

Tolerability and clinical efficacy of oral immunotherapy with house dust mites in a model of canine atopic dermatitis: a pilot study

Rosanna Marsella

University of Florida, College of Veterinary Medicine, Gainesville, FL 32610-0126, USA

Correspondence: Rosanna Marsella, PO Box 100126, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610-0126, USA.
E-mail: marsellar@vetmed.ufl.edu

Sources of Funding

This study was funded partly by the American Academy of Veterinary Dermatology and a grant from the College of Veterinary Medicine of the University of Florida.

Conflict of Interest

No conflicts of interest have been declared.

Abstract

Atopic dermatitis (AD) is a chronic, life-long disease. In humans, immunotherapy (IT) is the only treatment that can alter the course of AD. Oral IT is appealing owing to the ease of administration and the potential for increased compliance. The purposes of this study were to investigate the tolerability, clinical efficacy and effects on allergen-specific IgE of oral IT using a canine AD model. Thirteen atopic beagles sensitized to house dust mites (HDMs) were randomly divided into two groups. One group received daily oral doses of HDMs while the other group received vehicle only for 7 months. The investigator evaluating the dogs was blinded to the allocation of treatments. Prior to and after 2 and 7 months of IT, dogs were challenged daily with HDMs for 3 days concurrently, and clinical signs were scored using a modified Canine Atopic Dermatitis Extent and Severity Index (CADESI). Prior to and at completion of oral IT, serum was collected for measurement of allergen-specific IgE. Oral IT was well tolerated, and no adverse effects were noted. Analysis of variance showed no significant effect of time, group and group $\times$ time interaction for CADESI scores. In addition, there were no significant differences in allergen-specific IgE levels. In conclusion, it appears that oral administration of HDMs is well tolerated in these atopic beagles but that this protocol was not sufficient to induce clinical improvement. Further, longer-term studies will be necessary to explore the potential of oral IT in veterinary medicine.

Accepted 21 January 2010

Introduction

Atopic dermatitis (AD) is a common, chronic, life-long disease in both dogs and humans. Allergen-specific immunotherapy (ASIT) has been successfully used in both human and veterinary medicine for long-term treatment of atopic disease.^{1–5} It also has the potential to prevent worsening of atopic disease in humans.^{6,7} The exact mechanisms of ASIT are still under investigation. Many aspects of the immune responses, including antibody production, cytokine secretion and T cell activation are significantly altered by ASIT.⁸ In particular, ASIT seems to modulate cytokine profiles from a T helper 2 (Th2) dominated response [e.g. increased interleukin-4 (IL-4) and IgE synthesis] typical of atopic cases^{9–12} towards a T helper 1 (Th1) response.^{13–16} Some of the discrepancies in cytokine profiles observed in the canine studies may be partly explained by the small number of cases evaluated, which may not be sufficient to compensate for confounding factors, such as the variability in the number of allergies, duration of the disease, age and breed.^{14,15}

In veterinary medicine, ASIT is traditionally administered by the subcutaneous route and involves the injection of progressively increasing doses of allergens.^{3,17} Although many owners feel comfortable with either the practice of giving the injection themselves or with taking the dog to the veterinarian for the injections, the injectable route can represent a significant challenge in other cases, and can significantly and negatively affect compliance.

Oral administration of allergens has been shown to be safe and effective in decreasing airway responsiveness and allergen-specific IgE in a rodent model¹⁸ and other immunological parameters in canine models of allergic conjunctivitis.¹⁹ Within the oral route, the sublingual approach is widely practised in European countries and is the most common form of ASIT. This approach is not limited to respiratory manifestations of atopic disease but is used for AD.⁵ The sublingual treatment route is also currently of great interest in the USA.²⁰ Recent studies in human medicine, furthermore, have demonstrated the use of sublingual immunotherapy (IT) for many forms of hypersensitivity, ranging from food allergies to AD.²¹ From this point onwards in this manuscript, we will refer to the oral route as a route in which the allergen is not applied sublingually but it is fed to and ingested by the patient.

No studies are currently available on the safety and efficacy of oral administration of allergens in dogs. The identification of a safe, orally administered, effective treatment that could alter the course of the disease

would be of tremendous benefit to both owners and affected dogs with AD. Since sublingual administration of allergens is potentially challenging in dogs and a previous study reported the efficacy of oral administration of allergens in a canine experimental model,¹⁹ the oral route was selected for a preliminary investigation in the present study. Evaluation of the efficacy can be challenging in a clinical trial using dogs with naturally occurring disease belonging to different breeds, with multiple and different allergies and living in different environments. Large numbers of dogs would be needed to control for these confounding factors. Thus, a pilot investigation on the safety and efficacy of this treatment modality would be easier in an experimental model of AD in which dogs are monosensitized, and housed in controlled and uniform conditions.

