수의학석사학위논문

Evaluation of Oclacitinib on Skin Barrier Function in Dogs with Allergic Dermatitis

알레르기성 피부염을 지닌 개에서 Oclacitinib의 피부장벽 기능에 대한 평가

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김 현 정

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ABSTRACT

Pruritus is one of the main factors in the progression of canine allergic dermatitis. Pruritus-inducing behaviors, such as scratching and rubbing, impair the skin barrier. Consequently, the damaged skin barrier aggravates the severity of allergic dermatitis by enhancing penetration of allergens. Oclacitinib is a janus kinase 1 (JAK-1) inhibitor that blocks the signals of IL-31, a pruritogenic cytokine. Because of the mechanism, oclacitinib has been used to reduce pruritus in dogs with allergic dermatitis. The purpose of the study was to evaluate the effect of oclacitinib on skin barrier

function in dogs with allergic dermatitis by measuring transepidermal water loss (TEWL), while assessing its efficacy and safety. Oclacitinib was administered for 84 days; twice a day for the first 2 weeks and then once a day for the remaining period (day 0-28: n=22, day 29-84: n=8). In addition to TEWL, the canine atopic dermatitis extent and severity index-4 (CADESI-4), pruritus visual analog scale (PVAS) and owner satisfaction were measured to evaluate the efficacy of oclacitinib on days 0, 14, 28, 56, and 84. Any abnormal health conditions during the experimental period were recorded and blood samples were collected on days 0, 28, and 84 to evaluate the safety of the medication. The administration of oclacitinib decreased both CADESI-4 and PVAS values significantly from baseline at all assessment points, regardless of the daily dosage (p<0.05). Unlike CADESI-4 and PVAS, TEWL values decreased significantly from baseline only on day 14 for the total TEWL value, including ventral neck and axilla-specific TEWL values (p<0.05). In conclusion, oclacitinib was found to exert a remarkable effect on skin barrier function when the drug was administered twice daily. Although the skin barrier function seemed to be aggravated with the reduction in daily dosage, the changes did not markedly affect visible skin condition or the severity of pruritus. Most owners were content with the oclacitinib treatment for their dogs and the medication was used safely in most patients without causing any significant adverse events. Therefore, this study showed that oclacitinib was effective and safe treatment for the control of canine allergic dermatitis.

Keywords: allergic dermatitis, oclacitinib, skin barrier function, pruritus, dog

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CONTENTS

INTRODUCTION

Pruritus plays a major role in the progression of canine allergic dermatitis [7]. The unpleasant sensation due to allergic dermatitis could make dogs scratch, rub, or lick their bodies, and these behaviors cause skin damage [22]. Through the impaired skin barrier, the penetration of allergens is facilitated [5] and cause inflammatory process that potentially induces pruritus resulting in scratching, which is called “pruritus-scratch” cycle [22]. In this cycle, nervous system is known to be a crucial component of pruritus [22]. Pruritus mediators that are released upon inflammation stimulate the receptors on pruritus-specific sensory neurons, which convey signals to the region of the brain associated with pruritus sensation [22]. In the neuronal pathway, interleukin (IL)-31 plays a key role as a pruritogenic cytokine by activating janus kinase (JAK) 1 enzyme which is involved in signal transduction of various pruritogenic, pro-inflammatory, and pro-allergic cytokines [1, 6, 8, 19, 21]. This concept has led many researchers to have increased interest in the interaction between IL-31 and JAK 1 to control the vicious cycle of canine allergic dermatitis.

Oclacitinib (Apoquel® , Zoetis ; FlorhamPark, NJ, USA) is a predominant JAK-1 inhibitor that blocks the signals of IL-31 [3, 8]. With the feature of oclacitinib, it targets pruritus-associated neuronal pathways and it has been suggested as a new alternative medication for dogs with allergic dermatitis [3, 7, 11]. The efficacy of oclacitinib has been proved in many studies through evaluation of canine atopic dermatitis extent and severity index (CADESI) and pruritus visual analog scale (PVAS) [3, 4]. CADESI is an

index for grading skin lesions [18] and PVAS is a scale used for the assessment of pruritus intensity [9].

In addition to these two methods, transepidermal water loss (TEWL) which is defined as the amount of water passing from inside a body to the outside through the epidermis has been used as a research tool to evaluate skin barrier function not only in human but also in canine dermatology [2, 5, 10, 24]. Dogs with allergic dermatitis are known to have impaired skin barrier function and higher TEWL values than dogs with healthy skin [2, 17]. Since impaired skin barrier function is considered a crucial factor for allergic sensitization by increasing allergen penetration [13], TEWL assessment has been used to evaluate the effect of skin treatments in dogs with allergic dermatitis such as atopic dermatitis [10, 24]. However, the effect of oclacitinib on TEWL in canine allergic dermatitis has not been assessed so far. Therefore, this study was to evaluate the effect of oclacitinib on skin barrier function via TEWL assessment and to investigate its efficacy and safety in canine allergic dermatitis.

