median %			
Reduction in Lesional Scores			
Mean/Median %	NA	67%*	33% (owner) to
Reduction in Pruritus Scores			50% (clinician)
% Dogs with ≥ 50% Reduction	NA	60%*	30%
in Lesional Scores			
% Dogs with ≥ 50% Reduction	0%	70%*	40% (owner) to
in Pruritus Scores			60% clinician

Abbreviations: BID: twice daily; NA: not available.

*data calculated using 'last carry forward rule'

arofylline RCT, the treatment appeared to be effective with 50–67% reduction from baseline in lesion and pruritus scores, respectively. Sixty and 70% of the 10 dogs treated with arofylline exhibited a 50% improvement in their lesional or pruritus scores (calculation made from data extracted from the author's table, with 'last values carried forward' used to replace scores missing in case of study drop-out).³⁴

Pentoxifylline (10 mg kg⁻¹ twice daily for 4 weeks) was found to be more effective than placebo in reducing erythema and pruritus scores.²⁵ Arofylline administration (1 mg kg⁻¹ twice daily for 4 weeks) was found to be as effective as prednisone (0.25–0.5 mg kg⁻¹ twice daily for 1 week, then decreased), or prednisone and arofylline combined.³⁴

One of 13 dogs experienced anorexia, depression and vomiting while receiving papaverine.⁵⁰ Pentoxifylline administration reportedly did not lead to any clinical adverse drug effects.²⁵ In contrast, the intake of arofylline was followed by vomiting in seven dogs (70%), lethargy in one (10%) and polyuria in one (10%).³⁴ Four of ten dogs (40%) treated with arofylline did not complete the study, two of them because of development of unacceptable vomiting.

Treatment with leukotriene inhibitors

Four trials, encompassing 82 subjects with AD, evaluated the use of leukotriene inhibitors for treatment of canine AD (Table 10).^{22,26,28,51} One of the studies was funded by the manufacturer.²²

Administration of the unknown CysLT₁ antagonist was not followed by a significant reduction in pruritus

compared with placebo, but there was a nonsignificant trend towards reduction of investigator-assessed erythema (estimated at ≈ 27% based on the published figure) when dogs were treated with this medication.⁵¹ Similarly, the prescription of zafirlukast led to initial 'fair' or 'good' reduction in owner-evaluated pruritus in 4/18 (22%) subjects, but sustained efficacy was verified only for 2 of them (11%).²⁸ Short-duration treatment with WY-50295 was not associated with significant reduction of either clinician-assessed erythema, pruritus, self-trauma, papules/pustules, scales/crusts or overall scores or owner-graded pruritus, lesions or erythema values.²² Treatment with zileuton for 4 weeks led to a median reduction from baseline of clinician-assessed erythema or clinician- and owner-graded pruritus scores of 0%. The 50% benchmark reduction in erythema or pruritus scores was reached by 3/9 dogs (33%) during zileuton administration (data obtained from the authors).²⁶

The reduction of lesional and pruritus scores was not found to be significantly different between the unknown CysLT₁ antagonist or WY-50295 and their respective placebo.^{22,51} After 30 days, zileuton-treated dogs had significantly lower investigator-graded erythema scores compared with placebo. Pruritus scores were not significantly different between zileuton and placebo administration.²⁶

Adverse drug events were not discussed for the unknown CysLT₁ antagonist.⁵¹ Two dogs vomited during treatment with zafirlukast.²⁸ The administration of WY-50295 led to owner-perceived adverse drug events in 10% of study subjects (flatulence, sleepiness, weight loss, excitability, exacerbation of clinical signs).²²

Table 10. Trials reporting treatment with leukotriene inhibitors

Citation (Reference)	Thomsen, 1993 (51)	DeBoer, 1994 (22)	Crow, 2001 (26)	Senter, 2002 (28)
Quality of Evidence	A2	A2	A4	B2
Randomization	unclear	unclear	unclear	inadequate
(Allocation Generation)				
Randomization	unclear	unclear	unclear	inadequate
(Allocation Concealment)				
Masking of Outcome Assessor	adequate	adequate	adequate	inadequate
Intention-to-Treat Analyses	inadequate	inadequate	adequate	no statistical analyses
Quality of Inclusion of	poorly-characterized	well-characterized	well-characterized	well-characterized
Study Subjects				
# Dogs Entered in Trial (Total)	22	31	9	20
# Dogs Entered in Trial	22	31	9	20
(AD only)				
# Dogs with AD Treated	11?	31	9	20
with LT Inhibitor				
Length of Trial (Length	3 (3)	4 (1.5)	9 (4)	4 (2) + 4 to verify
LT Inhibitor Treatment) (wks)				sustained efficacy
Pharmacological Intervention	unknown	WY-50295	zileuton	zafirlukast
	cysteinyl leukotriene	5-lipoxygenase	5-lipoxygenase	cysteinyl leukotriene
	receptor antagonist	specific inhibitor	specific inhibitor	receptor antagonist
	17–33 mg kg ⁻¹ BID	25 mg kg ⁻¹ BID	2 mg kg ⁻¹ TID	5–30 mg dog ⁻¹ BID
				depending on weight
Mean/Median %	27%	–3%	0%	NA
Reduction in Lesional Scores				
Mean/Median %	0%	15%	0% (owners and	NA
Reduction in Pruritus Scores			investigators assessed)	
% Dogs with ≥ 50% Reduction	NA	NA	33%	NA
in Lesional Scores				
% Dogs with ≥ 50% Reduction	NA	NA	33% (owners and	22% (11% sustained)
in Pruritus Scores			investigators-assessed)	
Other Outcome Measures	NA	NA	NA	NA

Abbreviations: BID: twice daily; TID: three times daily; NA: not available.

Treatment with zileuton for one month did not induce any adverse clinical effects, but low elevation of serum activity of alanine aminotransferase was noted in one dog.²⁶

Treatment with prostaglandin analogues and inhibitors

Misoprostol A 4-week open study⁵² and a 3-week placebo-controlled blinded RCT³³ evaluated the efficacy of treatment with the PGE₁ analogue misoprostol (Table 11). The RCT was funded by the drug manufacturer.³³

In both trials, the clinician-assessed lesional scores and the owner-graded pruritus values were significantly lower at the end of the study than at baseline.^{33,52} At the end of the RCT, and compared with subjects receiving placebo, dogs treated with misoprostol exhibited significantly higher percentage reduction from baseline of pruritus scores, but not of lesional values.³³

Adverse drug effects, consisting of mild intermittent vomiting or diarrhoea were observed in 33% of dogs of the first study and only in one dog (8%) in the RCT.^{33,52}

Aspirin As part of an open study, aspirin was given to 45 dogs exhibiting pruritus, 19 of them diagnosed with fairly characterized nonseasonal (14) or seasonal (5) atopy (Table 11).⁴⁰ Owners reported a satisfactory

control of pruritus only in one dog (2%). Partial pruritus reduction, albeit insufficient to satisfy owners, was seen in four additional subjects (9%). Adverse drug events were observed in two patients.

Treatment with topical antipruritic drugs

Pramoxine Seventeen dogs with fairly characterized AD were treated successively with two commercially available formulations of pramoxine-containing cream rinses (Relief, DVM Pharmaceuticals, Miami, FL; Dermal-Soothe, EVSCO Pharmaceuticals, Buena, NJ) as part of an open trial of 4 weeks' duration (quality of evidence: C3).⁵³ Study subjects were bathed in baby shampoo, then one pramoxine-containing rinse was applied to the coat twice weekly for 2 weeks, after which the other formulation was used similarly for another 2 weeks. Statistical analyses were not reported.

Overall, a good reduction (51–75%) in pruritus was assessed subjectively by the owners for seven dogs (41%). Such improvement was seen with Relief in five subjects (29%), and with Dermal-Soothe in three patients (18%). One dog improved with both formulations. The antipruritic effect was estimated to last 48 h. Adverse drug events were reported for six dogs (35%). They consisted principally of increased pruritus immediately after application of the rinse (Dermal-Soothe: four dogs; Relief: one dog).