An experimental model for canine AD has been identified in a colony of atopic beagles sensitized to house dust mites (HDMs).²² These dogs develop a pruritic dermatitis that is clinically, histologically and immunologically identical to naturally occurring AD after environmental challenge with HDMs.²² This model avoids potential confounding factors because the dogs are monosensitized and are kept in a controlled environment. The aim of this study was to evaluate the effect of oral IT on clinical scores and serum allergen-specific IgE in a prospective, randomized, blinded, controlled study.

Materials and methods

All procedures used in this study were approved by the Institutional Animal Care and Use Committee of the University of Florida.

Animals

Thirteen atopic beagles, epicutaneously sensitized to *Dermatophagoides farinae* at a young age and known to develop AD upon environmental exposure to *D. farinae*, were used. At 3 weeks of age, a pure culture of *D. farinae* (RMB83M, Greer Laboratories, >99% pure whole bodied natural milled *D. farinae*) was painted on axillae and groin twice weekly for a total of 12 weeks. One gram of *D. farinae* culture was mixed with sterile saline (2.5 mL) to create a thick paste (400 mg/mL), and each puppy received 0.3 mL of HDM mixture with every application. The paste was applied to small areas of skin in the axillae or inguinal areas using a soft brush. Successful sensitization was demonstrated by: (i) development of lesions at the sites of application of the paste; (ii) flare up of dermatitis clinically compatible with AD upon environmental allergen challenge;^{22,23} (iii) positive intradermal skin test reactivity 15 min after the intradermal injection of *D. farinae* at 25 protein nitrogen units/mL (positive reaction defined at 2 or higher on subjective evaluation where 0 is the score of the saline injection and 4 + is the score of the histamine injection site); and (iv) positive allergen-specific titres²⁴ [>150 ELISA Antigen (EA) units on ALLERCEPT® Heska Corporation, Fort Collins, CO, USA] for *D. farinae*. According to the manufacturer's recommendations for this serology testing, results higher than 150 EA are considered 'positive'.

Treatments

The atopic beagles were randomly divided into two groups. One received the active ingredient ($n = 7$) and the other received the vehicle only ($n = 6$). The investigator evaluating the dogs was blinded to the treatment allocation. The dogs in the active ingredient group received 10 mg of HDM culture (the same whole bodied natural milled *D. farinae* used for the sensitization) mixed with a tablespoonful of cream cheese every day for 7 months, while the vehicle group received plain cream cheese. The dose and choice of mixing the allergen with cream cheese were based on a previ-

ous study in dogs in which it was suggested that mixing the allergen with dairy products would minimize the degradation of the allergen by the gastrointestinal tract.¹⁹ Cream cheese was preferred over milk, which was used in the study by Zemmann *et al.*,¹⁹ in an attempt to increase the time taken for the dogs to finish the portion. More specifically, the cream cheese was applied on the inside of the cheeks and on the hard palate to encourage the dog to lick it rather than swallow it immediately. Increasing the duration of allergens in the oral cavity has been reported to increase efficacy of therapy in human medicine.²⁵

In the study Zemmann *et al.*,¹⁹ it was also reported that 60 days of oral administration of allergen was sufficiently long to observe a clinical benefit.¹⁹ Because of this, the present study was originally planned to be 2 months long. If no difference was detected between the two groups after 2 months of oral IT, the plan was to continue the study for an additional 5 months. Technicians administering the treatments were instructed to monitor on a daily basis for adverse effects (e.g. vomiting, diarrhoea, urticaria, angioedema and oral pruritus).

Animals and housing

Dogs were housed in a research facility at the University of Florida in cement runs that were washed daily using a high temperature and pressure wash (water and bleach). Filters were changed routinely. Stuffed toys, carpets, soft bedding or anything that could trap dust were not allowed in the runs. The walls of the runs and filters were checked monthly to ensure the absence of HDMs in the environment in between challenges (all the results were below detection level of the MITE-T-Fast™ Allergen Detection System, Aveho Biosciences; data not presented).

Environmental challenges

All dogs were environmentally challenged with HDMs prior to and after 2 and 7 months of oral IT. The challenge with HDMs has been described elsewhere.²² Briefly, 50 mg of HDMs (natural *D. farinae*, Greer; 1.6 mL of 31.25 mg/mL solution) was placed on the bottom of each of their kennels. Dogs were confined in the kennels for 3 h/day for 3 days in a row.