MATERIALS AND METHODS

1. Study design

The present study was a non-blinded, single-arm trial. Basically, all dogs that participated in the study were required to receive oclacitinib (Apoquel®, Zoetis; FlorhamPark, NJ, USA) for at least 28 days ± 2 days and some of them whose owners approved the extended treatment continued to receive oclacitinib up to day 84 ± 2 days. Assessments were carried out on days 0, 14, 28, 56, and 84.

2. Animals and management

All animals were client-owned dogs diagnosed as allergic dermatitis. The diagnosis of allergic dermatitis was based on medical history, typical clinical signs, positive results of serum allergen-specific IgE test, food elimination trials to confirm food allergy, and/or intradermal skin test. The dogs were fed on commercial hypoallergenic diets during oclacitinib treatment. The exclusion criteria included dogs with ectoparasitosis and severe infection; dogs with immunosuppressive conditions such as demodicosis, hyperadrenocorticism, hypothyroidism, or progressive malignant tumor; dogs that did not receive proper medication; dogs withdrawn from the study by their owners for any reason; and pregnant dogs and lactating bitches. They were not allowed to receive any immunosuppressive drugs such as glucocorticoids or cyclosporine but allowed to take antibiotics if needed. The

purpose of the study was fully explained to the owners and written informed consent was obtained from all owners.

3. Drug administration

Dogs were administered with oclacitinib at a dose of 0.4-0.6 mg/kg orally twice a day for 14 days and then once a day as maintenance therapy. Day 1 was defined as the first day of dosing.

4. Evaluation Procedure

4.1 Lesion severity

CADESI-4 is a four-point scale used to score lesion severity. It was designed to score skin lesions such as erythema, lichenification, alopecia, and excoriation as follows: none (score 0), mild (score 1), moderate (score 2), and severe (score 3) [18]. The maximal score of CADESI-4 is 180 and the proposed limits of mild, moderate, and severe skin lesions are 10, 35, and 60, respectively [18]. CADESI-4 was evaluated only for dogs that received oclacitinib as scheduled and it was measured by a designated veterinarian to minimize data variation.

4.2 Pruritus

The PVAS scale consists of six levels of pruritus, represented on a 10-cm line, categorized as follows [3]: normal dog with no itching (0 cm); very mild and occasional episodes of itching (2 cm); more frequent episodes of mild itching when the dog is awake with occasional episodes of itching at night (4 cm); regular episodes of moderate itching when the dog is awake (6 cm); prolonged episodes of severe itching when the dog is awake and even when the dog is eating, playing, exercising, or distracted (8 cm); extremely severe itching with continuous scratching, chewing and/or licking, regardless of the surrounding circumstances or activities of the dog (10 cm). PVAS was evaluated only for dogs that received oclacitinib as scheduled and it was measured by the respective owners.

4.3 Skin barrier function

TEWL was evaluated with evaporimeter (vapometer® SWL-3, Delfin Technologies Ltd., Kuopio, Finland), a closed chamber that is unaffected by ambient air flows, thereby reducing the variability in values [2]. The procedure was carried out in a designated room to minimize possible variations in ambient temperature and humidity. The ambient temperature (20-23℃) and relative humidity (20-40%) of the room were within the manufacturer's recommended range. On the day of assessment, dogs were not allowed to be washed [20]. TEWL measurement was carried out three times for each site on each designated day and then the median values were used for analysis. The normal TEWL range has not been established in dogs

yet but in humans. The mean TEWL values were reported to be 8.2 ± 4.9 g/h/m^2 for forearm anterior, 18.3 ± 9.4 g/h/m^2 for forehead, and 13.1 ± 7.1 g/h/m^2 for cheek in healthy women [14]. The regions for the TEWL measurement were chosen based on the density of hair as follows: left side of medial pinna, ventral neck, axilla, and inguinal regions, since the TEWL values measured on the sparsely haired regions such as ear and inguinal regions are known to show no significant changes over 48 hours [16]. In this study, total TEWL values with the sum of TEWL for all four regions and region-specific TEWL values were analyzed respectively. TEWL were evaluated only for dogs that received oclacitinib as scheduled and it was measuerd by a designated veterinarian to minimize data variation.

4.4 Owner satisfaction

The owners were asked if they were satisfied with the oclacitinib treatment for their dogs on each assessment day. The extent of owner satisfaction was expressed on a scale of 1−100 points and the results were categorized as follows: 100-75, strongly satisfied; 74-50, satisfied; 49-25, neutral; and 24-1, dissatisfied.

4.5 Safety

All dogs received at least one dose of oclacitinib and were included in safety assessment. Any abnormal health conditions during the study were recorded by asking owners on every designated assessment day and they

were required to report any adverse events occurred to their dogs on oclacitinib treatment by making a call when they were away from a hospital. Hematologic and serum chemical parameters were evaluated on days 0, 28, and 84.

