

An open study on the efficacy of a recombinant Der f 2 (*Dermatophagoides farinae*) immunotherapy in atopic dogs in Hungary and Switzerland

Nina Fischer* , Noémi Tarpataki†, Federica Leidi‡, Ana Rostaher*  and Claude Favrot* 

*Dermatology Unit, Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Winterthurerstrasse 260, 8057 Zurich, Switzerland

†Department and Clinic of Internal Medicine, University of Veterinary Medicine, István utca 2, Budapest, 1078, Hungary

‡Centro Veterinario Preluna, Via Preluna 24, Comano, 6949, Switzerland

Correspondence: Nina Fischer, Dermatology Unit, Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Winterthurerstrasse 260, 8057 Zurich, Switzerland. E-mail: nfischer@vetclinics.uzh.ch

Background – Previously published studies evaluating a recombinant Der f 2-based immunotherapy have demonstrated efficacy in the treatment of dogs experimentally and naturally sensitized to house dust mites (HDM). Der f 2 sensitization is thought to play a minor role in European atopic dogs sensitized to HDM.

Objective – The study evaluated the short-term efficacy of a recombinant Der f 2 product in the treatment of naturally sensitized atopic dogs in Switzerland and Hungary.

Animals – Fifteen atopic dogs with positive test reactions to *Dermatophagoides farinae* (Df).

Material and Methods – Recombinant Der f 2 allergens were injected subcutaneously at increasing doses once weekly for 6 weeks. Canine Atopic Dermatitis Extent and Severity Index (CADESI-04), pruritus Visual Analog Scale (pVAS) and medication scores were assessed at days 0 and 42. Efficacy was recorded as excellent, good, fair or poor, depending on the number of scores decreasing by more than 50%.

Results – Mean CADESI, pVAS and medication scores at inclusion were 35, 6 and 15 (SD = 30, 2, 7), respectively. At Day 42 the scores decreased to 8, 3 and 5, respectively (Wilcoxon matched pairs signed rank tests $P = 0.0002$, 0.002 and 0.001). Four dogs were classified as excellent responders with a reduction of >50% in all three scores. Nine dogs were classified as good (five) or fair (four) responders and scores deteriorated in two dogs.

Conclusion – These data suggest that recombinant Der f2 allergens may be as effective and show benefit faster than traditional allergen immunotherapy in European dogs sensitized to Df.

Introduction

Atopic dermatitis (AD) is a genetically predisposed inflammatory and pruritic allergic skin disease which is often associated with the production of allergen-specific IgE against environmental allergens including house dust mites (HDM).¹ Allergen specific immunotherapy (ASIT) is the only aetiological treatment available and is

frequently used for the therapy of canine AD.¹ Unfortunately, ASIT protocols and allergens are not standardized and the response rate, time to response, and number of included antigens have not been assessed in well-controlled studies. Allermune® (ZENOAG; Tokyo, Japan), is licensed in Japan and Korea for the treatment of canine AD, combines a recombinant protein, Der f 2, and a pullulan adjuvant. Allermune® was developed based on studies showing that over 75% of atopic Japanese dogs were sensitized to Der f 2.^{2,3} Allermune® has been shown to be effective and safe for the therapy of Der f 2-sensitized laboratory dogs,⁴ and a study from Japan demonstrated >80% efficacy of Allermune® in the treatment of naturally occurring atopic dogs.⁵

Data on the prevalence of Der f 2 sensitization in Europe are conflicting and mainly suggest a low prevalence.^{6,7} Because Allermune® has thus far only been tested in Japanese dogs and dogs experimentally sensitized to Der f 2, the goal of this study was to evaluate the short-term efficacy of Allermune® in atopic European dogs showing positive test reactions to *Dermatophagoides farinae* (Df).

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Abbreviations: AD, Atopic dermatitis; ASIT, Allergen specific immunotherapy; CADESI-04, Canine Atopic Dermatitis Extent and Severity Index; HDM, house dust mites; pVAS, pruritus Visual Analog Scale.