Clinical evaluations

Clinical signs were evaluated using a modified Canine AD Extent and Severity Index (CADESI)²² prior to and 6 h after the beginning of each HDM exposure, and then once daily for a total of 5 days for each challenge. Briefly, the dog's body was divided into small sections and each received a score from 0 (absent) to 3 (severe) for each of the clinical signs evaluated (diffuse erythema, erythematous macules, papules, excoriations and alopecia).

Measurement of allergen-specific IgE

Blood samples (8 mL) were drawn from each dog before and at the end of oral IT (at 7 months). Serum samples were sent to Heska Corporation (Fort Collins, CO, USA) for measurement of *D. farinae*-specific IgE without any information regarding the study. Results higher than 150 EA units on ALLERCEPT® are considered 'positive'.

Statistical analysis

Clinical scores and allergen-specific IgE levels were analysed using repeated-measures analyses of variance (ANOVA). Group and time were evaluated as variable factors. At each time point, Student's unpaired *t*-tests were also used for comparison between the two groups. All analyses were performed using the statistical software package SAS System for Windows version 9.0 (SAS Institute, Cary, NC, USA); $P < 0.05$ was considered significant. All data are presented as means $\pm$ standard deviation, unless otherwise indicated.

Results

The atopic dogs included three intact males and ten intact females (age ranging from 3 to 6 years). Clinical signs of

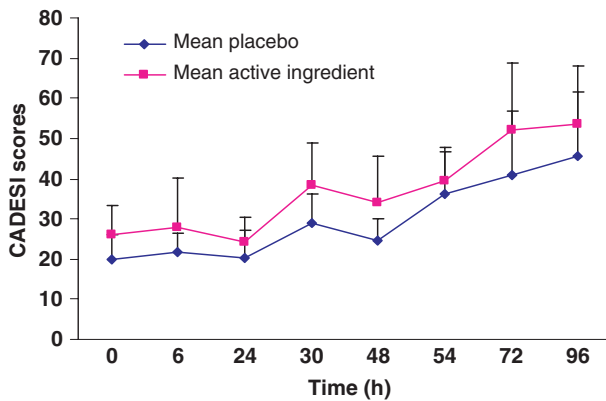


Figure 1. Means and standard deviations of clinical scores (CADESI) recorded for the allergen challenge prior to starting oral IT (baseline). No significant differences were detected between the two treatment groups at any point following allergen challenge.

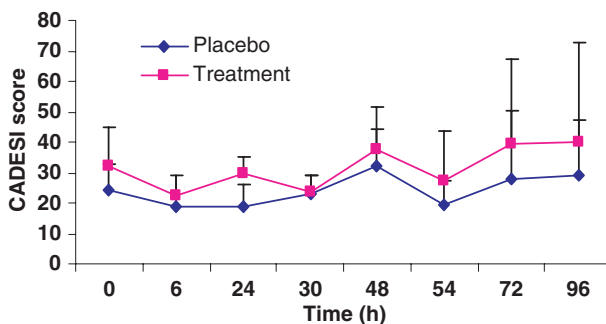


Figure 2. Means and standard deviations of clinical scores (CADESI) recorded for the allergen challenge after 2 months of oral immunotherapy. No significant difference was detected between the two treatment groups at any point following allergen challenge.

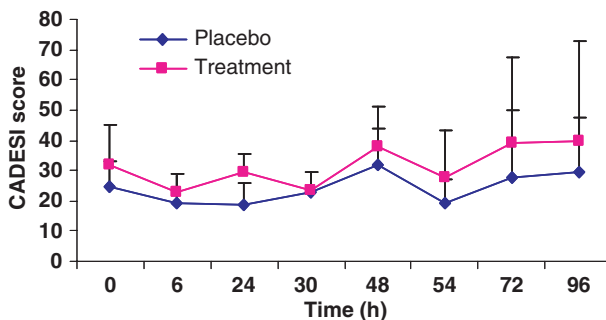


Figure 3. Mean and standard deviations of clinical scores (CADESI) recorded for the allergen challenge at the conclusion of the study after 7 months of oral immunotherapy. No significant difference was detected between the two treatment groups at any point following allergen challenge.

AD flared up in all atopic dogs after exposure to *D. farinae* regardless of the group allocation and the duration of oral IT. Moderate to severe erythema and pruritus developed on the muzzle, ears, groin and interdigital spaces. The treatment was well tolerated, and no adverse effects were recorded.