Table 11. Trials reporting treatment with prostaglandin inhibitors

Citation (Reference)	Olivry, 1997 (52)	Olivry, 2003 (33)	Scott, 1988 (40)
Quality of Evidence	C2	A3	C2
Randomization (Allocation Generation)	none	adequate	none
Randomization (Allocation Concealment)	none	adequate	none
Masking of Outcome Assessor	inadequate	adequate	inadequate
Intention-to-Treat Analyses	inadequate	adequate	no statistical analyses
Quality of Inclusion of Study Subjects	fairly-characterized	well-characterized	fairly-characterized
# Dogs Entered in Trial (Total)	20	20	45
# Dogs Entered in Trial (AD only)	20	20	19
# Dogs with AD Treated with Active Drug	20	12	19
Length of Trial (Length Drug Treatment) (wks)	4 (4)	3 (3)	6 (1)
Pharmacological Intervention	misoprostol 5 µg kg ⁻¹ TID	misoprostol 5 µg kg ⁻¹ TID	aspirin 25 mg kg ⁻¹ TID
Mean/Median % Reduction in Lesional Scores	53%	29%	NA
Mean/Median % Reduction in Pruritus Scores	39%	30%	NA
% Dogs with ≥ 50% Reduction in Lesional Scores	61%	27%	NA
% Dogs with ≥ 50% Reduction in Pruritus Scores	56%	36%	NA
Other Outcome Measures	NA	NA	satisfactory control of pruritus in 2% of dogs as assessed by the owner

Abbreviations: TID: three times daily; NA: not available.

Capsaicin A small blinded placebo-controlled crossover RCT evaluated the efficacy of 0.025% capsaicin lotion or placebo applied twice daily for 6 weeks to 12 dogs with well-characterized AD (quality of evidence: A3).³⁰ All dogs completed the study and ITT analyses were thus available.

After capsaicin treatment, the median improvement from baseline owner and investigator-assessed pruritus scores were 33 and 0%, respectively. Clinically relevant, ≥ 50% reduction in these two scores were achieved by 25 and 8% of the dogs (values calculated from individual case data provided by the authors). Compared with placebo, capsaicin led to significant decreases in owner but not investigator pruritus scores after 6 weeks of application. Other than an increase in owner-graded pruritus during the first week of treatment, adverse drug effects of capsaicin therapy were not discussed.

Treatment with immune-modulating antibiotics

There were three open trials that evaluated the efficacy of immune-modulating antibiotics for treatment of canine AD (Table 12).^{40,50,54}

Altogether, administration of these antibiotics led to an owner-assessed satisfactory control of pruritus in only 4⁴⁰ to 5%⁵⁴ of study subjects. Vomiting or decreased appetite were seen in 4 of 45 dogs (9%) given erythromycin; adverse drug effects were not observed with doxycycline; 1 of 19 dogs given the tetracycline–niacinamide combination exhibited severe diarrhoea.

Treatment with Chinese herbal and homeopathic preparations

A company-funded blinded RCT tested the efficacy of a Chinese herbal compound compared with placebo in 50 dogs with fairly characterized AD (quality of evidence: A2).²⁷ The active intervention consisted of a mixture of three plants (*Glycyrrhiza uralensis*, *Paeonia lactiflora*, *Rehmannia glutinosa*; P07P, Phytopharm plc, Godmanchester, UK), and the preparation was added to the subjects' food once daily for 8 weeks at a dosage of 200 mg kg⁻¹. Intention-to-treat analyses were not available, and statistical comparisons were performed using data from 47 of 50 dogs.

At the last visit, the median percentage improvement from baseline of investigator-assessed erythema and surface damage (alopecia, scaling, crusting, excoriation, hyperpigmentation and lichenification) were 4% worsening and 0%, respectively (unpublished data provided by the authors). The median change in owner-graded pruritus was nil. However, 4, 21 and 25% of the dogs exhibited 50% reduction from baseline of erythema, surface damage and owner-assessed pruritus scores, respectively.

Compared with placebo, P07P administration for 8 weeks did not lead to a significantly higher improvement of any score evaluated. However, significantly more dogs were withdrawn from the trial due to worsening of clinical signs in the placebo group than in P70P-receiving dogs (difference between groups: 32% [95% CI: 5–58%]).

Table 12. Trials reporting treatment with immune-modulating antibiotics

Citation (Reference)	Scott, 1988 (40)	Scott, 1993 (50)	Beningo, 1999 (54)
Quality of Evidence	C2	C3	C3
Randomization (Allocation Generation)	none	none	none
Randomization (Allocation Concealment)	none	none	none
Masking of Outcome Assessor	inadequate	inadequate	inadequate
Intention-to-Treat Analyses	no statistical analyses	no statistical analyses	no statistical analyses
Quality of Inclusion of Study Subjects	fairly-characterized	fairly-characterized	poorly-characterized
# Dogs Entered in Trial (Total)	45	13	19
# Dogs Entered in Trial (AD only)	19	8	19
# Dogs with AD Treated with Active Drug	19	8	19
Length of Trial (Length Drug Treatment) (wks)	6 (1)	3 (1.5) + 4 to verify sustained efficacy	2 (2) + 4 to verify sustained efficacy
Pharmacological Intervention	erythromycin 11 mg kg ⁻¹ TID	doxycycline 3 mg kg ⁻¹ BID	tetracycline + niacinamide 250–500 mg of each TID
Mean/Median % Reduction in Lesional Scores	NA	NA	NA
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA
% Dogs with ≥ 50% Reduction in Lesional Scores	NA	NA	NA
% Dogs with ≥ 50% Reduction in Pruritus Scores	NA	7% (not sustained)	5% (sustained)
Other Outcome Measures	satisfactory control of pruritus in 4% of dogs	NA	NA

Abbreviations: BID: twice daily; TID: three times daily; NA: not available.

Adverse drug events were recorded for five dogs receiving the herbal preparation (mild diarrhoea: four dogs; flatulence: one dog).

Twenty-one dogs with fairly characterized AD were treated for 3 weeks with an orally administered commercial homeopathic complex (Skin and Seborrhea Remedy, HomeoPet, West Hampton Beach, NY).³¹ This remedy contained sulfur, staphysagria, psorinum, graphites and arsenicum album. After 3 weeks, dogs were switched to a placebo. If any improvement was noted during treatment with the remedy or placebo, a second prescription of 4 weeks was given to verify whether the beneficial effect was repeatable and sustainable. The order of the interventions was not randomized, and only owners were kept blinded to the nature of treatment (quality of evidence: B2). Statistical analyses were not performed. Only one dog (5%) had a repeatable and sustained 'fair' (26–50%) reduction in the degree of pruritus, as determined by the owners. Four dogs exhibited initial pruritus improvement that was not sustained thereafter. One dog was reported to vomit after the administration of the remedy, and it was withdrawn from the study.

Treatment with tricyclic antidepressants

Doxepin The tricyclic antidepressant, doxepin, was prescribed at 10–30 mg three times daily to 30 pruritic dogs (21 with AD) as part of a blinded trial (quality of

evidence: B2).¹⁹ Statistical analyses were not available. A satisfactory (i.e. 'good-to-excellent') antipruritic efficacy was not reported for any dogs. Adverse drug effects were observed in four patients (13%) (vomiting, two dogs; trembling and panting, two dogs; somnolence, one dog), and they led to discontinuation of the drug in two subjects.

Amitriptyline A second tricyclic antidepressant, amitriptyline, was given to 31 pruritic dogs (17 with AD) in an open study (quality of evidence: C2).⁵⁵ This drug was administered at 1 mg kg⁻¹ twice daily for 1 week, and if an excellent response was noted, it was prescribed for four more weeks to verify sustained efficacy. Statistical analyses were not performed. At the end of the trial, a 'good-to-excellent' response (e.g. ≥ 50% reduction in pruritus) was assessed by the owner in 10 of 31 dogs (32%) but only in 3 of 17 dogs (18%) with AD. Adverse drug events, consisting of somnolence, vomiting and abnormal behaviour) were reported for two dogs (6%).

