Acta Scientiae Veterinariae, 2024. 52(Suppl 1): 933.

CASE REPORT
Pub. 933

ISSN 1679-9216

Canine Atopic Dermatitis - Efficacy of Sublingual Immunotherapy

Minseok Choi[1], Taesik Yun[1], Dohee Lee[1], Yoonhoi Koo[2], Yeon Chae[1], Hakhyun Kim[1], Mhan-Pyo Yang[1] & Byeong-Teck Kang[1]

ABSTRACT

***Background*:** Canine atopic dermatitis (CAD) is a hereditary pruritic and inflammatory allergic skin disease associated with elevated IgE levels. Although, several treatments for CAD exist, allergen-specific immunotherapy (ASIT) is the only treatment that induces tolerance to pathogenic allergens. Sublingual immunotherapy (SLIT) is effective, convenient, and safe. This case report describes the successful treatment of a dog with atopic dermatitis using SLIT, emphasizing the efficacy and safety of SLIT as a long-term management strategy for CAD.

***Case*:** A 3-year-old spayed female Dachshund presented with non-seasonal chronic pruritus and generalized alopecia. The onset of pruritus occurred at 6 months of age, and its severity, measured by the pruritus visual analog scale, score was 5 out of 10. Dermatological examination revealed alopecia and scales on the dorsum and tail, and alopecia, lichenification, and crust on the medial side of the forelimbs. Diagnostic tests confirmed superficial pyoderma and *Malassezia* dermatitis. Initial treatment included amoxicillin/clavulanate, itraconazole, and a shampoo containing chlorhexidine gluconate and miconazole nitrate. An elimination diet trial was performed using a commercial diet to diagnose canine adverse food reaction (CAFR). However, 11 days after treatment initiation, the microbial and fungal skin infections and pruritus did not improve. Prednisolone was subsequently prescribed to alleviate pruritus and evaluate the response to glucocorticoids. At 24 days after the administration of prednisolone, pruritus reduction and lesion improvement were observed. Thereafter, prednisolone was tapered to 0.5 mg/kg EOD and discontinued 38 days after the initial administration. After prednisolone discontinuation, cytology did not reveal any cocci or *Malassezia* sp. Therefore, treatment with amoxicillin/clavulanate and itraconazole was discontinued. Two weeks after the discontinuation of prednisolone, pruritus relapsed, and cytology revealed no infection. The dog was initially treated with oclacitinib and planned to be managed with ASIT following an intradermal skin test at 2 weeks later. A provocative challenge was performed after the pruritus, and the lesions were well managed with oclacitinib. Because the clinical signs did not worsen, CAFR was excluded. The Favrot criteria was used to diagnose CAD by ruling out other skin conditions. An intradermal skin test was performed for 27 allergens, and oclacitinib was administered for SLIT, with allergens showing a positive reaction. After the administration of SLIT and oclacitinib, pruritus was well controlled and no recurrence was observed. At 763 days and 1638 days after the commencement of SLIT, oclacitinib and SLIT were discontinued, respectively. Notably, 9 months after discontinuing SLIT, complete remission of CAD was observed.

***Discussion*:** ASIT is used in veterinary medicine to treat CAD. A comprehensive clinical study found that SLIT has a success rate of 55%. The oral mucosa's low pro-inflammatory cell counts underscores SLIT's safety. Considering its efficacy and safety, ASIT was initiated with SLIT. ASIT can take > 12 months to improve CAD. Therefore, oclacitinib was prescribed to control pruritus. Complete remission of CAD was confirmed at the time of writing 9 months after SLIT discontinuation. This case indicates that SLIT could be an effective and safe therapeutic option for the long-term management of CAD.

Keywords: dogs, canine atopic dermatitis, immunotherapy, sublingual immunotherapy.