5. Statistical analyses

Efficacy assessments were analyzed with IBM SPSS statistics software, version 23 (SPSS Inc., Chicago, IL, USA). Normality of values was assessed by Shapiro-Wilk test. To compare the difference in results between baseline and each assessment point for different dosages, a paired t-test or Wilcoxon signed rank test was used based on the normality of values. p-values < 0.05 were considered statistically significant.

RESULTS

1. Demographics

In total, 24 dogs were enrolled in the study. Shih-tzu (20.8%) and Poodle (16.6%) were the most common breeds and the rest was comprised of Maltese, Dachshund, Labrador Retriever, French Bulldog, Beagle, Lakeland Terrier, Bull Terrier, Bichon Frise, and Pekingese. All dogs were pure breeds with 33.3% female and 66.6% male dogs of which 12.5% of the dogs were sexually intact. The mean age was 6.9 (1-14) years and the mean weight was 9.1 (3.2-32) kg (Table 1). Prior to the administration of oclacitinib, the mean values of CADESI and PVAS were 56.5 ± 19.7 and 6.9 ± 1.6, respectively. The TEWL median values on day 0 were as follows: 24.3 (13.8-47.9) g/h/m^2 on Lt. medial pinna, 40.0 (25.2-116.8) g/h/m^2 on Lt. ventral neck, 29.0 (16.0-88.4) g/h/m^2 on Lt. axilla, and 12.7 (9.4-22.1) g/h/m^2 on Lt. inguinal area, with a total value of 107.1 (71.2-311.6) g/h/m^2.

2. Study completion

Among the 24 dogs enrolled, two dogs were withdrawn due to the occurrence of demodicosis during the study. Therefore, a total of, 22 dogs were administered with oclacitinib at least for 28 days (± 2 days). Among the 22 dogs, 8 continued to receive the medication up to day 84 (± 2

days).

3. Clinical evaluation

3.1 Lesion severity

The mean CADESI-4 values declined significantly from 56.5 ± 19.7 to 35.0 ± 20.1, 31.7 ± 21.8, 23.4 ± 12.5, and 25.3 ± 11.0 on days 14, 28, 56, and 84, respectively (p<0.05; Figure 1).

3.2 Pruritus

The mean PVAS values declined significantly from 6.9 ± 1.6 to 2.4 ± 1.5, 4.3 ± 1.8, 3.2 ± 2.3, and 2.4 ± 1.6 on days 14, 28, 56, and 84, respectively (p < 0.05; Figure 2). Although the values tend to rebound on day 28, values on day 56 and 84 showed a decreasing trend.

3.3 Skin barrier function

With regard to region-specific TEWL values, the results varied depending on the measured regions. Significant differences were observed only on day 14 for the left side of ventral neck and axilla (p<0.05; Figure 3A). The median TEWL values of ventral neck reduced from 40.0 (14.8-76.8) to 23.3

(7.8-11.4) g/h/m^2, and the values of axilla reduced from 29.0 (13.0-59.5) to 17.2 (5.6-9) g/h/m^2 on day 14. In case of the left side of medial pinna and inguinal region, no significant differences were observed during the study (Figure 3A). In case of total TEWL, all the median values following treatment were lower than the value of baseline. However, the significant difference was founded only on day 14 by decreasing from 107.1 (71.2-311.6) g/h/m^2 to 68.7 (53.0-109.3) g/h/m^2 (p<0.05; Figure 3B).

3.4 Owner satisfaction

The percentage of owners with a score more than 75 out of 100 points (a rating of highly satisfied), was 76.2, 52.4, 87.5, and 87.5% on days 14, 28, 56, and 84, respectively. The percentage of owners with a score between 50 and 74 (a rating of satisfied), was 28.6, 47.6, 0, and 12.5% on days 14, 28, 56, and 84 respectively. The percentage of owners with a score between 25 and 49 (a rating of neutral), was 0, 4.8, 12.5, and 0% on days 14, 28, 56, and 84, respectively. No scores of less than 25 (a rating of dissatisfied) were recorded for the oclacitinib treatment (Figure 4).

4. Safety evaluation

4.1 Abnormal clinical signs

Among the 24 dogs enrolled, 2 were withdrawn from the study due to

the occurrence of demodicosis within the first 4 weeks of therapy. The abnormal clinical signs were as follows: vomiting (16.6%, 4 dogs), lethargy (12.5%, 3 dogs), polydipsia (8.3%, 2 dogs), aggression, anorexia, and diarrhea (4.1%, 1 dog each). Most clinical signs were mild, transient, and resolved spontaneously with continued dosing. Cystitis and pancreatitis were also found (4.3%, 1 dog each) and the administration of oclacitinib was temporally skipped while resolving the adverse events.

4.2 Hematology and serum chemistry

Most of the changes in hematological and serum chemistry values were minor, remained within laboratory reference ranges, nor accompanied with any clinical signs. There were a few remarkable changes such as a decrease in neutrophil or platelet count (12.5%, 3 dogs each) and an increase in total cholesterol (16.6%, 4 dogs), alanine aminotransferase (ALT) (8.3%, 2 dogs), and alkaline phosphatase (ALP) (4.1%, 1 dog).