Treatment with miscellaneous drugs

Ascorbic acid Another open study described the antipruritic effect of ascorbic acid (vitamin C) given at 250–1000 mg for 1 week to 23 dogs with signs historically and clinically suggestive of AD (poorly characterized) (quality of evidence: C2).⁵⁶ The administration was prolonged for four more weeks in case of ≥ 50% reduction in pruritus. Such benchmark was not reached

by any dog receiving ascorbic acid alone. Adverse drug reactions were not observed.

AHR-13268 The benzoic acid derivative AHR-13268 (AH Robins Research Laboratories, Richmond, VA) is a compound that belongs to a family of chemicals that exhibits antihistaminic, antiserotonergic, antileukotriene and mast cell-stabilizing effects.²¹ This drug was evaluated in a company-sponsored double-blinded placebo-controlled crossover RCT of 4 weeks' duration (quality of evidence: A2). Thirty-one dogs were treated with 13–22 mg kg⁻¹ of AHR-13268 or placebo once daily, before interventions were reversed. Intention-to-treat analyses were not reported. After treatment with AHR-13268 investigator-graded pruritus, erythema, self-trauma, papules/pustules or scaling/crusting scores were not significantly different than those noted in dogs receiving placebo. In contrast, owner-assessed pruritus and lesions, but not erythema scores, were significantly lower after treatment with the active drug compared with placebo. Overall, owners of 11/29 dogs (38%) reported moderate or better improvement from the active medication. From data provided by the leading author, we calculated that the median percentage change from baseline owner-assessed pruritus scores was 0% after drug administration. Only 1 of 30 dogs (3%) exhibited a $\geq 50\%$ reduction in such scores during treatment with AHR-13268. Nine dogs (29%) exhibited adverse drug events after receiving this drug.

Cyproheptadine The antipruritic effect of the serotonin inhibitor and type-1 histamine receptor antagonist cyproheptadine has been tested in a small blinded RCT²⁰ and two randomized trials described above (Table 13).^{43,46}

The RCT yielded an owner assessment of satisfactory control of pruritus in one dog (6%), yet this benefit was not repeatable. The response to cyproheptadine was similar to that of placebo.²⁰ In one of the randomized trials from England, 17% of dogs exhibited complete remission of pruritus.⁴³ A significant improvement in pruritus, but not erythema, was noted by the investigator in the other study.⁴⁶ Appetite stimulation was reported in two of these studies.^{20,43}

Tranilast In an open study, the drug tranilast (10 mg kg⁻¹ day⁻¹) was given for 2–4 weeks to 10 of 21 dogs with allergic skin disease (quality of evidence: C3).⁴⁴ Half of the dogs exhibited a 33–66% improvement in clinical signs during tranilast administration.

DISCUSSION

In this document, 40 clinical trials evaluating the efficacy of 41 different pharmacological interventions for treatment of canine AD were reviewed systematically. Clinical inferences from this analysis must be weighed against an assessment of internal and external validity.

Table 13. Trials reporting treatment with cyproheptadine

Citation (Reference)	Scott, 1992 (20)	Paterson, 1994 (43)	Paterson, 1995 (46)
Quality of Evidence	A3	B2	B2
Randomization (Allocation Generation)	unclear	unclear	unclear
Randomization (Allocation Concealment)	unclear	unclear	unclear
Masking of Outcome Assessor	adequate	unclear	unclear
Intention-to-Treat Analyses	no statistical analyses	no statistical analyses	adequate
Quality of Inclusion of Study Subjects	fairly-characterized	well-characterized	well-characterized
# Dogs Entered in Trial (Total)	16	30	32
# Dogs Entered in Trial (AD only)	10	30	32
# Dogs with AD Treated with Antihistamine	10	30	32
Length of Trial (Length Antihistamine Treatment) (wks)	3 (1.5) + 4 to verify sustained efficacy	6 (1) + 4 to verify sustained efficacy	32 (1) + 4 to verify sustained efficacy
Pharmacological Intervention	cyproheptadine 1–4 mg BID	cyproheptadine 2.5–10 mg TID	cyproheptadine 2.5–10 mg TID
Mean/Median % Reduction in Lesional Scores	NA	NA	NA
Mean/Median % Reduction in Pruritus Scores	NA	NA	NA
% Dogs with $\geq 50\%$ Reduction in Lesional Scores	NA	NA	NA
% Dogs with $\geq 50\%$ Reduction in Pruritus Scores	6% (sustained 0%)	NA	NA
Other Outcome Measures	NA	17% of dogs with satisfactory (complete) pruritus control assessed by owners	significant improvement in pruritus, but not in erythema, scores as assessed by clinician

Abbreviations: BID: twice daily; TID: three time daily; NA: not available.

Validity

Internal validity There are several biases (selection, detection, performance and attrition) that could diminish the *internal validity* of this analysis.⁵⁷

The process of randomization is aimed at the generation of treatment groups comparable in regards to known or unknown confounding factors.⁵⁷ The efficacy of randomization depends upon the generation of allocation sequences by truly random methods and from the adequate concealment of treatment sequences.⁵⁸ Lack of appropriate randomization schemes could lead to *selection bias*.⁵⁷ In this systematic review, selection bias could have occurred because only half of the trials reviewed were randomized trials.

Furthermore, investigators and/or dog owners were aware of the intervention in approximately half of the studies discussed herein, thus the assessment of outcome could have been influenced by *detection bias*.⁵⁷ Comparison of open and blinded designs for CsA,^{16,39} misoprostol,^{33,52} terfenadine^{23,45} and cypiroheptadine^{20,43,46} provide likely examples of such bias. Indeed, the assessment of efficacy in these open studies is about twice as good than that of corresponding blinded RCTs.

In the trials evaluated in this review, evidence of *performance bias* (e.g. one group of dogs was treated preferentially with medications in addition to that being evaluated) was not found.

Attrition bias could be introduced by both *deviations from protocol* and/or *loss to follow-up*.⁵⁷ Violation of eligibility criteria and nonadherence to treatment are possible causes of deviation from protocol. In most of the studies included in this review, deviations from protocol were not discussed as a separate matter. In some recent trials, however, this specific issue or an assessment of owner compliance were recorded in individual sections.^{16,33,36} *Loss to follow-up* is the parameter that refers to the unavailability of study subjects because they refuse to participate (e.g. 'drop-out'), cannot be contacted, or adverse drug events or medical issues develop and justify their withdrawal for health concerns.⁵⁷ To alleviate bias due to heavy loss to follow-up, ITT analyses are performed.¹²

In 32 of 40 studies included in this review, ITT analyses were not conducted. Attrition of enrolled subjects was found in approximately half of the trials. Missing values attained 30% of patients in one study, and these could lead to over-interpretation of true treatment effect.³⁴ In this trial, for example, 4 of 10 dogs treated with the drug evaluated did not complete the study because of adverse events, but the effectiveness of this medication was reported to be not significantly different than that of oral prednisone.

In few randomized trials, all patients were available for evaluation at study end, thus statistical analyses used ITT principles.^{25,26,30,46} In rare studies published recently, specific ITT analyses were performed using the 'last-value-carry-forward' rule.^{16,33,35,36}

Altogether, attrition of subjects only totalled 91/1607

dogs (6%), therefore we believe that this parameter was an unlikely source of bias in this review.

In summary, the internal validity of this systematic review is affected by the nonrandomized design of half of the trials studied, the high number of unmasked studies, a sometimes high attrition rate and the scarcity of ITT analyses. Clinical inference from study results must be weighed in light of these concerns.

External validity From the selection of subjects enrolled in the trials, the nature and duration of treatments administered, the assessed modalities of outcome, and level of care settings will depend on the *external validity* of the trials reviewed herein.

Many studies discussed in this review were published before 1995, and they enrolled subjects that included not only dogs with AD, but also patients diagnosed with other allergic skin diseases such as flea allergy dermatitis and 'food allergy', or even uncharacterized 'allergic' pruritus. In most studies, outcome variables were not differentiated between dogs with AD and those with other afflictions. Such loose inclusion criteria could lead to over- or underestimation of true treatment efficacy for canine AD. In most recent trials, however, enrolled patients were restricted to those affected with AD, and criteria for inclusion were comparable with recent guidelines.^{14,15} This discrepancy in enrolment between older and recent trials provides some uncertainty as to whether the conclusions of this systematic review could be generalized to the entire population of dogs with AD.