DOI: 10.22456/1679-9216.135386

Received: 22 September 2023 Accepted: 21 December 2023 Published: 28 January 2024

[1]Laboratory of Veterinary Internal Medicine and Dermatology, College of Veterinary Medicine, Chungbuk National University (CBNU), Cheongju, Republic of South Korea. [2]College of Veterinary Medicine, Kyungpook National University (KNU), Daegu, Republic of South Korea. CORRESPONDENCE: B.-T. Kang [kangbt@cbnu.ac.kr]. Laboratory of Veterinary Internal Medicine and Dermatology, College of Veterinary Medicine - CBNU. Cheongju, Chungbuk 28644, Republic of South Korea.

INTRODUCTION

Canine atopic dermatitis (CAD) is a hereditary, pruritic, and inflammatory allergic skin disease associated with elevated IgE levels [6]. CAD is associated with a multifactorial combination of environmental and genetic factors that induce skin barrier impairment and dysregulated immune responses [11]. Many symptomatic treatments are available for CAD, such as glucocorticoids, oclacitinib, and cyclosporine; however, these treatments are unable to regulate the pathogenic mechanisms of the disease [4]. Allergen-specific immunotherapy (ASIT) is a CAD treatment that induces tolerance to pathogenic allergens [4]. Sublingual immunotherapy (SLIT) is effective, convenient, and safe [1,12]. This case report describes the successful treatment of a bitch with atopic dermatitis using SLIT.

CASE

A 3-year-old spayed bitch Dachshund presented with non-seasonal chronic pruritus and generalized alopecia. The onset of pruritus occurred at 6 months of age, and the pruritus visual analog scale (pVAS) score was 5 out of 10. The dog primarily lived indoors, and ectoparasite prevention was not performed over the last three years. There had no history of increased pruritus or food-induced gastrointestinal symptoms related to food consumption. Before presentation, the bitch was intermittently administered corticosteroids and antibiotics; however, clinical signs recurred upon medication discontinuation. Dermatological examination revealed alopecia and scales on the dorsum and tail, as well as and alopecia, lichenification, and crust on the medial side of the forelimbs (Figure 1). Differential diagnoses included microbial skin infections, fungal skin infections, ectoparasite infestations, and allergic skin diseases. Comprehensive diagnostic tests, including cytology, skin scraping, Wood's lamp, dermatophyte test medium (DTM), and Sabouraud's dextrose agar (SDA) culture, were performed. Cytology indicated the presence of *Malassezia* sp., cocci, and degenerated neutrophils in the axilla, dorsum, and tail. Deep skin scraping did not reveal ectoparasites. Wood's lamp examination found no fluorescence, and DTM and SDA cultures did not yield dermatophytes. Diagnostic tests confirmed superficial pyoderma and *Malassezia* dermatitis.

Itraconazole [Ashicona®[1] - 10 mg/kg, SID] was administered for the therapeutic diagnosis of dermatophytosis and treatment of *Malassezia* dermatitis. Shampoo Malaseb®[2] [chlorhexidine gluconate and miconazole nitrate] and Lactamox®[3] [amoxicillin/clavulanate 25 mg/kg, BID] were prescribed. To investigate the possibility of canine adverse food reaction (CAFR), an elimination diet trial was conducted using a commercial diet [Royal Canin hypoallergenic®][4].

Despite 4 days of antibiotic and antifungal treatment, pruritus and papules on the lower dorsum worsened. A week-long administration of ivermectin [Ivermed®][5] was employed as a therapeutic measure to rule out ectoparasite infection; however, clinical signs persisted without improvement. Subsequently, ivermectin was discontinued and prednisolone [Solondo®[6] - 0.5 mg/kg, SID] was prescribed to alleviate pruritus and to evaluate the response to glucocorticoids.

After 24 days of prednisolone administration, a significant reduction in pruritus was observed, and the lesions improved. Consequently, prednisolone[6] [0.5 mg/kg EOD] was tapered to and eventually discontinued 38 days following the initial administration. Upon discontinuation of prednisolone, cytology did not reveal any cocci or *Malassezia* sp. Since cocci were not detected on cytological examination, amoxicillin/clavulanate was discontinued. Similarly, itraconazole was also discontinued after 3 consecutive fungal cultures using DTM and SDA revealed negative results. The bitch responded well to oral prednisolone, fulfilled 5 Favrot's criteria, and was provisionally diagnosed with CAD.