4.3 Concomitant medications

Various antibiotics such as amoxicillin, cefovecin, cephalexin and ciprofloxacin were administered during the study. Among the 22 dogs which finished the study as scheduled, 7 (31.8%) received antibiotics temporally due to the mild infection that occurred before oclacitinib treatment, but these animals did not show any adverse events during the administration of antibiotics.

DISCUSSION

The present study proved that oclacitinib improved visible skin lesions and the severity of pruritus associated with canine allergic dermatitis as confirmed through assessment of CADESI-4 and PVAS values, which were similar to the results of previous studies [3, 4, 12]. Even though PVAS values showed a fluctuating pattern, both CADESI-4 and PVAS values after treatment significantly reduced from their baseline regardless of the daily dosages administered during the study. It is believed that the observed pattern in PVAS values was related to the daily dosage reduction, since many owners reported that their dogs seemed to scratch more often when the daily dosage was reduced to half by reducing its frequency from twice to once daily.

Regarding the effect of oclacitinib on skin barrier function, total TEWL values were more influenced by the daily dosage of oclacitinib than the other two parameters were, especially CADESI-4. In the present study, significant changes in total TEWL values including ventral neck and axilla-specific values from baseline were reported only on day 14 when oclacitinib was administered twice daily. However, no significant differences were observed after the dosage was reduced to half i.e., from twice daily to once daily. The changes in TEWL values might be related to the increased severity of pruritus due to the reduction of daily dosage after the first 2 weeks of treatment. The daily dosage reduction might trigger and increase pruritus-related behaviors such as scratching or rubbing, as shown in the

results of PVAS, and these behaviors might damage the skin barrier resulting in the increase in TEWL values. However, the extent of skin barrier damage did not seem severe enough to aggravate visible skin lesions, since all the CADESI-4 values following treatment significantly reduced from baseline regardless of the daily dosages. This can be explained by the fact that the TEWL evaluation detects disturbances in the protective function of skin barrier at an early stage, even before they are visible [15]. In the present study, both total TEWL and region-specific TEWL were analyzed. For a better understanding of the effect of oclacitinib on skin barrier function, the assessment of total TEWL seemed to be more reliable than the assessment of a region specific TEWL since all dogs had lesions at different regions and if an investigator selects only one or a few regions for TEWL assessment, the result could be biased. In a previous study analyzing the influence of cyclosporine on TEWL, the mean TEWL value was calculated from 10 different regions and showed a significant decline with cyclosporine treatment; 6 out of 10 regions contributed to the statistical significance [24]. Similarly, the present study, two of the four regions contributed to the statistical significance of total TEWL.

During the study, most owners found the oclacitinib treatment acceptable for their dog. In particular, the majority of owners showed strong satisfaction throughout the study period. Although the percentage of owners who were 'strongly satisfied' decreased sharply on day 28, when the frequency of the daily dosage was reduced to half, this percentage dramatically rebounded on day 56 and accounted for a high portion of owners until the end of the study, similar to the results for PVAS. From the evaluation of the owners, it was inferred that the abrupt reduction of daily dose could negatively influence the owner's compliance for the therapy.

With respect to the recovery pattern in PVAS and the owner satisfaction scores from day 56 onwards, it would be important to explain the fluctuations of the effect of oclacitinib to owners before starting therapy, in order to enhance compliance.

Regarding safety, treatment with oclacitinib did not cause any significant adverse events and most of them were mild and transient. There were a few dogs that required cessation and temporary discontinuation of oclacitinib treatment due to the development of adverse events such as demodicosis, cystitis, and pancreatitis. First, one dog diagnosed with demodicosis was incorrectly administered oclacitinib with the wrong regimen (twice daily for 3 weeks) by the owner. Second, the dog that developed cystitis was found to have a medical history of cystitis before the oclacitinib treatment. Finally, in the case of the dog diagnosed as pancreatitis, oclacitinib administration was repeated after the resolution of pancreatitis and the adverse event did not reoccur. Therefore, it was unclear if oclacitinib was responsible for the adverse events. For concomitant medication, various antibiotics were used temporarily during oclacitinib administration and these combination therapies were well tolerated by most dogs. With regard to the parameters of clinical pathology, abnormal changes outside of the reference ranges were observed in some dogs. However, most of these were transient and unaccompanied by any correlated clinical signs. In one dog, ALP levels increased above the reference range during the study. However, the dog was found to have a high ALP level before oclacitinib treatment and no abnormal clinical signs were accompanied.

The present study was limited by several factors. First, the number of dogs receiving oclacitinib up to 84 days was small. For a better understanding of

the result of oclacitinib administration for more than 1 month, a further study with larger number of dogs might be needed. Second, the subjects were client-owned dogs. Because of the background, it was somewhat difficult to control all the factors that could affect TEWL values. Although we guided the owners on what to avoid during the trial, a few of them patted their dogs with a dry towel or had their dogs clipped on or near the day of assessment. Since towel drying and clipping are known to increase TEWL by causing damage to skin [16, 23], it is assumed that these behaviors diluted the possible positive effect of oclacitinib on skin barrier function.