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Materials and methods

This multicentre open study was carried out in Switzerland and Hungary; including cases from university veterinary hospitals in Budapest and Zurich, and a private practice in Comano, Switzerland.

Animals

Privately owned atopic dogs with nonseasonal pruritus and positive test results for Df were included in this study. Dogs were diagnosed based on published criteria, with exclusion of food allergy, treatment of ectoparasites and secondary microbial infections, if needed. Dogs with seasonal pruritus were excluded from this study. The study was conducted during the winter season to minimize the possible effects of pollination. Concomitant medications (steroids, antihistamines, antibiotics, oclacitinib, ciclosporin and topical products) were allowed and recorded for each dog.

Table 1. Medication scores used to grade the medication consumption initially (Day 0) and on Day 42 in dogs receiving recombinant Der f2 immunotherapy

No concurrent medication	0
Shampoo therapy	5
Ear medication (topical)	5
Other topical therapy	5
Antihistamines	10
Frequent antibiotics (>21 days)	20
Less frequent (<21 days)	10
Prednisolone	
≥1 mg/kg/day	40
0.5–1 mg/kg/day	30
0.2–0.5 mg/kg/day	20
≤0.2 mg/kg/day	10
Ciclosporin (5 mg/kg)	
Once daily	30
Every other day	20
Every three days	10
Every four days	5
Oclacitinib (0.4–0.6 mg/kg)	
Twice daily	40
Once daily	30
Every other day	20
Every three days	10

Allergen testing

Dogs were recruited on the basis of positive reactions to Df based on commercial serological testing. In 11 dogs, allergen-specific IgE levels were reported with the Heska Allercept™ system (Heska AG; Fribourg, Switzerland). In one dog, serology was performed using a macELISA (IDEXX Diavet AG; Bäch, Switzerland) and in three dogs, from Hungary, allergen-specific IgE serology was performed using the Polycheck® ELISA Kit (Biocheck GmbH; Münster, Germany).

Treatment

Allermune® was used following the manufacturer's instructions. Briefly, increasing dosages (0.1, 0.5, 1.0, 2.0, 5.0 and 10 µg) dissolved in 1 mL saline were injected by a veterinarian subcutaneously once weekly for six weeks. The patients were monitored for 30 min post-injections for any adverse reactions.

Clinical assessment

Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04), pruritus Visual Analog Scale (pVAS) and medication scores were assessed at study inclusion (Day 0) and completion of the treatment (Day 42) for each patient by the same investigator.^{8–10} The method for evaluation of medication score used in this study was as published previously, and was slightly adapted for this study purpose by inclusion of additional medications (occlacitinib and ciclosporin); see Table 1.⁹ Efficacy was defined based on the following criteria.

Response definition	Criteria (scores CADESI, medication and pVAS)
Excellent	≥50% improvement of all three scores
Good	≥50% improvement of any two scores
Fair	≥50% improvement of only one score
Poor	<50% improvement of each score or deterioration of at least one score

Statistical analysis

As one of the datasets was not normally distributed, Wilcoxon matched pairs signed rank tests were used to compare CADESI, pVAS and medication scores at inclusion and after the last injection (Graphpad 7; La Jolla, CA, USA).

Results

Animals

Fifteen dogs completed the six week study. Twelve dogs were enrolled in Switzerland and three dogs were

Table 2. Breed, response and sensitization pattern of each dog recruited for Der f2 recombinant allergen immunotherapy