Within 2 weeks of prednisolone discontinuation, pruritus recurred, and cytology did not indicate any infection. Therefore, this recurrence of the clinical signs of CAD is considered drug-responsive. Given the persistence of clinical signs for more than 3 months per year and the assumption that relapse of the clinical signs was drug-responsive, the bitch was planned to be managed with ASIT. An intradermal skin test (IDST) was scheduled to define IgE-mediated hypersensitivity and select allergens suitable for inclusion in ASIT. With IDST scheduled 2 weeks later, oclacitinib [Apoquel®[7] - 0.4 mg/kg, BID] was prescribed for 14 days as a substitute for prednisolone to control pruritus. A 12-week elimination diet trial was conducted, and pruritus and lesions were well managed with oclacitinib. Therefore, a provocative challenge was undertaken, and CAFR was excluded because clinical signs did not worsen.

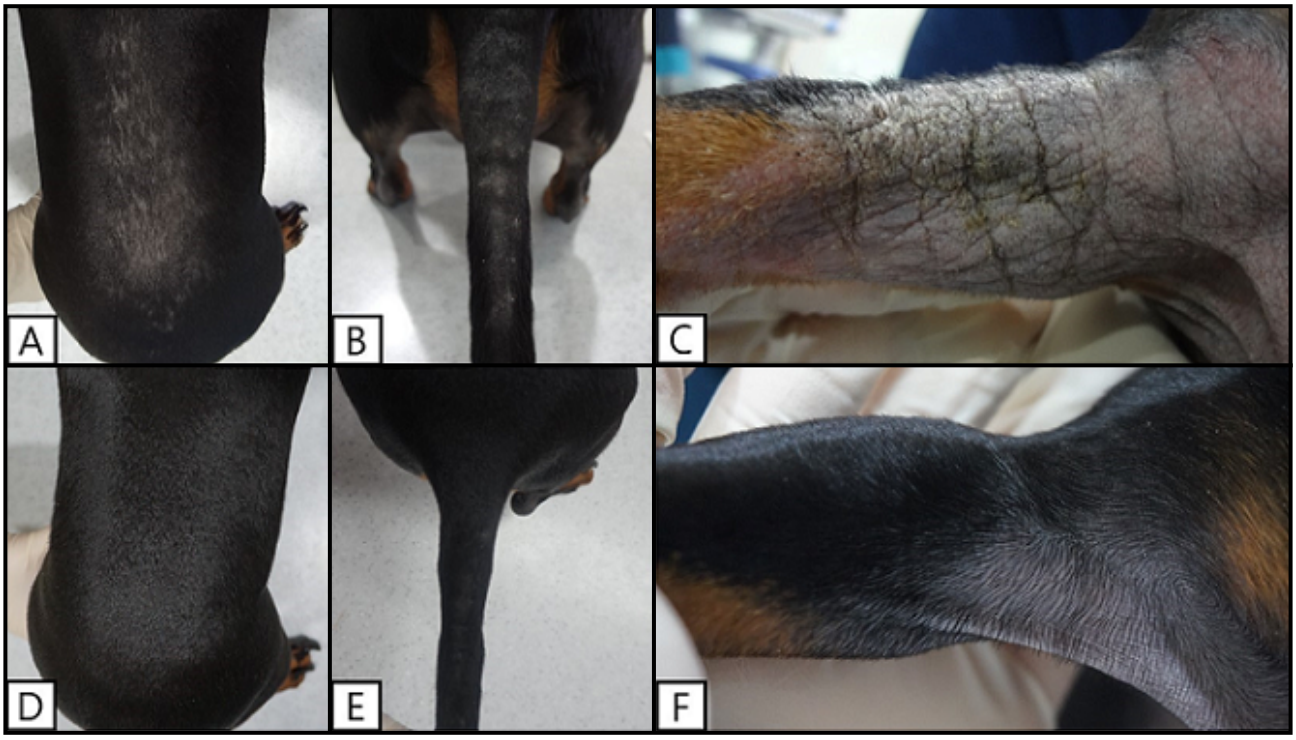

Figure 1. A 3-year-old spayed bitch Dachshund. A-C: Photographs of the physical examination at the initial visit. The pVAS was 5 out of 10. Alopecia and scale are observed on the lower dorsum (A) and tail (B). Lichenification and crust are observed on the medial side of the upper region of the forelimb (C). D-F: Photographs 9 months after discontinuing SLIT. The pVAS was 1. Note the marked improvement in lesions [Lower dorsum (D); Tail (E); Medial side of the upper region of the forelimb (F)].