In conclusion, the present study proved that oclacitinib improved skin barrier function by reducing the total TEWL value including some region-specific TEWL values significantly from baseline when administered twice daily. Even though TEWL tended to get worsen with the reduction of daily dosage by half, the change did not markedly aggravate the visible skin condition and the severity of pruritus compared to that at baseline as confirmed by the CADESI-4 and PVAS values. Lastly, most owners were satisfied with oclacitinib treatment throughout the study and the medication was used safely in most patients without causing any severe adverse effects. Therefore, oclacitinib was proven effective and safe for the control of canine allergic dermatitis throughout the study.

Table 1. Baseline characteristics of enrolled dogs

Case	Breed	Age	Sex	Weight
1	Shih-tzu	14	Castrated Male	7.1
2	Shih-tzu	8	Castrated Male	5.8
3	Shih-tzu	9	Spayed Female	4.4
4	Maltese	8	Castrated Male	3.4
5	Dachshund	10	Castrated Male	7.2
6	Shih-tzu	10	Castrated Male	6.7
7	Poodle	2	Spayed Female	3.6
8	Golden Retriever	2	Female	32
9	French Bulldog	8	Spayed Female	9.6
10	Beagle	14	Castrated Male	17.6
11	Lakeland Terrier	1	Spayed Female	6.3
12	Poodle	4	Castrated Male	3.2
13	Bull terrier	7	Female	15.5
14	Maltese	6	Castrated Male	4.9
15	Bull dog	4	Spayed Female	17
16	Maltese	6	Castrated Male	5.1
17	Beagle	14	Castrate Male	17.6
18	Bichon Frise	5	Spayed Female	4.7
19	French Bulldog	2	Castrated Male	20.2
20	Poodle	2	Castrated Male	4
21	Pekingese	13	Castrated Male	5.9
22	Bichon Frise	5	Castrated Male	6.7

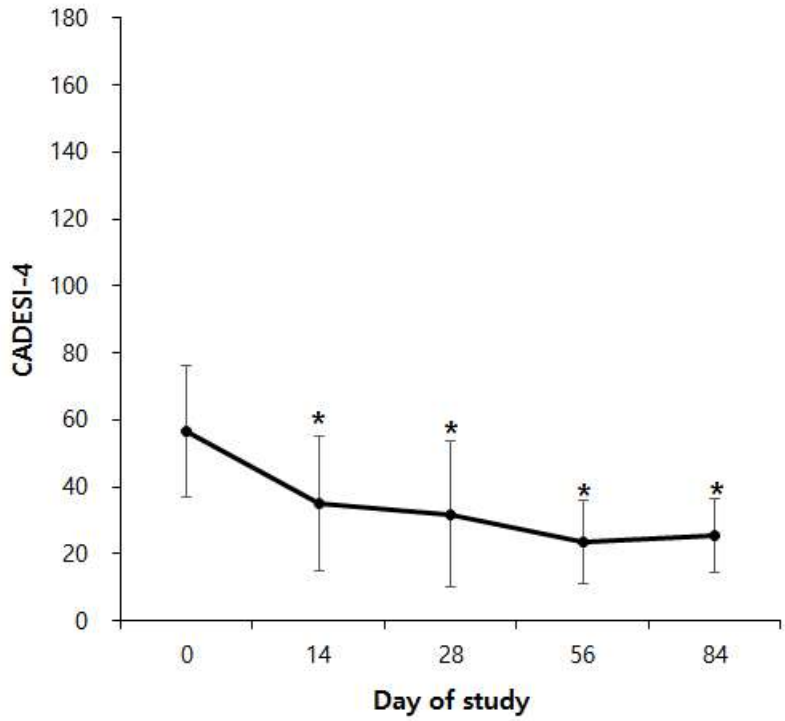

Figure 1. Changes in canine atopic dermatitis extent and severity index-4 values. (Day 0-14: n = 22, Day 56-84: n = 8) Results are expressed as mean value ± SD. * ; significant difference from baseline (p<0.05).