Overall, the type, dosage, frequency, route and length of administration of the multiple drugs tested appropriately reflect the 'standard-of-care' protocols used in general and specialty veterinary practices. During the last 20 years, however, there has been a steady increase in the duration of the clinical trials. In the 1980s and early 1990s, most studies tested drugs for no longer than 1^{19,40} or 2 weeks,^{18,41} whereas the most recent trial extended to 16 weeks³⁶ a duration that is more relevant to the chronic and recurrent nature of canine AD. It is conceivable that the performance of a short non-blinded trial would be more conducive to development of a strong placebo effect than a blinded RCT lasting longer than one month.

In the earliest studies, the assessment of treatment efficacy was limited to a subjective evaluation by the owner of the antipruritic effect of the drug tested. In general a 'good-to-excellent' assessment was estimated to reflect a $\geq 50\%$ reduction in pruritus. With rare exceptions,^{21,22,51} trials published before 1995 did not report outcome measures that included a change in skin lesion scores during treatment. In 1997, a nonvalidated lesional score was developed (Canine Atopic Dermatitis Extent and Severity Index – CADESI).⁵² Modifications of this score have been used in some recent studies^{16,33,35,36,49} and limited information of validation of this score has been provided.³⁵ Since the late 1990s, outcome measures of clinical trials generally have included changes in owner (and/or investigator)-

assessed pruritus scores and investigator (and/or owner)-graded skin lesion scores.^{16,25–27,29,30,32–36,39,49} Global evaluations of treatment efficacy by owners and investigators sometimes were added.^{16,27,29,36,39,49} It is felt, therefore, that the outcome measures evaluated in most early trials were restricted inadequately to the subjective assessment of a single clinical sign of AD, pruritus. In most recent studies, however, a broader and more adequate evaluation of treatment effect was made from the assessment of pruritus and/or skin lesion scores by either owners and/or clinicians. Nevertheless, it should be kept in mind that the parameters that theoretically would be evaluated most reliably (e.g. investigator-graded lesional scores) might not be those that are most meaningful to owners and patient well-being (e.g. sleep disturbance, scratching, biting).

The great majority of the studies reviewed here were performed in referral university hospitals, thus reflecting specialized secondary or tertiary veterinary care settings. Few trials had enrolled patients coming solely from general practice (primary care) or from a combination of primary and secondary care settings.^{36–38,43,46,48,49} The predominant enrolment of dogs at referral institutions could lead to a bias toward selection of dogs with a more severe AD phenotype. It is not known whether clinical signs of such patients would respond better, or worse, than those of dogs with milder disease, which would be seen by general practitioners.

Altogether, several factors such as loose enrolment criteria, short duration of treatment, limited evaluation of outcome measures and predominance of secondary care centres threaten the external validity of this systematic review. These parameters must be taken into account before therapeutic decision-making.

Publication bias

In systematic reviews, *publication bias* can occur because of the nature of studies selected, language barriers or due to variable quality of result reporting.

In this review, we restricted our analysis to studies published in peer-reviewed journals, and we did not include the rare unpublished trial that had been presented at major veterinary dermatology meetings. Because trials in which an intervention is ineffective often are not published,⁵⁹ this approach of excluding unpublished studies could overestimate true treatment effect. It was felt, however, that reviewing meeting's abstracts would not yield enough details to provide meaningful interpretation of the study design and the intervention benefit and harm. Moreover, screening of proceedings books of meetings of both European and American associations or World Congresses revealed fewer than five unpublished trials enrolling dogs with AD.

Our literature search revealed that only 10% of trials had been published in non-English languages, and the authors or other members of the International Task Force on Canine AD were fluent in such languages. It is conceivable that trials published in other languages

might not have been indexed in the searched databases. However, we feel that only rare studies would have escaped our search of various medical and veterinary databases as well as bibliographies of other trials and book chapters.

The quality of reporting of studies overall was not of the highest quality, with information on critical issues such as study design, enrolment and attrition of subjects or outcome measures insufficiently provided. This flaw was alleviated by the request of additional information from leading authors of the most recent RCTs. In all but one case, individual subject data or additional parameters were provided.

Overall, we believe that if present, publication bias was weak, and it should not prevent decision of treatment based on interpreting the results of this systematic review.

Evidence of treatment efficacy

In all, 17 trials, including 12 RCTs, provide evidence that the administration of placebo results in clinically relevant reduction in pruritus in some dogs with AD (median: 9%). Improvement in skin lesions with placebo appears to be less common and of lower magnitude than that of pruritus. Seasonal exacerbation of clinical signs is one of the factors shown to be associated with strong placebo effect. Therefore, clinical inference of potential efficacy of any drug must take into account the frequency and magnitude of placebo effect in dogs with AD.

Efficacy of glucocorticoids A single trial, published recently, reported the effectiveness of topical GC for treatment of canine AD.²⁹ Whereas this study provides *fair evidence of high efficacy and low harm* of short-term treatment with 0.015% triamcinolone solution spray, the beneficial effect of other topical GC formulations cannot be inferred from the evidence derived from this trial.

Two open studies,^{37,38} a blinded controlled trial¹⁹ and three blinded RCTs^{34–36} provide *good evidence of high efficacy* of anti-inflammatory dosages (0.5 mg kg⁻¹ day⁻¹) of oral prednisone/prednisolone/methylprednisolone for treatment of canine AD. Adverse drug effects are common, usually of mild severity, and they appear dependent on the length of administration. Therefore, the benefit of long-term GC therapy must be weighed against the risk of development of adverse drug effects impacting on health and quality of life.

Efficacy of calcineurin inhibitors Four trials, including three blinded RCTs,^{16,35,36} provide *good evidence of high efficacy* of CsA, administered at 5.0 mg kg⁻¹ once daily for up to 16 weeks, to treat dogs with AD. Adverse drug events are seen commonly, but they appear to be intermittent and of mild to moderate severity. Even though toxicological studies have established the relative safety of CsA administered to Beagle dogs at 45 mg kg⁻¹ day⁻¹ for 1 year,⁶⁰ its long-term safety

in dogs, albeit at lower dosages, is not known beyond this duration.

A single small pilot RCT, enrolling eight subjects, provides only *fair evidence of medium efficacy* of compounded 0.3% tacrolimus lotion for short-term treatment of canine AD.

Efficacy of antihistamines Overall, eight studies of grade lower than blinded RCT provide *fair evidence of no or low efficacy* of the first-generation sedating type-1 histamine receptor antagonists chlorpheniramine, pheniramine, diphenhydramine, hydroxyzine, promethazine and trimeprazine for treatment of canine AD.^{19,37,40–43,46} Four nonblinded RCT provide *fair evidence of medium efficacy* of clemastine,^{19,41,42,46} but one refutes such effectiveness.⁴³ Finally, one blinded RCT provides *fair evidence of medium efficacy* of treatment of canine AD with a combination of chlorpheniramine and hydroxyzine.⁴⁹ Adverse drug effects of first-generation antihistamines are seen in < 20% of dogs and consist most commonly of drowsiness. As a group, there is conflicting evidence of benefit of first-generation type-1 histamine receptor antagonists for treatment of canine AD.

Two studies, including one RCT provide *fair evidence of no or low efficacy* of the second-generation low-sedation type-1 histamine receptor antagonists astemizole and loratadine.^{19,24} There is *conflicting evidence of efficacy* for the use of terfenadine.^{23,45,48} Two open studies and one blinded trial provide *fair evidence of medium efficacy* of oxatamide for treatment of canine AD.^{18,44,47} Adverse drug effects of second-generation antihistamines were not reported commonly, even though both terfenadine^{61–63} and astemizole^{64–66} are known to induce potentially fatal cardiac arrhythmia in dogs. In all, trials with second-generation antihistamines have led to contradictory evidence of their benefit, and there is potential for grave harm when some drugs are used.