Two weeks after oclacitinib administration, IDST was performed using commercial extracts of 27 allergens (Greer extracts®)[8]. The IDST showed positive reactions for *GS Rhizopus* Mix, Cat Epithelia, *Dermatophagoides farina,* and *D. pteronyssinus*. SLIT was initiated in accordance with the manufacturer's protocol, which included a 3-week build-up phase followed by a maintenance phase (Figure 2). The SLIT formulation comprised aqueous allergens selected from the positive IDST results (6800 protein nitrogen unit/mL) combined with 50% glycerin. Concurrent administration of SLIT and oclacitinib[7] [0.4 mg/kg, SID] effectively controlled pruritus (Figure 2).

At 301 days after the commencement of SLIT, oclacitinib was gradually tapered to assess the sole effect of SLIT. Recurrence of pruritus was observed upon tapering oclacitinib to [0.4 mg/kg] EOD. Resuming oclacitinib [0.4 mg/kg] SID effectively alleviated pruritus, prompting its continued prescription for 105 days. At 413 days after SLIT initiation, oclacitinib was progressively tapered over 1 year and eventually discontinued 763 days following the onset of SLIT. After oclacitinib discontinuation, no infections were identified, and pruritus was well managed. SLIT was discontinued 1638 days after onset to assess clinical signs without SLIT administration (Figure 2). At the time of writing, 9 months after SLIT discontinuation, no recurrence of clinical signs has been observed, affirming complete remission of CAD (Figures 1 & 2).

DISCUSSION

ASIT has been used in veterinary medicine for the treatment of CAD and is administered by subcutaneous injection or sublingual administration. A large clinical study reported that SLIT has a reasonable success rate of 55%, comparable to that of subcutaneous immunotherapy (SCIT) [1]. The oral mucosa has a lower number of pro-inflammatory cells such as mast cells and eosinophils, which lowers the risk of allergic inflammation. This property of the oral mucosa contributes to the safety of SLIT [12]. Considering its efficacy and safety, ASIT was initiated with SLIT in this case.

In human patients, side effects of SLIT, including itching, swelling of the lips, and inflammation under the tongue, have rarely been reported [10]. While in dogs, the most common side effects of SLIT include hypersalivation, oral itching, generalized pruritus, and erythema [9]. In this case, SLIT administration did not lead to any of these side effects and was well tolerated.