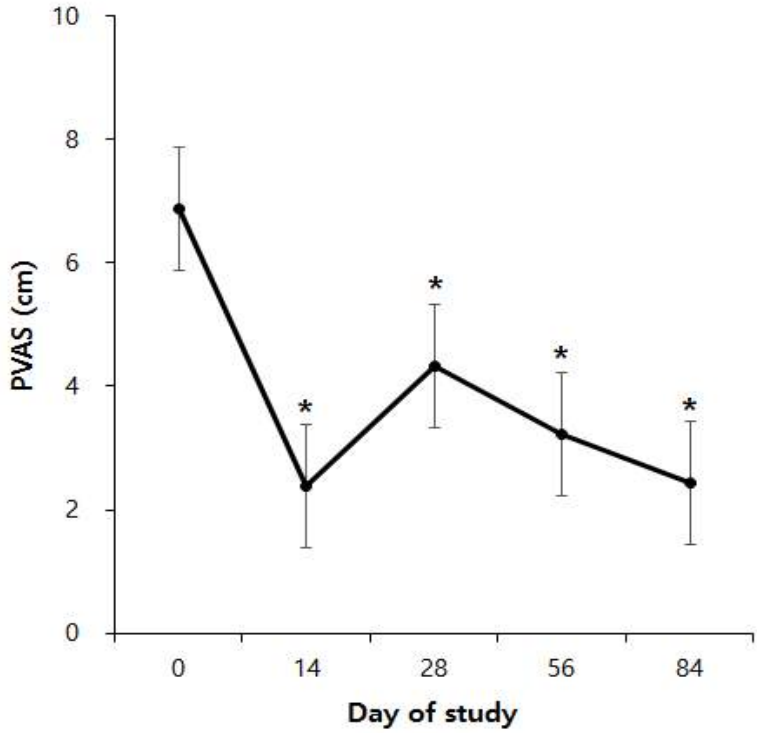

Figure 2. Changes in pruritus visual analog scale values.
(Day 0-14: n = 22, Day 56-84: n = 8). Results are expressed as mean value ± SD. * ; significant difference from baseline (p<0.05).

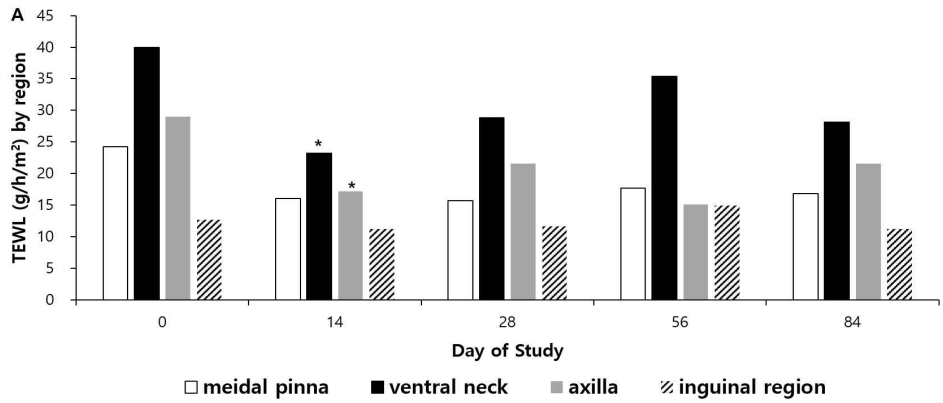

Figure 3A. Changes in regional transepidermal water loss values. (Day 0-14: n = 22, Day 56-84: n = 8). * ; significant difference from baseline (p<0.05).

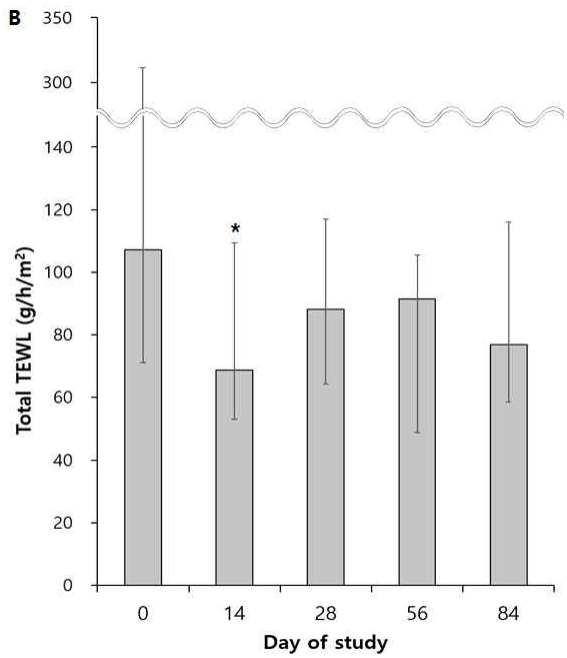

Figure 3B. Changes in total transepidermal water loss values. (Day 0-14: n = 22, Day 56-84: n = 8). Results are expressed as median value with IQR. * ; significant difference from baseline (p<0.05).