Efficacy of phosphodiesterase inhibitors One trial each of the phosphodiesterase inhibitors provide *limited evidence of no efficacy* of papaverine, and *fair evidence of efficacy* of pentoxifylline (medium potency at 10 mg kg⁻¹ twice daily for 4 weeks) and arofylline (medium-to-high potency at various dosing schemes).^{25,34,50} Adverse drug events are not seen often with pentoxifylline, but they are common with arofylline, often leading dog owners to discontinue drug administration. The benefit of phosphodiesterase-repressing drugs appears to increase with their inhibiting potential and their isoenzyme specificity. However, treatment with the type-4 phosphodiesterase-targeting drug arofylline was associated with unacceptable vomiting.

Efficacy of leukotriene inhibitors Altogether, four trials,^{22,26,28,51} most of them RCTs, provide *good evidence for no or low efficacy* of leukotriene synthesis inhibitors or receptor antagonists for alleviation of

clinical signs in dogs with AD. Adverse drug events are seen occasionally, and they appear to be of mild severity.

Efficacy of prostaglandin analogues and inhibitors One open study and a blinded RCT^{33,52} provide *fair evidence of medium efficacy* of the prostaglandin analogue misoprostol (5 µg kg⁻¹ three times daily for up to 6 weeks) to treat dogs with AD. Mild digestive adverse drug events such as vomiting and diarrhoea are seen in few patients. There is *limited evidence of no efficacy* of the prostaglandin inhibitor aspirin for treatment of this disease.

Efficacy of topical antipruritic drugs For topical antipruritic agents, one single small open trial provides *limited evidence of medium efficacy* of pramoxine, and one small RCT provides *fair evidence of low-to-medium efficacy* of topical capsaicin. The benefit of pramoxine appears to be short-lived. The application of capsaicin can trigger a temporary increase in pruritus.

Efficacy of immune-modifying antibiotics Taken together, three open studies^{40,50,54} provide *limited evidence of no efficacy* of the immune-modulating antibiotics erythromycin, doxycycline and tetracycline–niacinamide for pruritus reduction in dogs with canine AD. Of note is that such antibiotics could be considered to treat cutaneous bacterial infections that are often present during the course of canine AD.

Efficacy of miscellaneous drugs Three randomized trials^{20,43,46} provide *conflicting evidence of no or low efficacy* of the serotonin and histamine antagonist cyproheptadine. Administration of this drug commonly triggers an increase in appetite.

Two open studies reported *limited evidence of variable efficacy* of the tricyclic antidepressants doxepin and amitriptyline.^{19,55} One RCT provides *fair evidence of no to low efficacy* of Chinese herbal therapy.²⁷ There is *limited evidence of no or low efficacy* of commercial homeopathic complex remedy³¹, ascorbic acid⁵⁶ and AHR-13268.²¹ There is *limited evidence of medium efficacy* of tranilast.⁴⁴

CONCLUSION

Implications for practice

At the beginning of 2003, taking into consideration the evidence of benefit and harm of the pharmacological interventions reviewed here, several recommendations for treatment of canine AD can be made:¹⁷

- 1 There is *good evidence* for recommending the use of oral GC and oral CsA.
- 2 There is *fair evidence* for recommending the use of topical triamcinolone spray, topical tacrolimus, oral pentoxifylline, oral misoprostol, and an oral chlorpheniramine–hydroxyzine combination.

Table 14. Comparative monthly cost of treatment induction with recommended drugs

Medication – Dosage & Frequency	Dose	Prescription	Cost (US\$)
cyclosporine (brand) – 5 mg kg ⁻¹ QD	10 kg dog: 50 mg QD	60 capsules of 25 mg	\$102.00
	20 kg dog: 100 mg QD	30 capsules of 100 mg	\$193.00
	40 kg dog: 200 mg QD	60 capsules of 100 mg	\$386.00
cyclosporine (generic) – 5 mg kg ⁻¹ QD	10 kg dog: 50 mg QD	60 capsules of 25 mg	\$83.00
	20 kg dog: 100 mg QD	30 capsules of 100 mg	\$164.00
	40 kg dog: 200 mg QD	60 capsules of 100 mg	\$328.00
misoprostol (brand) – 5 µg kg ⁻¹ TID	10 kg dog: 50 µg TID	45 tablets of 100 µg	\$36.00
	20 kg dog: 100 µg TID	90 tablets of 100 µg	\$72.00
	40 kg dog: 200 µg TID	90 tablets of 200 µg	\$101.00
pentoxifylline (brand) – 10 mg kg ⁻¹ BID	10 kg dog: 100 mg BID	15 tablets of 400 mg	\$10.00
	20 kg dog: 200 mg BID	30 tablets of 400 mg	\$19.00
	40 kg dog: 400 mg BID	60 tablets of 400 mg	\$40.00
methylprednisolone (brand) – 0.4 mg kg ⁻¹ BID	10 kg dog: 4 mg BID	60 tablets of 4 mg	\$33.00
	20 kg dog: 8 mg BID	120 tablets of 4 mg	\$66.00
	40 kg dog: 16 mg BID	240 tablets of 4 mg	\$132.00
prednisone (generic) – 0.5 mg kg ⁻¹ BID	10 kg dog: 5 mg BID	60 tablets of 5 mg	\$8.00
	20 kg dog: 10 mg BID	60 tablets of 10 mg	\$10.00
	40 kg dog: 20 mg BID	60 tablets of 20 mg	\$13.00

Abbreviations: QD: once daily; BID: twice daily; TID: three times daily.

3 There is *insufficient evidence for or against* recommending the use of other oral first- or second-generation type-1 histamine receptor antagonists, aspirin, Chinese herbal therapy, an homeopathic complex remedy, tricyclic antidepressants, ascorbic acid, AHR-13268, cyproheptadine, papaverine, immune-modulating antibiotics or tranilast and topical pramoxine or capsaicin.

4 There is *fair evidence against* recommending the use of oral aroxylline, leukotriene synthesis inhibitors and cysteinyl leukotriene receptor antagonists.

Cost–benefit assessment

In therapeutic decision making, not only should the evidence of benefit vs. harm be considered, but the cost-to-benefit ratio also must be taken into account. Local (Raleigh, NC, USA) branches of three leading national pharmacies were contacted in January 2003. The average monthly cost of treatment induction with the orally administered drugs recommended above is compared in Table 14. Of note is that during maintenance therapy, dosages and/or frequency of administration will often be reduced.

Implications for research

This systematic review confirmed the lack of trials evaluating the efficacy of some pharmacological interventions that are commonly used for canine AD. Examples of such interventions needing testing are long-lasting injectable formulations of GC, 1% hydrocortisone lotions and rinses, oatmeal-containing shampoos and rinses, lipid-containing shampoos and emollient conditioners as well as antihistamine shampoos and rinses.

This analysis also highlighted the need for additional RCT-grade evaluation of the orally administered first-generation antihistamines (e.g. hydroxyzine, chlorpheniramine, diphenhydramine, clemastine), the second-generation antihistamine oxatomide, the phosphodiesterase inhibitor pentoxifylline, the prostaglandin analogue misoprostol, Chinese herbal preparations, tricyclic antidepressants (amitriptyline, doxepin), the serotonin–histamine antagonist cyproheptadine and the antiediator tranilast. Topical drugs needing further RCT evaluation comprise tacrolimus, pramoxine and capsaicin. The efficacy and harm of long-term treatment (greater than one year) with injectable and/or oral GC and CsA formulations should also be tested. Because of differing mechanisms of action, the potential synergism of immediate-reaction inhibitors (e.g. antihistamines) with those preventing late-phase reactions (e.g. misoprostol or pentoxifylline) must be evaluated.

For treatment of canine AD, there are potentially effective drugs that could be tested in pilot studies followed by RCTs. These medications include oral azathioprine and second-generation antihistamines known to be safe in dogs (cetirizine, fexofenadine). Topical drugs of interest include doxepin, pimecrolimus and GC formulations of various potencies.

Whenever applicable and relevant to the drug used, we recommend that subgroup analyses be made between atopic patients with pruritus associated with mild or no skin lesions (e.g. pruritus *sine materia*) and those with *bona fide* moderate to severe AD. Dogs with additional atopic conjunctivitis and/or rhinitis should also be evaluated separately. Indeed, antihistamines could be more effective in dogs with minimal disease

or with pruritus associated with conjunctivitis/rhinitis than in those with more severe and chronic skin lesions.