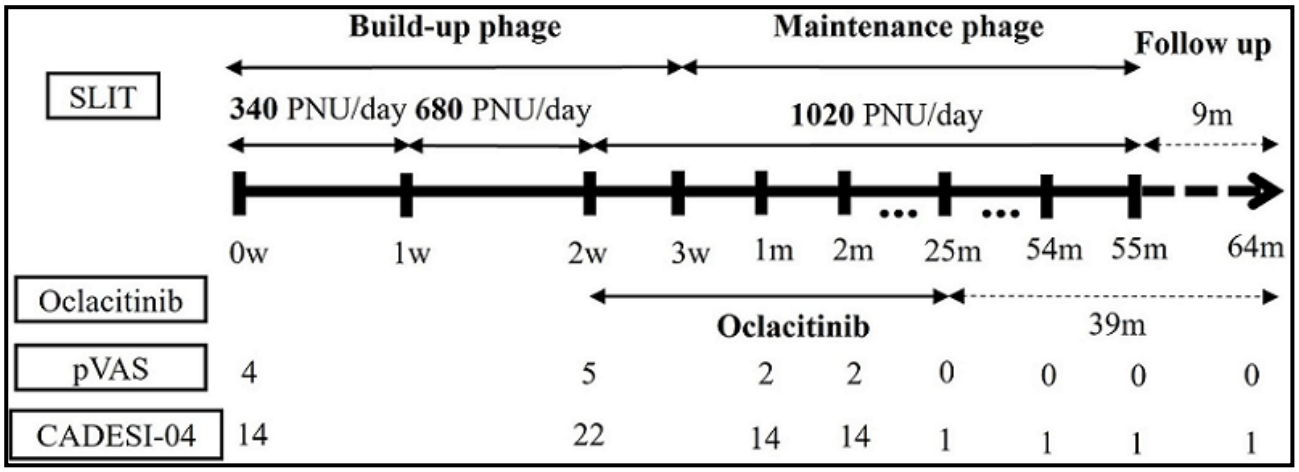

Figure 2. A 3-year-old spayed bitch Dachshund. Treatment history of SLIT and oclacitinib, and changes of pVAS and Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4 score. SLIT included 2 phases: a 3-week build-up phase followed by a maintenance phase. Diagram shows the treatment duration (straight lines) and duration after discontinuing treatment (dotted lines). At the time of writing, SLIT had been administrated for 55 months and discontinued for 9 months, and oclacitinib had been administrated for 25 months and discontinued for 39 months.

It is important to note that ASIT often necessitate > 12 months to show noticeable improvements in CAD. Therefore, during this period, systemic medication to control pruritus can be utilized. These medications not only manage pruritus but also affect the success rate of ASIT. Research investigating the impact of concurrent systemic medications to ASIT success has shown that dogs receiving a combination of SLIT and oclacitinib or SLIT and cyclosporine had a higher success rate compared to those treated with SLIT and glucocorticoid [4]. In another study investigating the safety of oclacitinib and cyclosporine in dogs, three times more gastrointestinal side effects were identified with cyclosporine than with oclacitinib [7]. Given its effectiveness and safety profile, oclacitinib was prescribed for pruritus control.

ASIT is the only treatment modality for CAD capable of modifying certain pathogenetic mechanisms [14]. ASIT modulates the cytokine profile from type 2 T helper cell-dominated responses to type 1 T helper cell responses, accompanying by an increase in regulatory T cells and interleukin-10 [8]. Notably, increases in allergen-specific IgG and decreases in allergen-specific IgE have been observed in dogs treated with ASIT [13]. Remarkably, similar changes have been noted in humans up to a year after ASIT termination. In this case, the maintenance of remission after termination of SLIT may have been induced by this change [3]. In a study that identified the owner's assessment of CAD treatment, 4 of 90 dogs had complete remission with ASIT [2]. In another study, 1 of 7 dogs treated with SLIT showed complete CAD remission [5]. These dogs showed complete remission of clinical signs, eliminating the need for further ASIT. In this case, dog achieved complete CAD remission at the time of writing 9 months after discontinuing SLIT. The dog did not require any anti-allergic treatment, and pruritus was effectively managed without infection recurrence.

After discontinuing ASIT, clinical signs of CAD often recur in humans [8]. Therefore, it is recommended that owners monitor their dogs for any CAD recurrence.

The use of SLIT in this dog ensured the complete remission of CAD without any side effects. The findings strongly suggest that SLIT holds promise as an effective and safe therapeutic option for the long-term management of CAD.

MANUFACTURERS

[1]Ashish Life Science. Maharashtra, India.
[2]Dechra Veterinary Products. Uldum, Denmark.
[3]A Progen Pharma. Gyeonggi-do, South Korea.
[4]Royal canin. Aimargues, France.
[5]Mediispecs. Tamil Nadu, India.
[6]Yuhan. Seoul, South Korea.
[7]Zoetis Inc. Parsippany-Troy Hills, NJ, USA.
[8]Greer Laboratories Inc. Lenoir, NC, USA.

Acknowledgments. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1A2C1012058) and the Basic Research Lab Program (2022R1A4A1025557) through the NRF of Korea, funded by the Ministry of Science and ICT.

Declaration of interest. The authors declare no conflicts of interest. The authors are solely responsible for the content and writing of the article.