Analysis of variance revealed no significant effect of time, group and group $\times$ time interaction for CADESI

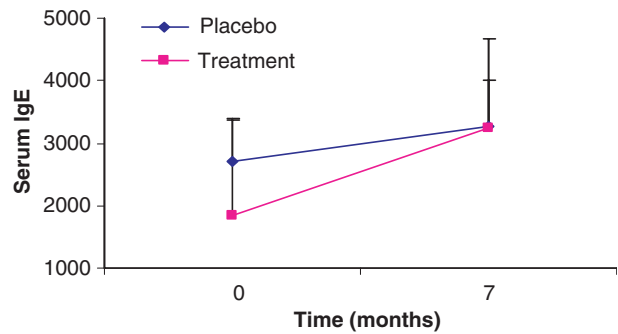


Figure 4. Mean and standard deviations of *D. farinae*-specific IgE of the active ingredient and vehicle groups measured in ELISA antigen units. No significant difference was noted after 7 months of oral administration of immunotherapy.

scores for either 2 or 7 months therapy (Figures 1–3). No significant differences were found for the allergen-specific IgE levels between groups and over time (Figure 4).

Discussion

In this pilot, placebo-controlled study, oral administration of *D. farinae* daily for 7 months to atopic beagles was found to be safe, although it did not induce a significant decrease of clinical signs or allergen-specific IgE. The lack of adverse effects found in this pilot study is in line with the reported safety and excellent tolerability of both oral and sublingual ASIT with single or multiple allergens in human medicine.^{26–28}

In human medicine, currently the main route of oral ASIT is sublingual. Sublingual ASIT is an established treatment option for allergic rhinitis in many European countries, but is not approved in the USA and is considered investigational. Sublingual ASIT has, however, received increasing attention in the USA as an alternative to subcutaneous IT for treatment of allergic rhinitis and asthma.²⁹ More than 30 randomized controlled trials have been published documenting the safety profile of this type of treatment. The most frequently reported adverse effect is oral itching or swelling, followed by gastrointestinal complaints. These are invariably described as mild and easily managed by temporarily adjusting the dose. Systemic adverse events (asthma, urticaria and angioedema) occur sporadically, but their rate has not been different from the placebo groups. None of the dogs in this study showed any evidence of oral pruritus or any other adverse effects.

Although ASIT has been used for years in human medicine for the treatment of asthma, its use for AD is relatively new.³⁰ In a recent open pilot study, the efficacy of sublingual IT in cases with AD and HDM allergy was investigated and found to be promising.³¹ Cases were treated with sublingual ASIT containing both *Dermatophagoides pteronyssinus* and *D. farinae* extracts for 12 months, and a 46% reduction in clinical scores in comparison with baseline value was reported. Treatment with dust mites was very well tolerated, and allowed a gradual and relevant reduction of concomitant therapies with topical corticosteroids or immunosuppressants. The authors concluded that further controlled trials were needed to

confirm the potential clinical benefit of sublingual ASIT in cases with AD due to dust allergies. Both total and allergen-specific IgE serum levels were significantly reduced after therapy. The difference in results between our study and that study may be due to both the duration of treatment and the route of administration (sublingual versus oral).

Efficacy of oral administration of allergens in humans is linked to the duration of allergen in the oral cavity,^{25,29,32} so every effort was made to decrease the speed at which the dogs would eat the cream cheese. The cream cheese was chosen specifically because it would require some licking and hopefully more time spent to finish the portion. Since beagles can be very food-oriented, some dogs were able to swallow the dose rather quickly, and this could have contributed to the lack of efficacy. In humans, the pure oral route of IT has been abandoned due to its inferior efficacy³³ compared with the sublingual route, and a similar situation may apply to veterinary medicine. Future studies evaluating the efficacy of sublingual versus oral ASIT for longer periods of time are needed to address this issue.

The lack of effect of oral IT on allergen-specific IgE is not in line with a previous report in which allergen-specific IgE levels decreased in HDM-sensitive animal models even after oral treatment with HDM for as little as 15 days.¹⁶ In that study, oral administration of high doses of allergens was evaluated as a way to imitate sublingual IT, and the effects of oral administration of *D. farinae* on allergen-induced inflammation and airway hyper-responsiveness were investigated using an asthmatic rat model.¹⁸ The results indicated that this prevented airway hyperresponsiveness in a dose-dependent manner and significantly reduced serum total and allergen-specific IgE levels. The dose of allergen used ranged from 0.5 to 5 mg/kg/day; maximal effects were achieved at dose of 5 mg/kg/day, which were comparable to those of dexamethasone at 1.0 mg/kg/day. Although a direct comparison between the two formulations of *D. farinae* is not possible, the dose might have been higher than the one used in the present study.