Whenever a RCT is reported, authors are urged strongly to follow the CONSORT guidelines adopted by editors of leading biomedical journals (<http://www.consort-statement.org> – page last accessed 15 January 2003). The present systematic review uncovered several caveats that need to be addressed in future publications reporting trials.

We recommend that investigators limit their enrolment of study subjects to those affected with AD. Care must be taken to extensively describe the methodology of diagnosis of this disease and compare it to current guidelines.^{14,15} Whenever clinicians wish to also include patients affected with other entities, criteria of outcome in each disease subgroup must be established *a priori*. A power calculation must justify the number of subjects enrolled in the trial.

After pilot studies suggest the effectiveness of the tested drug, or in lieu of a preliminary open study, investigators are advised to design a RCT with masking of patients and observers. When reporting such trial, documentation of the method of randomization and its concealment are critically needed. Information on the presence of investigator and/or owner masking and the strategy used for such blinding must be disclosed. Attrition of subjects during the study, either from violation of protocol and/or loss to follow-up must be described carefully. Intention-to-treat analyses (i.e. studying all patients included) should be performed solely or in addition to 'per protocol' analyses (i.e. studies limited to dogs finishing the trial without violation).

We recommend that an assessment of relevant skin lesions (primary and secondary) and pruritus by the investigator and/or the dog owner be made at least before and at the end of the trial. For grading skin lesions and pruritus, well-known and validated schemes or analogue scales should be used preferentially. A global subjective evaluation of treatment efficacy, by both investigators and owners would be of additional interest. We propose that the primary outcome measures of treatment efficacy consist *a minima* of the percentage improvement from baseline skin lesion and pruritus scores. The percentage of study subjects whose score increases (i.e. clinical signs worsen), decreases to the $\geq 50\%$ clinically relevant benchmark, or are reduced to nil (i.e. complete remission) should be documented. For each primary and secondary outcome, the estimated effect size and its precision (e.g. 95% CI) should be provided. Scatter plots of individual lesion/pruritus scores and/or percentage change from baseline could aid in the assessment of treatment efficacy. Box-and-whisker plots would provide adequate evaluation of data spread.

A detailed discussion of adverse drug events, including those leading to withdrawal from the study must be included.

Statistical analyses should be set *a priori* and detailed accordingly. Statistical comparison of signalment and disease severity parameters at study onset

is needed to ensure randomization effectiveness. Comparison of pre- and post-treatment values should be performed within each treatment and control group. Also, comparison between groups should be made both for individual pre- and post-treatment scoring schemes but also for percentage improvement from baseline of such scores. The report of odds ratio of treatment success in the active vs. control group, along with the 95% confidence interval bracketing such ratio will be of additional interest.

An evaluation of internal and external validity should be included in the discussion, and the relevance of the study results to clinical practice, including both benefit-to-harm and cost-to-benefit assessments, should be made. Finally, study results should be interpreted in the context of currently available evidence of efficacy of other drugs used for treatment of canine AD.

Potential for conflict of interest

Several drug companies distributing products discussed herein (DVM Pharmaceuticals, Sandoz Pharma, Novartis Animal Health, Searle and Virbac) have supported research projects undertaken recently by the leading authors (TO and RSM). Moreover, agreements for consulting activities with Novartis Animal Health have been on file with NC State University (TO) since 1998 and with Colorado State University (RSM) since 2000. None of these companies was provided with the content of this document prior to presentation at the 2003 Annual Meeting of the American Academy of Veterinary Dermatology & American College of Veterinary Dermatology, where a short version of this review was available in the meeting notes.

ACKNOWLEDGEMENTS

The authors thank Dr Malcolm Roberts (NC State University, Raleigh) and Dr Kerstin Bergvall (University of Uppsala, Sweden) for their constructive criticism of the manuscript. We are grateful to Professor Hywel Williams (Department of Evidence-Based Dermatology, University of Nottingham, UK) for his thorough review of this document and his valuable comments.

REFERENCES

1. Leung, D.Y., Hanifin, J.M., Charlesworth, E.N. *et al.* Disease management of atopic dermatitis: a practice parameter. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology Work Group on Atopic Dermatitis. *Annals of Allergy Asthma and Immunology* 1997; **79**: 197–211.
2. Hoare, C., Li Wan Po, A., Williams, H. Systematic review of treatments for atopic eczema. *Health and Technology Assessment* 2000; **4**: 1–191.

3. Smethurst, D., MacFarlane, S. Atopic eczema. *Clinical Evidence* 2002; **8**: 1664–82.
4. Olivry, T., Sousa, C.A. The ACVD Task Force on Canine Atopic Dermatitis (XIX): General principles of therapy. *Veterinary Immunology and Immunopathology* 2001; **81**: 311–16.
5. Olivry, T., Sousa, C.A. The ACVD Task Force on Canine Atopic Dermatitis (XX): glucocorticoid pharmacotherapy. *Veterinary Immunology and Immunopathology* 2001; **81**: 317–22.
6. Deboer, D.J., Griffin, C.E. The ACVD Task Force on Canine Atopic Dermatitis (XXI): antihistamine pharmacotherapy. *Veterinary Immunology and Immunopathology* 2001; **81**: 323–30.
7. Marsella, R., Olivry, T. The ACVD Task Force on Canine Atopic Dermatitis (XXII): nonsteroidal anti-inflammatory pharmacotherapy. *Veterinary Immunology and Immunopathology* 2001; **81**: 331–45.
8. Moher, D., Cook, D.J., Eastwood, S. *et al.* Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999; **354**: 1896–900.
9. Olivry, T., DeBoer, D.J., Griffin, C.E. *et al.* The ACVD task force on canine atopic dermatitis: forewords and lexicon. *Veterinary Immunology and Immunopathology* 2001; **81**: 143–6.
10. Olivry, T., Marsella, R., Hillier, A. The ACVD Task Force on Canine Atopic Dermatitis (XXIII): are essential fatty acids effective? *Veterinary Immunology and Immunopathology* 2001; **81**: 347–62.
11. Griffin, C.E., Hillier, A. The ACVD Task Force on Canine Atopic Dermatitis (XXIV): allergen-specific immunotherapy. *Veterinary Immunology and Immunopathology* 2001; **81**: 363–84.
12. Guyatt, G., Cook, D., Devereaux, P.J. *et al.*, eds. *Users' Guides to the Medical Literature – Essentials of Evidence-Based Clinical Practice*. AMA Press, Chicago, 2002: 81–120.
13. Leonard, T., Williams, H., Delamere, F. Cochrane skin group. *The Cochrane Library, Volume 4*. Update Software, Oxford, 2002.
14. Griffin, C.E., Deboer, D.J. The ACVD Task Force on Canine Atopic Dermatitis (XIV): clinical manifestations of canine atopic dermatitis. *Veterinary Immunology and Immunopathology* 2001; **81**: 255–69.
15. Deboer, D.J., Hillier, A. The ACVD Task Force on Canine Atopic Dermatitis (XV): fundamental concepts in clinical diagnosis. *Veterinary Immunology and Immunopathology* 2001; **81**: 271–6.
16. Olivry, T., Steffan, J., Fisch, R.D. *et al.* Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs. *Journal of the American Veterinary Medical Association* 2002; **221**: 370–7.
17. Anonymous. Task force ratings. In: US Preventive Services Task Force, ed. *Guide to Clinical Preventive Services*, 2nd edn. U.S. Department of Health and Human Services; Office of Public Health and Science; Office of Disease Prevention and Health Promotion, Washington, DC, 1996: 861–2.
18. Yoxall, A.T. A clinical trial of oxatamide in canine atopic dermatitis. *Trends in Veterinary Pharmacology and Toxicology* 1980; **6**: 348–9.
19. Paradis, M., Scott, D.W., Giroux, D. Further investigations on the use of nonsteroidal and steroidal anti-inflammatory agents in the management of canine pruritus. *Journal of the American Animal Hospital Association* 1991; **27**: 44–8.
20. Scott, D.W., Miller, W.H., Decker, G.A., *et al.* Failure of cypiroheptadine hydrochloride as an antipruritic agent in allergic dogs: results of a double-blinded, placebo-controlled study. *Cornell Veterinarian* 1992; **82**: 247–51.
21. Deboer, D.J., Moriello, K.A., Pollet, R.A. The efficacy of AHR-13268, an anti-allergenic compound, in the management of pruritus caused by atopic disease in dogs. *American Journal of Veterinary Research* 1992; **53**: 532–6.
22. Deboer, D.J., Moriello, K.A., Pollet, R.A. Inability of a short duration treatment with a lipoxygenase inhibitor to reduce clinical signs of canine atopy. *Veterinary Dermatology* 1994; **5**: 13–16.
23. Scott, D.W., Miller, W.H., Cayatte, S.M. *et al.* Failure of terfenadine as an antipruritic agent in atopic dogs – results of a double-blinded, placebo-controlled study. *Canadian Veterinary Journal – Revue Vétérinaire Canadienne* 1994; **35**: 286–8.
24. Paradis, M. Nonsteroidal antipruritic drugs in dogs and cats: an update. *Bulletin of the Canadian Academy of Veterinary Dermatology* 1996; **3**–7.
25. Marsella, R., Nicklin, C.F. Double-blinded cross-over study on the efficacy of pentoxifylline for canine atopy. *Veterinary Dermatology* 2000; **11**: 255–60.
26. Crow, D.W., Marsella, R., Nicklin, C.F. Double-blinded, placebo-controlled, cross-over pilot study on the efficacy of zileuton for canine atopic dermatitis. *Veterinary Dermatology* 2001; **12**: 189–95.
27. Nagle, T.M., Torres, S.M., Horne, K.L. *et al.* A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of a Chinese herbal product (P07P) for the treatment of canine atopic dermatitis. *Veterinary Dermatology* 2001; **12**: 265–74.
28. Senter, D.A., Scott, D.W., Miller, W.H. Jr Treatment of canine atopic dermatitis with zafirlukast, a leukotriene-receptor antagonist: a single-blinded, placebo-controlled study. *Canadian Veterinary Journal* 2002; **43**: 203–6.
29. DeBoer, D.J., Schafer, J.H., Salsbury, C.S. *et al.* Multiple-center study of reduced-concentration triamcinolone topical solution for the treatment of dogs with known or suspected allergic pruritus. *American Journal of Veterinary Research* 2002; **63**: 408–13.
30. Marsella, R., Nicklin, C.F., Melloy, C. The effects of capsaicin topical therapy in dogs with atopic dermatitis: a randomized, double-blinded, placebo-controlled, cross-over clinical trial. *Veterinary Dermatology* 2002; **13**: 131–9.
31. Scott, D.W., Miller, W.H., Senter, D.A. *et al.* Treatment of canine atopic dermatitis with a commercial homeopathic remedy: a single-blinded, placebo-controlled study. *Canadian Veterinary Journal – Revue Vétérinaire Canadienne* 2002; **43**: 601–3.
32. Marsella, R., Nicklin, C.F. Investigation on the use of 0.3% tacrolimus lotion for canine atopic dermatitis: a pilot study. *Veterinary Dermatology* 2002; **13**: 203–10.
33. Olivry, T., Dunston, S.M., Rivierre, C. *et al.* A randomized controlled trial of misoprostol monotherapy for canine atopic dermatitis: effects on dermal cellularity and cutaneous tumor necrosis factor- α . *Veterinary Dermatology* 2003; **14**: 37–46.