Breed	Response	Positive allergen serology test			
		<i>Dermatophagoides farinae</i>	<i>Ascaris siro</i>	<i>Malassezia</i>	Pollen (at least one positive)
1 West Highland white terrier	Excellent	Positive	Positive		
2 French bulldog	Fair	Positive	Positive	Positive	Positive
3 Dobermann	Poor	Positive	Positive	Positive	
4 Mastino	Excellent	Positive	Positive	Positive	Positive
5 French bulldog	Excellent	Positive			
6 West Highland white terrier	Excellent	Positive	Positive	Positive	Positive
7 Boxer	Good	Positive	Positive		Positive
8 Carlin	Good	Positive	Positive	Positive	Positive
9 French bulldog	Fair	Positive	Positive		Positive
10 Beagle	Fair	Positive	Positive	Positive	Positive
11 Golden retriever	Good	Positive	Positive	Positive	Positive
12 Bull terrier	Good	Positive	Positive		Positive
13 Mixed breed	Fair	Positive			
14 Cavalier King Charles spaniel	Good	Positive			
15 French bulldog	Poor	Positive	Positive		

Most dogs showed multiple reactions to various allergens, but five dogs were only positive for house dust mites (*Dermatophagoides farinae* and *Ascaris siro*).

enrolled in Hungary. The study group consisted of nine female and six male dogs; all were neutered except for one intact male. The mean age was 3.9 years (range: 1–8 years), see Table 2 for details of the cases recruited.

Allergen serology test results

Table 2 shows the sensitization pattern of each dog based on allergen-specific IgE-serology. Five of 15 dogs were positive solely to mites [three to Df, and two to Df and *Acarus siro* (As)]; all other dogs were positive for multiple allergens.

Clinical response

An overall response rate of 60% (nine of 15 dogs) was recorded, with an excellent response after two to three weeks of treatment in four dogs and a good response in five dogs. Four dogs improved in only one score and were classified as fair responders, and in the remaining two dogs, at least one score increased and so these two dogs were classified as treatment failures.

The pre- and post-treatment scores of each dog are shown in Figure 1a–c. The mean CADESI-4 score at Day 0 was 35 and decreased to 13 on Day 42 after six weeks of treatment ($P = 0.0002$), mean pVAS was 6 on Day 0 and decreased to 3 by Day 42 ($P = 0.002$), and medication score was initially 15 and decreased to 6 on Day 42 ($P = 0.001$). After treatment, immunomodulating therapy (glucocorticoids, oclacitinib and ciclosporin) could be stopped in seven of 15 dogs (47%), three dogs had mild residual pruritus which was well controlled with just topical therapy, and three dogs required no other supportive therapy.

No major side effects were recorded; eight of 15 dogs showed signs of local pain during the injection.

Discussion

This study demonstrated a good to excellent improvement of the clinical status in 60% of HDM-test positive atopic dogs treated with Allermune® in Switzerland and Hungary. This response rate is similar to previous studies on subcutaneous and intralymphatic ASIT using crude Df extracts. A previous study reported an even higher response rate in 84.6% (11 of 13) of treated dogs, but in that study the clinical criteria as well as study length were different from our study, and a direct comparison with our data is therefore difficult.⁵ However, similar to that study,⁵ in 47% of our cases withdrawal of immunomodulating medications was possible.

Given that no commercially available Der f 2 test exists, it is important to assess whether Der f 2 immunotherapy may be helpful in the treatment of Df sensitized dogs in the absence of this information. In one study, only 28% of European dogs showed positive IgE serology against Der f 2.⁶ However, another study performed in Portugal and Spain challenged these findings and suggested that Der f 2 reactivity is prevalent, at least in Southern European atopic dogs.³ Whether the nine dogs in our study which responded well to Allermune® were sensitized specifically to Der f 2, whereas the other six dogs were sensitized to other Df antigens and therefore did not respond well to the treatment, could not be assessed in