In humans, many protocols and doses have been used for sublingual IT, but in general, these protocols require higher doses of allergen (50–100 times higher) than traditional subcutaneous ASIT.^{34–36} Whether the same applies to veterinary cases is unknown. In the present study, the dose selected was one-fifth of the dose used for the challenges, because it was deemed to be the highest dose that the dogs could tolerate on a daily basis without flaring up with severe AD and requiring rescue therapy. This estimation was based on previous unpublished pilot studies. How this dose relates to the dose used in clinical practice for subcutaneous ASIT is unknown, because a pure culture was used for the present study rather than the solution used for skin testing and subcutaneous ASIT. While the pure culture is measured in grams, the skin test solution is expressed in protein nitrogen units per millilitre of solution. None of the formulations currently provides information regarding the amount of main allergens relevant to dogs. Studies in human medicine highlight how the allergenic content of preparations used for skin test and ASIT can be quite different and how these differ-

ences need to be taken into consideration when formulating therapy.³⁷

Duration of treatment is another important factor affecting ASIT efficacy.^{3,34–36} Despite the report of efficacy after 2 months in an allergic model in dogs,¹⁹ this length of therapy, as well as a treatment of 7 months, were not able to induce significant clinical benefits in the present study. The reasons for the different results can be multiple, and include the different type of allergy model as well as the age of the dogs (adults versus infants).¹⁹ One of the reasons why this study ended after 7 months was financial, owing to the high boarding cost of the dogs and the cost of the *D. farinae* culture. Although future studies may consider a different and more cost-effective formulation of the allergen, the present study used the same preparation as for the challenges to assure consistency of antigenic stimulation.

It is important to remember that this study was done using an experimental model of canine AD. Although this model has been shown to closely mimic the spontaneous disease and reproduce clinical and immunological features of AD,^{22,38,39} it is possible that these dogs might have a decreased propensity to respond to IT compared with individuals having the natural disease. This study was designed as vehicle controlled and expected to be shorter than an equivalent study on subcutaneous IT (i.e. 12 months); thus, a third group undergoing subcutaneous IT was not included in the original design. Since this study was not controlled with a group undergoing subcutaneous IT, the potential, although unlikely, explanation that these dogs simply do not respond to any form of IT cannot be ruled out. Future studies evaluating the efficacy of subcutaneous IT in this experimental model are necessary to address this hypothesis as well as larger studies using oral IT in dogs with natural AD.

In summary, a lack of clinical benefit was found in this pilot controlled study on the oral administration of *D. farinae* in an experimental model of canine AD. Further studies evaluating longer-term therapy as well as different modalities of administration are necessary before final conclusions can be made on the usefulness of orally administered allergens in veterinary medicine.

Acknowledgements

The author thanks William Perlstein for assistance with the statistical analysis and Greer Laboratories for graciously providing some of the allergen required to extend the duration of this study.

References

1. Verhagen J, Taylor A, Akdis CA *et al.* Advances in allergen-specific immunotherapy. *Expert Opinion on Biological Therapy* 2005; 5: 537–44.
2. Zur G, White SD, Ihrke PJ *et al.* Canine atopic dermatitis: a retrospective study of 169 cases examined at UC Davis, 1992–1998. Part II. Response to hyposensitization. *Veterinary Dermatology* 2002; 13: 103–11.
3. Loewenstein C, Mueller RS. A review of allergen-specific immunotherapy in human and veterinary medicine. *Veterinary Dermatology* 2009; 20: 84–98.