34. Ferrer, L., Alberola, J., Queralt, M. *et al.* Clinical anti-inflammatory efficacy of arofyline. A new selective phosphodiesterase-4 inhibitor, in dogs with atopic dermatitis. *Veterinary Record* 1999; **145**: 191–4.
35. Olivry, T., Rivierre, C., Jackson, H.A. *et al.* Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. *Veterinary Dermatology* 2002; **13**: 77–87.
36. Steffan, J., Alexander, D., Brovedani, F. *et al.* Comparison of cyclosporine A with methylprednisolone for treatment of canine atopic dermatitis: a parallel blinded randomized controlled trial. *Veterinary Dermatology* 2003; **14**: 11–22.
37. Reddy, N.R.J., Umesh, K.G., Rao, M., Rai, T. Therapeutic evaluation of pheneramine maleate and prednisolone as antipruritic agents in dogs. *Indian Veterinary Journal* 1992; **69**: 259–61.
38. Guaguère, E., Lasvergeres, F., Arfi, L. Efficacy of oral methylprednisolone in the symptomatic treatment of allergic dermatitis [in French]. *Pratique Médicale et Chirurgicale de L'Animal de Compagnie* 1996; **31**: 171–5.
39. Fontaine, J., Olivry, T. Treatment of canine atopic dermatitis with cyclosporine: a pilot clinical study. *Veterinary Record* 2001; **148**: 662–3.
40. Scott, D.W., Buerger, R.G. Nonsteroidal antiinflammatory agents in the management of canine pruritus. *Journal of the American Animal Hospital Association* 1988; **24**: 425–8.
41. Paradis, M., Lemay, S., Scott, D.W. The efficacy of clemastine (Tavist), a fatty acid-containing product (Derm Caps), and the combination of both products in the management of canine pruritus. *Veterinary Dermatology* 1991; **2**: 17–20.
42. Miller, W.H., Scott, D.W., Wellington, J.R. A clinical trial on the efficacy of clemastine in the management of allergic pruritus in dogs. *Canadian Veterinary Journal – Revue Vétérinaire Canadienne* 1993; **34**: 25–7.
43. Paterson, S. Use of antihistamines to control pruritus in atopic dogs. *Journal of Small Animal Practice* 1994; **35**: 412–19.
44. Hayasaki, M., Kondoh, M., Konno, K. *et al.* Evaluation of anti-allergic drugs for canine allergic dermatitis [in Japanese]. *Journal of the Japanese Veterinary Medical Association* 1994; **47**: 29–33.
45. Umesh, K.G., Reddy, N.R.J., Rai, M.T. Therapeutic evaluation of terfenadine in canine allergic skin diseases – a preliminary study. *Indian Veterinary Journal* 1995; **72**: 418–19.
46. Paterson, S. Additive benefits of EFAs in dogs with atopic dermatitis after partial response to antihistamine therapy. *Journal of Small Animal Practice* 1995; **36**: 389–94.
47. Héripert, D. Oxatomide (Tinset ND), the value of this antihistamine in canine allergology field – results of an open study (136 cases) [in French]. *Pratique Médicale et Chirurgicale de L'Animal de Compagnie* 1996; **31**: 51–6.
48. Umesh, K.G., Rajeevalochan, S., Ravindra, S.L. Evaluation of terfenadine and hydroxyzine as antipruritic agents in dogs. *Indian Veterinary Journal* 1998; **75**: 345–6.
49. Ewert, G., Daems, T. Treatment of canine atopic dermatitis by a fatty acid copolymer: comparative double blind study [in French]. *Pratique Médicale et Chirurgicale de L'Animal de Compagnie* 2001; **36**: 401–8.
50. Scott, D.W., Cayatte, S.M. Failure of papaverine hydrochloride and doxycycline hyclate as antipruritic agents in pruritic dogs: results of an open clinical trial. *Canadian Veterinary Journal* 1993; **34**: 164–6.
51. Thomsen, M.K., Kristensen, F., Elling, F. Species specificity in the generation of eicosanoids. Emphasis on leukocyte-activating factors in the skin of allergic dogs and humans. In: Ihrke, P.J., Mason, I.S., White, S.D., eds. *Advances in Veterinary Dermatology*, Vol. 2. Pergamon Press, Oxford, 1993: 63–78.
52. Olivry, T., Guaguère, E., Héripert, D. Treatment of canine atopic dermatitis with the prostaglandin E1 analog misoprostol: an open study. *Journal of Dermatological Treatment* 1997; **8**: 243–7.
53. Scott, D.W., Rothstein, E., Miller, W.H. A clinical study on the efficacy of two commercial veterinary pramoxine cream rinses in the management of pruritus in atopic dogs. *Canine Practice* 2000; **25**: 15–17.
54. Beningo, K.E., Scott, D.W., Miller, W.H. *et al.* Observations on the use of tetracycline and niacinamide as antipruritic agents in atopic dogs. *Canadian Veterinary Journal – Revue Vétérinaire Canadienne* 1999; **40**: 268–70.
55. Miller, W.H., Scott, D.W., Wellington, J.R. Nonsteroidal management of canine pruritus with amitriptyline. *Cornell Veterinarian* 1992; **82**: 53–7.
56. Miller, W.H., Scott, D.W., Wellington, J.R. Investigation on the antipruritic effects of ascorbic acid given alone and in combination with a fatty acid supplement to dogs with allergic skin disease. *Canine Practice* 1992; **17**: 11–13.
57. Jüni, P., Altman, D.G., Egger, M. Systematic reviews in health care – Assessing the quality of controlled clinical trials. *British Medical Journal* 2001; **323**: 42–6.
58. Altman, D.G. Randomisation. Essential for reducing bias. *British Medical Journal* 1999; **302**: 1481–2.
59. Oxman, A., Guyatt, G., Cook, D. *et al.* Summarizing the evidence. In: Guyatt, G., Rennie, D., eds. *Users' Guides to the Medical Literature – Essentials of Evidence-Based Medicine*. AMA Press, Chicago, 2002: 241–69.
60. Ryffel, B., Donatsch, P., Madörin, M. *et al.* Toxicological evaluations of cyclosporin A. *Archives of Toxicology* 1983; **53**: 107–41.
61. Lang, D.G., Wang, C.M., Wenger, T.L. Terfenadine alters action potentials in isolated canine Purkinje fibers more than acrivastine. *Journal of Cardiovascular Pharmacology* 1993; **22**: 438–42.
62. Otto, C.M., Greentree, W.F. Terfenadine toxicosis in dogs. *Journal of the American Veterinary Medical Association* 1994; **205**: 1004–6.
63. Usui, T., Sugiyama, A., Ishida, Y. *et al.* Simultaneous assessment of the hemodynamic, cardiomechanical, and electrophysiological effects of terfenadine on the *in vivo* canine model. *Heart and Vessels* 1998; **13**: 49–57.
64. Sugiyama, A., Aye, N.N., Katahira, S. *et al.* Effects of non-sedating antihistamine, astemizole, on the *in situ* canine heart assessed by cardiohemodynamic and monophasic action potential monitoring. *Toxicology and Applied Pharmacology* 1997; **143**: 89–95.
65. Nishimoto, M., Hashimoto, H., Ohmura, T. *et al.* Effects of astemizole on ventricular activation delay and RT intervals in a canine myocardial infarction model. *Biology and Pharmaceutical Bulletin* 1997; **20**: 1020–3.
66. Yamamoto, K., Tamura, T., Imai, R. *et al.* Acute canine model for drug-induced Torsades de Pointes in drug safety evaluation – influences of anesthesia and validation with quinidine and astemizole. *Toxicological Sciences* 2001; **60**: 165–76.