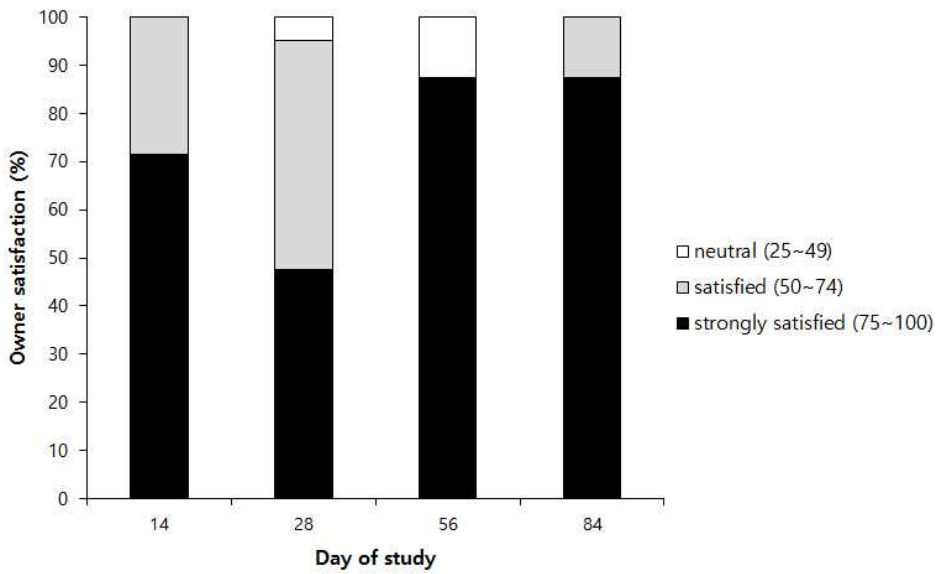

Figure 4. Owner satisfaction.

References

1. Carmi-Levy I, Homey B, Soumelis V. A modular view of cytokine networks in atopic dermatitis. *Clin Rev Allergy Immunol* 2011;41:245-253.

2. Cornegliani L, Vercelli A, Sala E et al. Transepidermal water loss in healthy and atopic dogs, treated and untreated: a comparative preliminary study. *Vet Dermatol* 2012;23:41-44.

3. Cosgrove SB, Wren JA, Cleaver DM et al. Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis. *Vet Dermatol* 2013;24:479-487.

4. Cosgrove SB, Wren JA, Cleaver DM et al. A blinded, randomized, placebo‐controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel®) in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2013;24:587-597.

5. Del Rosso JQ. Repair and maintenance of the epidermal barrier in patients diagnosed with atopic dermatitis: an evaluation of the components of a body wash-moisturizer skin care regimen directed at management of atopic skin. *J Clin Aesthet Dermatol* 2011;4:45-55.

6. Felsburg P. Overview of immune system development in the dog: comparison with humans. *Hum Exp Toxicol* 2002;21:487-492.

7. Gadeyne C, Little P, King VL et al. Efficacy of oclacitinib (Apoquel®) compared with prednisolone for the control of pruritus and clinical signs associated with allergic dermatitis in client-owned dogs in Australia. *Vet Dermatol* 2014;25:512-518.

8. Gonzales AJ, Humphrey WR, Messamore JE et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013;24:48-53.

9. Hill P, Lau P, Rybnicek J. Development of an owner-assessed scale to measure the severity of pruritus in dogs. *Vet Dermatol* 2007;18: 301-308.

10. Jung JY, Nam EH, Park SH et al. Clinical use of a ceramide-based moisturizer for treating dogs with atopic dermatitis. *J Vet Sci* 2013; 14:199-205.

11. Little PR, King VL, Davis KR et al. A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs. *Vet Dermatol* 2015;26:23-30.

12. Marsella R. Are transepidermal water loss and clinical signs correlated in canine atopic dermatitis? A compilation of studies. *Vet Dermatol* 2012;23:238-243.

13. Marsella R, and Samuelson D. Unravelling the skin barrier: a new paradigm for atopic dermatitis and house dust mites. *Vet Dermatol*

2009;20:533-540.

14. Mayrovitz HN, Bernal M, Brlit F et al. Biophysical measures of skin tissue water: variations within and among anatomical sites and correlations between measures. *Skin Res Technol* 2013;19:47-54.

15. Mündlein M, Valentin B, Chabicovsky R et al. Comparison of transepidermal water loss (TEWL) measurements with two novel sensors based on different sensing principles. *Sens. Actuators, A* 2008;142:67-72.

16. Oh WS, Oh TH. Measurement of transepidermal water loss from clipped and unclipped anatomical sites on the dog. *Aust Vet J* 2009; 87:409-412.

17. Olivry T. Is the skin barrier abnormal in dogs with atopic dermatitis? *Vet Immunol Immunopathol* 2011;144;11-16.

18. Olivry T, Saridomichelakis M, Nuttall T et al. Validation of the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4, a simplified severity scale for assessing skin lesions of atopic dermatitis in dogs. *Vet Dermatol* 2014;25:77-85.

19. Ong PY, Leung DM. Immune dysregulation in atopic dermatitis. *Curr Allergy Asthma Rep* 2006;6:384-389.

20. Pinnagoda J, Tupker RA, Agner T et al. Guidelines for transepidermal water loss (TEWL) measurement. A report from the Standardization Group of the European Society of Contact Dermatitis.

Contact Dermatitis 1990;22:164-178.

21. Schindler C, Levy DE, Decker T. JAK-STAT signaling: from interferons to cytokines. *J Biol Chem* 2007;282:20059-20063.

22. Steinhoff M, Bienenstock J, Schmelz M et al. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. *J Invest Dermatol* 2006;126:1705-1718.

23. Voegeli D. The effect of washing and drying practices on skin barrier function. *J Wound Ostomy Continence Nurs* 2008;35:84-90.