4. Werfel T, Breuer K, Rüeff F *et al.* Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy* 2006; 61: 202–5.
5. Darsow U, Wollenberg A, Simon D *et al.* ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *Journal of European Academy of Dermatology and Venereology* 2009; 24: 317–28.
6. Yang X. Does allergen immunotherapy alter the natural course of allergic disorders? *Drugs* 2001; 61: 365–74.
7. Walker C, Zuany-Amorim C. New trends in immunotherapy to prevent atopic diseases. *Trends in Pharmacological Sciences* 2001; 22: 84–90.
8. Taylor A, Verhagen J, Akdis CA *et al.* T regulatory cells in allergy and health: a question of allergen-specificity and balance. *International Archives of Allergy and Immunology* 2004; 135: 73–82.
9. Neumann C, Gutgesell C, Fliegert F *et al.* Comparative analysis of the frequency of house dust mite specific and non-specific Th1 and Th2 cells in skin lesions and peripheral blood of patients with atopic dermatitis. *Journal of Molecular Medicine* 1996; 74: 401–6.
10. Olivry T, Dean GA, Tompkins MB *et al.* Toward a canine model of atopic dermatitis: amplification of cytokine gene transcripts in skin of atopic dogs. *Experimental Dermatology* 1999; 8: 204–11.
11. Hayashiya S, Tani K, Morimoto M *et al.* Expression of T helper 1 and T helper 2 cytokine mRNAs in freshly isolated peripheral blood mononuclear cells from dogs with atopic dermatitis. *Journal of Veterinary Medicine Series A. Physiology, Pathology, Clinical Medicine* 2002; 49: 27–31.
12. Nuttall TJ, Knight PA, McAleese SM *et al.* T-helper 1, T-helper 2 and immunosuppressive cytokines in canine atopic dermatitis. *Veterinary Immunology and Immunopathology* 2002; 87: 379–84.
13. Moverare R. Immunological mechanisms of specific immunotherapy with pollen vaccines: implications for diagnostics and the development of improved vaccination strategies. *Expert Review of Vaccines* 2003; 2: 85–97.
14. Majori M, Caminati A, Corradi M *et al.* T-cell cytokine pattern at three time points during specific immunotherapy for mite-sensitive asthma. *Clinical and Experimental Allergy* 2000; 30: 341–7.
15. Shida M, Kadoya M, Park SJ *et al.* Allergen-specific immunotherapy induces Th1 shift in dogs with atopic dermatitis. *Veterinary Immunology and Immunopathology* 2004; 102: 19–31.
16. Mueller RS, Veir J, Fieseler KV *et al.* Use of immunostimulatory liposome-nucleic acid complexes in allergen-specific immunotherapy of dogs with refractory atopic dermatitis – a pilot study. *Veterinary Dermatology* 2005; 16: 61–8.
17. Colombo S, Hill PB, Shaw DJ *et al.* Effectiveness of low dose immunotherapy in the treatment of canine atopic dermatitis: a prospective, double-blinded, clinical study. *Veterinary Dermatology* 2005; 16: 162–70.
18. Xie QM, Wu X, Wu HM *et al.* Oral administration of allergen extracts from *Dermatophagoides farinae* desensitizes specific allergen-induced inflammation and airway hyperresponsiveness in rats. *International Immunopharmacology* 2008; 8: 1639–45.
19. Zemann B, Schwaerzler C, Griot-Wenk M *et al.* Oral administration of specific antigens to allergy-prone infant dogs induces IL-10 and TGF- β expression and prevents allergy in adult life. *Journal of Allergy and Clinical Immunology* 2003; 111: 1069–75.
20. Mastrandrea F. The potential role of allergen-specific sublingual immunotherapy in atopic dermatitis. *American Journal of Clinical Dermatology* 2004; 5: 281–94.
21. Incorvaia C, Mauro M, Cappelletti T *et al.* New applications for sublingual immunotherapy in allergy. *Recent Patents on Inflammation and Allergy Drug Discovery* 2009; 3: 113–7.
22. Marsella R, Olivry T, Nicklin C *et al.* Pilot investigation of a model for canine atopic dermatitis: environmental house dust mite challenge of high-IgE-producing beagles, mite hypersensitive dogs with atopic dermatitis and normal dogs. *Veterinary Dermatology* 2006; 17: 24–35.
23. Marsella R, Nicklin C, Lopez J. Studies on the role of routes of allergen exposure in high IgE-producing beagle dogs sensitized to house dust mites. *Veterinary Dermatology* 2006; 17: 306–12.
24. Saridomichelakis MN, Marsella R, Lee KW *et al.* Assessment of cross-reactivity among five species of house dust and storage mites. *Veterinary Dermatology* 2008; 19: 67–76.
25. Passalacqua G, Guerra L, Pasquali M *et al.* Efficacy and safety of sublingual immunotherapy. *Annals of Allergy Asthma and Immunology* 2004; 93: 3–12.
26. Agostinis F, Foglia C, Landi M *et al.* The safety of sublingual immunotherapy with one or multiple pollen allergens in children. *Allergy* 2008; 63: 1637–9.
27. Passalacqua G, Guerra L, Compalati E *et al.* The safety of allergen-specific sublingual immunotherapy. *Current Drug Safety* 2007; 2: 117–23.
28. Rienzo VD, Minelli M, Musarra A *et al.* Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clinical Experimental Allergy* 2005; 35: 560–4.
29. Esch RE. Sublingual immunotherapy. *Current Opinion in Otolaryngology & Head and Neck Surgery* 2008; 16: 260–4.
30. Novak N. Allergen-specific immunotherapy for atopic dermatitis. *Current Opinion in Allergy and Clinical Immunology* 2007; 7: 542–6.
31. Cadario G, Galluccio AG, Pezza M *et al.* Sublingual immunotherapy efficacy in patients with atopic dermatitis and house dust mites sensitivity: a prospective pilot study. *Current Medical Research and Opinion* 2007; 23: 2503–6.
32. Passalacqua G, Villa G, Altrineti V *et al.* Sublingual swallow or spit? *Allergy* 2001; 56: 578.
33. Canonica GW, Compalati E, Fumagalli F *et al.* Sublingual and oral immunotherapy. *Immunology and Allergy Clinics of North America* 2004; 24: 685–704.
34. Bousquet J, Van Cauwenberge P, Khaltaev N *et al.* Allergic rhinitis and its impact on asthma. *Journal of Allergy and Clinical Immunology* 2001; 108: S147–334.
35. Larenas-Linnemann D. Subcutaneous and sublingual immunotherapy in children: complete update on controversies, dosing, and efficacy. *Current Allergy and Asthma Reports* 2008; 8: 465–74.
36. Cox LS, Larenas Linnemann D, Nolte H *et al.* Sublingual immunotherapy: a comprehensive review. *Journal of Allergy and Clinical Immunology* 2006; 117: 1021–35.
37. Sander I, Fleischer C, Meurer U *et al.* Allergen content of grass pollen preparations for skin prick testing and sublingual immunotherapy. *Allergy* 2009; 64: 1486–92.
38. Marsella R, Olivry T, Maeda S. Cellular and cytokine kinetics after epicutaneous allergen challenge (atopy patch testing) with house dust mites in high-IgE beagles. *Veterinary Dermatology* 2006; 17: 111–20.
39. Marsella R, Girolomoni G. Canine models of atopic dermatitis: a useful tool with untapped potential. *Journal of Investigative Dermatology* 2009; 129: 2351–7.