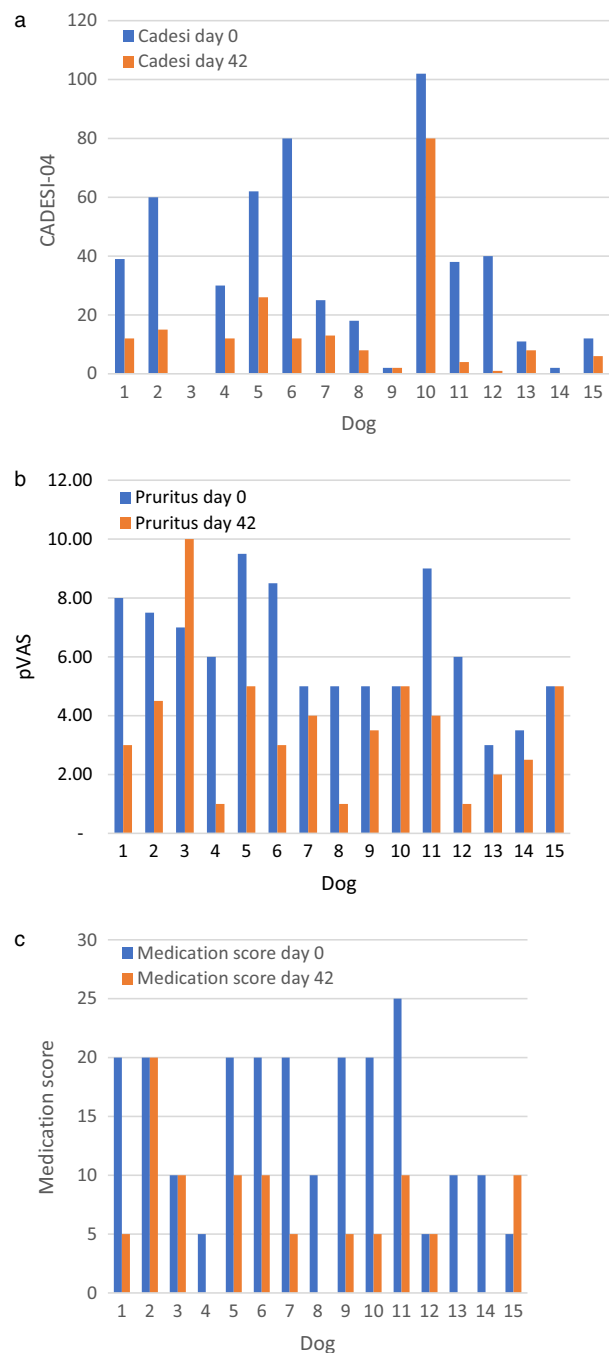


Figure 1. (a–c) Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI-04), pruritus Visual Analog Scale (pVAS) and medication scores for dogs given Der f 2 pullulan immunotherapy at Day 0 (blue columns) and at the end of the study on Day 42 (orange columns).

this study, and further studies addressing these questions are needed.

In agreement with a previous study there was no correlation between the sensitization pattern (polysensitized vs. monosensitized) and treatment outcome.⁵ Of the five dogs which were positive only to Df and As, two showed an excellent response, one showed a good response, one a fair response and one was classified as a treatment failure. Six of nine dogs showing an excellent or good response were polysensitized. Moreover, the two dogs classified as treatment failures were dogs not positive to

pollens. This study was conducted during the winter months and clinical signs were present in all study dogs during that time, supporting the role that house dust mites played a major role in the dermatitis. However, due to the short study period of just six weeks, long-term effects of the immunotherapy in dogs cosensitized to pollens are not known.

The role of the adjuvant pullulan in the treatment of AD is not fully understood. Pullulan is a polysaccharide composed solely of glucose and is frequently used in the pharmaceutical, food and cosmetics industries. It has been previously shown in mice that pullulan can reduce IgE production and induce the production of blocking IgG antibodies, and is therefore considered to reduce allergic reactions.¹¹ It is uncertain whether the efficacy of Allermune[®] is solely based on the recombinant Der f 2 allergen, or whether pullulan played a role in the clinical improvement seen in this short study. Patient improvement also may have been related to the relatively high concentration of allergens injected, as the dose of 10 µg injected at six weeks corresponds to the maximal dose previously used at the end of a much longer escalation protocol in humans.¹²

In conclusion, Allermune[®] can be considered to be an effective new AIT protocol in European dogs sensitized to Df. In comparison to SCIT and ILIT, it may achieve the same response rate with more rapid clinical improvement. Study limitations included small subject numbers, short follow-up time and lack of a control group; further studies including more dogs with a longer follow-up time and with a control group are needed.