REFERENCES

1 **DeBoer D.J. & Morris M. 2012.** Multicentre open trial demonstrates efficacy of sublingual immunotherapy in canine atopic dermatitis. *Veterinary Dermatology*. 23(1): 65.

2 **Dell D.L., Griffin C.E., Thompson L.A. & Griffies J.D. 2012.** Owner assessment of therapeutic interventions for canine atopic dermatitis: a long-term retrospective analysis. *Veterinary Dermatology*. 23(3): 228-e47. DOI: 10.1111/j.1365--3164.2012.01054.x.

3 **Durham S.R., Emminger W., Kapp A., Colombo G., de Monchy J.G., Rak S., Scadding G.K., Andersen J.S., Riis B. & Dahl R. 2010.** Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *The Journal of Allergy and Clinical Immunology*. 125(1): 131-138. DOI: 10.1016/j.jaci.2009.10.035.

4 **Fennis E.E.M., van Damme C.M.M., Schlotter Y.M., Sinke J.D., Leistra M.H.G., Bartels R.T. & Broere F. 2022.** Efficacy of subcutaneous allergen immunotherapy in atopic dogs: A retrospective study of 664 cases. *Veterinary Dermatology*. 33(4): 321-375. DOI: 10.1111/vde.13075.

5 **Fischer N.M., Rostaher A. & Favrot C. 2020.** A comparative study of subcutaneous, intralymphatic and sublingual immunotherapy for the long-term control of dogs with nonseasonal atopic dermatitis. *Veterinary Dermatology*. 31(5): 365-396. DOI: 10.1111/vde.12860.

6 **Halliwell R. 2006.** Revised nomenclature for veterinary allergy. *Veterinary Immunology and Immunopathology*. 114(3-4): 207-208. DOI: 10.1016/j.vetimm.2006.08.013.

7 **Little P.R., King V.L., Davis K.R., Cosgrove S.B. & Stegemann M.R. 2015.** A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs. *Veterinary Dermatology*. 26(1): 23-28. DOI: 10.1111/vde.12186.

8 **Loewenstein C. & Mueller R.S. 2009.** A review of allergen-specific immunotherapy in human and veterinary medicine. *Veterinary Dermatology*. 20(2): 84-98. DOI: 10.1111/j.1365-3164.2008.00727.x.

9 **Maina E. & Cox E. 2016.** A double blind, randomized, placebo controlled trial of the efficacy, quality of life and safety of food allergen-specific sublingual immunotherapy in client owned dogs with adverse food reactions: a small pilot study. *Veterinary Dermatology*. 27(5): 361-391. DOI: 10.1111/vde.12358.

10 **Maina E., Pelst M., Hesta M. & Cox E. 2017.** Food-specific sublingual immunotherapy is well tolerated and safe in healthy dogs: a blind, randomized, placebo-controlled study. *Biomedcentral Veterinary Research*. 13(1): 25. DOI: 10.1186/s12917-017-0947-1.

11 **Marsella R. 2021.** Advances in our understanding of canine atopic dermatitis. *Veterinary Dermatology.* 32(6): 547-451. DOI: 10.1111/vde.12965.

12 **Moingeon P., Batard T., Fadel R., Frati F., Sieber J. & Van Overtvelt L. 2006.** Immune mechanisms of allergen--specific sublingual immunotherapy. *Allergy*. 61(2): 151-165. DOI: 10.1111/j.1398-9995.2006.01002.x.

13 **Mueller R.S., Jensen-Jarolim E., Roth-Walter F., Marti E., Janda J., Seida A.A. & DeBoer D. 2018.** Allergen immunotherapy in people, dogs, cats and horses - differences, similarities and research needs. *Allergy*. 73(10): 1989-1999. DOI: 10.1111/all.13464.

14 **Olivry T., DeBoer D.J., Favrot C., Jackson H.A., Mueller R.S., Nuttall T., Prélaud P. & International Committee on Allergic Diseases of Animals. 2015.** Treatment of canine atopic dermatitis: 2015 updated guidelines from the International Committee on Allergic Diseases of Animals (ICADA). *Biomedcentral Veterinary Research*. 11: 210. DOI: 10.1186/s12917-015-0514-6.