Résumé La dermatite atopique (AD) est une maladie chronique, à vie. Chez l'homme, l'immunothérapie (IT) est le seul traitement pouvant altérer son développement. La facilité d'administration et le potentiel d'augmentation de l'observance font de l'IT orale un traitement séduisant. Les objectifs de cette étude étaient de déterminer la tolérabilité, l'efficacité clinique et les effets sur les IgE spécifiques d'allergènes d'une IT orale sur un modèle canin de AD. Treize Beagles atopiques sensibilisés aux acariens de la poussière de maison (HDM) ont été répartis au hasard en deux groupes. Pendant 7 mois, le premier groupe a reçu des doses orales quotidiennes d'HDM, l'autre groupe n'a reçu que l'excipient. L'investigateur examinant les

chiens n'avait pas connaissance du traitement alloué. Avant et après 2 et 7 mois d'IT, les chiens recevaient de l'HDM pendant 3 jours et les scores cliniques étaient évalués à l'aide d'un CADESI modifié (Canine AD Extent and Severity Index). Avant et après l'étude, les IgE spécifiques d'allergènes sériques étaient mesurés. L'IT orale a été bien tolérée et aucun effet secondaire n'a été observé. L'analyse de variance n'a montré aucun effet significatif du moment, du groupe et de l'interaction moment x groupe sur les scores CADESI. De plus, il n'y avait aucune différence significative entre les niveaux d'IgE spécifiques d'allergènes. En conclusion, il semble que l'administration orale d'HDM soit bien tolérée chez ces Beagles atopiques mais que ce protocole ne soit pas suffisant pour induire une amélioration clinique. Ainsi, des études sur une plus longue période seront nécessaires pour évaluer l'efficacité de l'IT orale en médecine vétérinaire.