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Résumé

Contexte – Les études antérieures évaluant une immunothérapie basée sur Der f 2 recombinant ont montré l'efficacité dans le traitement des chiens sensibilisés expérimentalement et naturellement aux acariens de la poussière de maison (HDM). La sensibilisation à Der f2 est sensée jouer un rôle mineur chez les chiens atopiques européens sensibilisés à HDM.

Objectif – L'étude évalue l'efficacité à court terme d'un produit de Der f2 recombinant dans le traitement des chiens atopiques sensibilisés naturellement en Suisse et en Hongrie.

Sujets – Quinze chiens atopiques avec des tests positifs à *Dermatophagoides farinae* (Df).

Matériel et méthodes – Les allergènes recombinant Der f 2 ont été injectés par voie sous cutanée à des doses croissantes une fois par semaine pendant six semaines. Un CADESI-04 (Canine Atopic Dermatitis Extent and Severity Index), un p VAS (pruritus Visual Analog Scale) et des scores de consommation médicamenteuse ont été évalués à jours 0 et 42. L'efficacité a été enregistrée comme excellente, bonne, modérée ou basse selon le nombre de scores diminuant de plus de 50%.

Résultats – Les scores moyens de CADESI, pVAS et de consommation médicamenteuse à l'inclusion étaient respectivement 35, 6 et 15 (SD = 30, 2, 7). A jour 42, les scores ont diminué respectivement à 8, 3 et 5 (test de comparaison pairée de Wilcoxon $P = 0.0002$, 0.002 et 0.001). Quatre chiens ont été classés comme excellents avec une diminution >50% des trois scores. Neufs chiens ont été classés comme bons (cinq) ou modérés (quatre) et les scores se sont aggravés pour deux chiens.

Conclusion – Ces données suggèrent que les allergènes recombinant Der f 2 peuvent être efficace et montrer de l'intérêt plus rapidement que les allergènes traditionnels d'immunothérapie chez les chiens européens sensibilisés à Df.

Resumen

Antecedentes – estudios publicados previamente que evalúan la inmunoterapia con Der f2 recombinante han demostrado eficacia en el tratamiento de perros experimental y naturalmente sensibilizados a los

ácaros del polvo doméstico (HDM). Se piensa que la sensibilización a Der f 2 juega un papel menor en los perros atópicos europeos sensibilizados a la HDM.

Objetivo – El estudio evaluó la eficacia a corto plazo de un producto Der f 2 recombinante en el tratamiento de perros atópicos naturalmente sensibilizados en Suiza y Hungría.

Animales – Quince perros atópicos con reacciones positivas a las pruebas para *Dermatophagoides farinae* (Df).

Material y métodos – los alérgenos recombinantes de Der f 2 se inyectaron por vía subcutánea en dosis crecientes una vez por semana durante 6 semanas. Se evaluaron el índice de gravedad y extensión de la dermatitis atópica canina (CADESI-04), escala visual analógica (pVAS) del prurito y medicación en los días 0 y 42. La eficacia se registró como excelente, buena, regular o deficiente, según el número de puntuaciones decrecientes en más del 50%.

Resultados – los valores medios de CADESI, pVAS y medicación al inicio fueron 35, 6 y 15 (SD = 30, 2, 7), respectivamente. En el día 42, los valores disminuyeron a 8, 3 y 5, respectivamente (pruebas de Wilcoxon de rango establecido pareadas $P=0,0002$; $0,002$ y $0,001$). Cuatro perros se consideraron como de respuestas excelente con una reducción de $> 50\%$ en los tres valores. Nueve perros se clasificaron como de respuesta buena (cinco) o regular (cuatro) y los valores empeoraron en dos perros.