Résumé L'efficacité des traitements proposés pour la dermatite atopique canine, à l'exclusion des acides gras essentiels et de l'immunothérapie spécifique d'allergènes, a été évaluée en se basant sur une revue systématique des études cliniques prospectives publiées entre 1980 et 2002. Les études ont été comparées pour leur conception (randomisation, aveugle, analyse des intentions de traiter, qualité d'enrolement des sujets), l'efficacité du traitement (amélioration des lésions cutanées ou du prurit) et les effets secondaires (type, gravité, fréquence). Une meta-analyse des résultats n'a pas été possible à cause de l'hétérogénéité des molécules évaluées. Quarante essais, représentant 1607 chiens, ont été identifiés. Il existe de bons arguments pour recommander l'utilisation des glucocorticoïdes par voie orale et la ciclosporine pour le traitement de la dermatite atopique canine, et des arguments suffisants pour utiliser la triamcinolone en spray, une lotion à base de tacrolimus, la pentoxifylline par voie orale ou le misoprostol par voie orale. Il n'existe pas suffisamment d'arguments pour recommander ou ne pas recommander l'utilisation des anti-histaminiques de première ou de seconde génération, les antidépresseurs tricycliques, la cyproheptadine, l'aspirine, les herbes chinoises, l'homéopathie, l'acide ascorbique, l'AHR-13268, la papavérine, les antibiotiques à propriétés immunomodulatrices, le tranilast, la pramoxine topique ou la capsaïcine. Enfin, il existe des arguments en défaveur de l'utilisation de l'arofylline, des inhibiteurs de synthèse des leucotriènes et des antagonistes des récepteurs aux leucotriènes.

Resumen La eficacia de las intervenciones farmacológicas utilizadas para el tratamiento de la dermatitis atópica (AD) canina, excepto la suplementación de ácidos grasos y la inmunoterapia alérgeno-específica, fue evaluada en base a una revisión sistemática de los ensayos clínicos prospectivos publicados entre los años 1980 y 2002. Los estudios fueron comparados con respecto a las características del diseño (asignación al azar y encubrimiento, enmascaramiento, análisis "intención de tratar" y la calidad de la inclusión de los sujetos en el estudio), al beneficio (mejora en lesiones de piel o puntuación del prurito) y al daño (tipo, severidad y frecuencia de las reacciones adversas a la droga) de las diferentes intervenciones. La realización de un Meta-análisis de todos los resultados reunidos no fue posible debido a la heterogeneidad de las drogas evaluadas. Cuarenta ensayos que alistaban 1607 perros fueron identificados. Existe una evidencia buena para recomendar el uso de glucocorticoides orales y la ciclosporina para el tratamiento del AD canina, y una evidencia adecuada o justa para usar el aerosol tópico del triamcinolona, la loción tópica del tacrolimus, la pentoxifilina oral o el misoprostol oral. La evidencia es escasa o está en contra de la recomendación de la prescripción oral de los antagonistas de primera y segunda generación del receptor de la histamina del tipo 1, de los antidepresivos tricíclicos, de la ciproheptadina, de la aspirina, de la terapia herbaria china, de un remedio complejo homeopático, del ácido ascórbico, del AHR-13268, de la papaverina, de antibióticos inmunomoduladores o del tranilast y de la pramoxina o de la capsaïcina tópica. Finalmente, hay una evidencia adecuada en contra de la recomendación del uso de la arofilina oral, de los inhibidores de la síntesis de leucotrienos y de los antagonistas orales del receptor para cistenil-leucotrienos.

Zusammenfassung Die Wirksamkeit pharmakologischer Behandlungen der atopischen Dermatitis des Hundes (AD) mit Ausnahme der Fettsäurensupplementierung und allergen-spezifischer Immuntherapie wurde auf Grund einer systematischen Literaturbewertung von zwischen 1980 und 2002 veröffentlichten, prospektiven klinischen Studien bewertet. Studien wurden bezüglich ihres Designs (Art der Randomisierung, Blind- oder Doppelblindstudie, "intention-to-treat" Analyse und Qualität der Patientenrekrutierung), Nutzen (Besserung der Hautläsionen oder Juckreizbewertung) und Schaden (Art, Schwere und Häufigkeit von Nebenwirkungen) der verschiedenen Interventionen beurteilt. Metaanalyse der Resultate war auf Grund der Heterogenität der bewerteten Medikamente nicht möglich. Vierzig identifizierte Studien umfassten 1607 Hunde. Orale Glukokortikoide und Zyklosporin können auf Grund guter Indizien für die Behandlung der AD des Hundes empfohlen werden, für die Verwendung von lokalem Triamcinolon-Spray, lokaler Tacrolimus-Lotion, oralem Pentoxifyllin oder oralem Misoprostol liegen ebenfalls einige Anzeichen vor. Es gibt keine ausreichenden Belege für oder gegen die Verschreibung von oralen Antihistaminika der ersten und zweiten Generation, trizyklischen Antidepressiva, Cyproheptadin, Aspirin, chinesischer Kräutertherapie, einer homöopathischen Mischung, Ascorbinsäure, AHR-13268, Papaverin, immunmodulierenden Antibiotika oder Tranilast und lokalem Pramoxin oder Capsaicin. Orales Arofyllin, Leukotriensyntheseschmitter und Cysteinyl-Leukotrienrezeptorenantagonisten sollten auf Grund der vorliegenden Indizien nicht empfohlen werden.