Resumen La dermatitis atópica (AD) es una enfermedad crónica de larga duración. En humanos, la inmunoterapia (IT) es el único tratamiento que puede alterar el curso de la AD. La inmunoterapia oral es atractiva debido a la facilidad de la administración y el mayor potencial de completar los tratamientos. El propósito de este estudio fue investigar la tolerabilidad, eficacia clínica y los efectos en la IgE específica de alérgeno, de la IT oral utilizando un modelo de AD canino. Trece perros Beagle atópicos sensibilizados para el acaro del polvo del hogar (HDM) se dividieron al azar en dos grupos. Un grupo recibió dosis diarias de HDM, mientras que el otro grupo recibió vehículo solo durante siete meses. El investigador evaluando los perros desconocía la distribución de los tratamientos. Antes y tras dos y siete meses de la IT, los perros fueron expuestos diariamente a HDM durante tres días seguidos y los signos clínicos se valoraron utilizando un índice modificado canino de extensión y severidad de la AD (CADESI). Antes y tras completar la IT, se obtuvo suero para medir las IgE específicas de alérgeno. La IT oral fue bien tolerada y no se observaron efectos adversos. El análisis de varianza demostró falta de efecto significativo en el tiempo, grupo e interacción grupo x tiempo para los valores de CADESI. Además, no hubo diferencias significativas en los niveles de IgE específicas de alérgeno. Concluimos que la administración oral de HDM se tolera bien en perros Beagle atópicos pero el protocolo no era suficiente para inducir mejoras clínicas. Estudios de mayor duración serán necesarios para explorar el potencial de la IT oral en medicina veterinaria.

Zusammenfassung Die atopische Dermatitis (AD) ist eine chronische lebenslange Erkrankung. Beim Menschen ist die Immuntherapie (IT) die einzige Behandlung, die den Verlauf von AD verändern kann. Aufgrund der einfachen Handhabung und Wahrscheinlichkeit verbesserter Compliance ist die orale IT reizvoll. Die Ziele dieser Studie waren es, die Verträglichkeit, die klinische Wirksamkeit und die Auswirkungen auf allergen-spezifisches IgE durch orale IT mit Hilfe eines caninen AD Modells zu untersuchen. Dreizehn atopische Beagles, die auf Hausstaubmilben (HDM) sensibilisiert waren, wurden nach dem Zufallsprinzip in zwei Gruppen eingeteilt. Eine Gruppe erhielt 7 Monate lang täglich orale Dosen von HDM, während die andere Gruppe nur das Trägermedium erhielt. Der Untersuchende, der die Hunde evaluierte, war gegenüber der Zuteilung der Behandlungen geblindet. Vor und nach 2 und 7 Monaten der IT wurden die Hunde an drei aufeinander folgenden Tagen täglich mit Hausstaubmilben gechallenged und die klinischen Zeichen mit Hilfe eines modifizierten Caninen AD Extent and Severity Index (CADESI) bewertet. Vor und bei Beendigung der oralen IT wurden Serum-Proben zur Messung von Allergen-spezifischem IgE genommen. Die orale IT wurde gut vertragen und es wurden keine Nebenwirkungen festgestellt. Die Varianzanalyse zeigte keine signifikante Auswirkung von Zeit, Gruppe und Interaktion von Gruppe x Zeit auf die CADESI Werte. Zusätzlich gab es keine signifikanten Unterschiede bei den Allergen-spezifischen IgE Werten. Zusammenfassend scheint die orale Verabreichung von HDM bei diesen atopischen Beagles gut toleriert zu werden, aber dieses Protokoll reichte nicht aus, um eine klinische Verbesserung zu erzielen. Weiters werden Langzeitstudien nötig sein, um die Möglichkeiten der oralen IT in der Veterinärmedizin zu eruieren.

要約 アトピー性皮膚炎(AD)は慢性で生涯にわたってみられる疾患である。ヒトでは免疫療法はADの経過を改善させる唯一の治療法である。経口免疫療法は投与の簡便さにおいて魅力的であり、コンプライアンスの向上も期待される。この研究の目的は犬ADモデルを使用して、経口免疫療法の許容性、臨床的な効果、アレルギー特異的IgEへの影響を調査することである。13頭のアトピーのビーグルをハウスダストマイト(HDM)に感作し、無作為に2つのグループに分割した。1つのグループは連日経口でHDMを投与し、もう一つのグループはプラセボを7ヶ月間投与した。犬を評価する調査員は投与の割り付けに関して知らされていなかった。実験前と免疫療法の2ヶ月後と7ヶ月後で、犬に対するHDMへの負荷を3日間連続して行った後に行われ、改正されたアトピー性皮膚炎皮膚重症度指数(CADESI)を使用して臨床症状をスコア化した。実験前と経口免疫療法の終了時に血清を採取し、アレルギー特異的IgEを測定した。経口免疫療法はよく寛容され、副作用は認められなかった。分散分析ではCADESIスコアにおいて時間、グループ、グループ対時間の相互作用で有意な結果は認められなかった。加えて、アレルギー特異的IgEレベルでは有意差はみられなかった。結論としてHDM経口投与はアトピービーグルでよく寛容されたが、このプロトコルでは十分な臨床的な改善を得ることはできなかった。さらなる、長期間の調査が獣医領域での経口免疫療法の可能性の探索に必要である。