Conclusión – estos datos sugieren que los alérgenos Der f2 recombinantes pueden ser tan efectivos y mostrar un beneficio más rápido que la inmunoterapia alérgica tradicional en perros europeos sensibilizados a Df.

Zusammenfassung

Hintergrund – Frühere Veröffentlichungen evaluierten eine Immuntherapie, die auf Der f2 basierte und eine Wirksamkeit bei der Behandlung von Hunden zeigte, die experimentell und natürlich auf Hausstaubmilben (HDM) sensibilisiert waren. Es wird angenommen, dass eine Der f2 Sensibilisierung bei atopischen Hunden, die auf HDM sensibilisiert sind, in Europa eine geringe Rolle spielt.

Ziel – Diese Studie evaluierte die Kurzzeit-Wirksamkeit eines rekombinanten Der f2 Produktes bei der Behandlung von natürlich sensibilisierten atopischen Hunden in der Schweiz und in Ungarn.

Tiere – Fünfzehn atopische Hunde mit positiven Hautreaktionen auf *Dermatophagoides farinae* (Df).

Material und Methoden – Es wurden rekombinante Der f2 Allergene in zunehmenden Dosen subkutan einmal wöchentlich 6 Wochen lang injiziert. Es wurden der Canine Atopic Dermatitis Extent and Severity Index (CADESI-04), die Pruritus Visual Analog Scale (pVAS) und Behandlungswerte an den Tagen 0 und 42 erfasst. Die Wirksamkeit wurde in Abhängigkeit einer Verminderung der Beurteilungswerte um 50% als exzellent, gut, durchschnittlich oder schlecht erfasst.

Ergebnisse – Durchschnittliche CADESI, pVAS und Behandlungswerte betrugen bei Aufnahme in die Studie 35, 6 bzw 15 (SD = 30, 2, 7). Am Tag 42 waren die Werte auf 8, 3 bzw 5 reduziert (Wilcoxon matched pairs signed rank tests $P=0.0002$, 0.002 und 0.001). Vier Hunde wurde als exzellente Responder mit einer Reduzierung auf $> 50\%$ in allen drei Beurteilungswerten klassifiziert. Neun Hunde waren als gute (fünf) oder durchschnittliche (vier) Responder klassifiziert und bei zwei Hunden wurden die Bewertungen schlechter.

Schlussfolgerung – Diese Daten weisen darauf hin, dass rekombinante Der f2 Allergene bei europäischen Hunden, die auf Df sensibilisiert waren, wirksam sein könnten und eine schnellere Verbesserung zeigen, als die traditionelle Allergen Immuntherapie.

要約

背景 – 組換えDer f2の免疫療法を評価した既存の公表された研究は、実験的かつ自然にハウスダストマイト(HDM)に感作された犬の治療における有効性を実証している。Der f 2感作は、HDMに感作されたヨーロッパのアトピー犬ではあまり重要な役割を果たさないと考えられている。

目的 – 本研究の目的は、スイスおよびハンガリーにおける自然感作アトピー犬の治療に対し、組換えDer f 2産物の短期有効性を評価することであった。

被験動物 – *Dermatophagoides farinae*(Df)に対する陽性試験反応を示した15頭のアトピー犬。

材料および方法 – 組換えDer f 2アレルゲンを、1回/1週間ごとに6週間、漸増用量で皮下注射した。犬アトピー性皮膚炎重症度指数(CADESI-04)、視覚的アナログ尺度(pVAS)および投薬スコアを0日目および42日目に評価した。有効性は、スコア数が50%以上減少することに応じて、優、良、可または不良と記録した。

結果 – 試験開始時の平均CADESI、pVASおよび投薬スコアは、それぞれ35、6および15(標準偏差 = 30、2、7)であった。42日目に、スコアはそれぞれ8、3および5に減少した(Wilcoxon matched pairs signed rank tests $P=0.0002$ 、 0.002 および 0.001)。4頭の犬は3スコア全てにおいて50%を下回る優秀な応答者として分類した。9頭の犬は、良(5頭)または可(4頭)の応答者に分類し、2頭の犬はスコアが悪化した。

結論 – 本研究データは、組換えDer f2アレルゲンは、Dfに感受性を示すヨーロッパの犬において、従来のアレルゲン免疫療法よりも効果的で、迅速な利益を示す可能性を示唆している。

摘要

背景 — 之前发表的关于评估重组Der f2抗原免疫疗法的研究,已经证实了其对实验犬和自然发病的屋尘螨(HDM)过敏犬的疗效。在HDM过敏的欧洲异位性犬身上,Der f2致敏被认为不那么重要。

目的 — 研究瑞士和匈牙利自然发病的异位性皮炎患犬,评估使用重组Der f2产品对其治疗的短期疗效。

动物 — 对粉尘螨(Df)测试有阳性反应的15只异位性犬。

材料和方法 — 以递增剂量皮下注射重组Der f2抗原,每周一次,持续6周。在第0天和第42天,进行犬异位性皮炎严重程度指数(CADESI-04)、瘙痒视觉类比量表(pVAS)及药物评分。根据分数递减超过50%的原则,划分疗效等级依次为优异、良好、一般或差。

结果 — CADESI、pVAS和药物平均评分分别为35、6和15(SD = 30,2,7)。在第42天,数值分别降至8、3和5(Wilcoxon匹配对符号秩和检验 $P = 0.0002$ 、 0.002 和 0.001)。四只犬疗效优异,在三项评分中数值均减少>50%。九只犬归类为疗效良好(5只)或一般(4只),两只犬的评分为差。

结论 — 这些数据表明,重组Der f2抗原对治疗Df过敏的欧洲犬可能有效,且显示比传统的抗原免疫疗法起效更快。

Resumo

Contexto — A eficácia da imunoterapia baseada em Der f 2 recombinante no tratamento de cães sensibilizados naturalmente e experimentalmente por ácaros da poeira doméstica (APD) já foi demonstrada em estudos publicados anteriormente. Acredita-se que a sensibilização por Der f 2 exerça função pouco expressiva em cães atópicos europeus sensibilizados por APD.

Objetivo — Este estudo avaliou a eficácia a curto prazo de um produto contendo Der f 2 recombinante no tratamento de cães atópicos naturalmente sensibilizados na Suíça e na Hungria.

Animais — Quinze cães atópicos com reações positivas para *Dermatophagoides farinae* (Df).

Materiais e métodos — Os alérgenos recombinantes Der f 2 foram injetados por via subcutânea em doses semanais crescentes, por seis semanas. O indicador de extensão e severidade da dermatite atópica canina 04 (*Canine Atopic Dermatitis Extent and Severity Index*, CADESI-04), a escala visual analógica de prurido (*Pruritus Visual Analog Scale*, pVAS) e os escores de medicação foram avaliados nos dias 0 e 42. A eficácia foi relatada como excelente, boa, média ou baixa, dependendo da redução do número dos escores em mais de 50%.

Resultados — Os valores médios dos escores CADESI, pVAS e de medicação na inclusão foram 35, 6 e 15 (DP = 30, 2, 7), respectivamente. No dia 42, houve redução nos escores médios para 8, 3 e 5, respectivamente (Teste de Wilcoxon pareado $P = 0.0002$, 0.002 e 0.001). As respostas de quatro cães foram classificadas como excelentes, apresentando redução >50% nos três escores. Já nove cães tiveram suas respostas classificadas como boas (cinco) ou médias (quatro) e dois cães apresentaram deterioração nos valores dos escores.

Conclusão — Os dados do presente estudo sugerem que os alérgenos recombinantes Der f 2 podem ser tão eficazes quanto a imunoterapia com alérgenos tradicionais e apresentar benefícios mais rapidamente em cães europeus sensibilizados por Der f 2.