24. Zając M, Szczepanik M, Wilkołek P et al. The influence of non-specific anti-pruritus treatment with cyclosporine A on transepidermal water loss (TEWL) in natural atopic dermatitis in dogs *Pol J Vet Sci* 2015;18:415-424.

25. Report for a clinical trial for the evaluation of the efficacy and the adverser effects of Oclacitinib Apoquel® in client-owned dogs with allergic dermatitis, Zoetis Korea 2016

Supplement 1. Consent form of the study

알러지 환자에 대한 Oclacitinib의 유효성 및 안전성 평가 임상시험 참가 동의서

환자명: **나이:** **성별:**

품종:

보호자명: **연락처:**

Oclacitinib은 아토피를 포함한 다양한 알러지 증상을 나타내는 반려견 환자들의 만성적인 가려움증을 비교적 빠르고 안전하게 완화시켜주는 약물로써 현재 FDA의 승인을 받아 미국에서 현재 120만 마리의 개에게 사용되어 온 약품입니다. 본 임상시험은 환자 당 약 3개월간 진행(0주차, 2주차, 4주차, 8주차, 12주차 내원)되며, 심한 통증을 유발할 수 있는 침습적인 검사를 제외한 전신 피부증상 평가, 피부표면 수분 손실도, 가려움증 평가 및 혈액검사(0주차, 4주차, 12주차)로 진행됩니다. 또한 임상시험 결과에 대한 환자의 정보만 노출 되며 보호자에 대한 정보는 공개되지 않습니다.

보호자_____는 위 참가 동의서의 안내사항을 모두 이해했으며, 알러지 환자에 대한 oclacitinib의 유효성 및 안전성 평가 연구를 위해 _____의 기본 신체검사 및 피부평가, 혈액검사, oclacitinib 복용에 동의합니다.

2016. . .

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국문초록

알레르기성 피부염을 지닌 개에서 Oclacitinib의 피부장벽 기능에 대한 평가

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소양감은 개 알레르기성 피부염을 진행시키는 주요 인자 중 하나이며, 몸을 긁거나 핥는 행동들은 유발시킴으로써 피부장벽의 기능을 손상시킨다. 피부장벽이 손상되면 외부에서 알레르기 유발성 물질들이 체내로 더욱 쉽게 침투하게 되며 결과적으로 알레르기성 피부염의 중증도가 악화된다. Oclacitinib은 Janus kinase 1 (JAK-1) 억제제로서 소양감 발생에 관여하는 사이토카인인 IL-31의 작용을 차단하는 주요 기전을 지닌 약제이며, 이러한 기전을 통해 개 알레르기성 피부염을 완화시키는 약제로서 사용되고 있다. 본 연구의 주요 목적은 경표피수분손실도(transepidermal water loss, TEWL)의 측정을 통해 개 알러지성 피부염에 대한 oclacitinib의 투여가 피부장벽 기능에 미치는 영향을 평가하는 것이였으며, 이 밖에도 oclacitinib

치료의 효과와 안전성을 전반적으로 평가하였다. 본 연구에서는 총 22 마리의 개에게 oclacitinib을 28 일간 투여하였으며, 그 중 8 마리는 보호자의 동의를 받아 추가 투여를 진행하여 총 84 일간 약제를 투여하였다. Oclacitinib은 초기 2 주간 하루 2회 투여 되었으며, 그 이후로는 유지요법으로서 하루 1회 투여되었다. Oclacitinib의 유효성 평가를 위해 TEWL 수치 뿐만 아니라, 아토피성 피부염의 범위 및 중증도를 평가하는 canine atopic dermatitis extent and severity index-4 (CADESI-4), 소양감의 정도를 평가하는 pruritus visual analog scale (PVAS) 및 보호자 만족도를 투여 전, 투여 후 14, 28, 56 및 84일에 평가하였다. 또한 oclacitinib의 안전성 평가를 위해 시험기간 동안 발생하는 부작용을 모두 기록하고, 투여 전, 투여 후 28 및 84일에 혈액 시료를 채취하였다. Oclacitinib의 투여 결과, CADESI-4 및 PVAS 수치가 모든 평가 시점에서 약제의 투여 횟수에 관계없이, 기저치 대비 유의하게 감소되었다(p<0.05). 앞선 결과와 달리 TEWL 수치의 경우, 기저치 대비 유의한 감소가 투여 후 14일에서만 나타났으며, 이러한 변화는 총 TEWL, 배측 목 부위 및 겨드랑이 부위의 TEWL 수치에서 확인되었다(p<0.05). 시험기간 동안 대부분의 보호자들은 oclacitinib 치료에 만족한다고 응답하였으며, 심각한 부작용은 관찰되지 않았다. 결론적으로 oclacitinib은 하루 2회 투여되었을 때 피부장벽 기능 개선에 유의한 효과를 나타낸다는 점을 확인할 수 있었다. 비록 일일 투여 횟수가 하루 1회로 감소함에 따라 피부장벽 기능이 다시 악화되는 경향을 보였지만, 이는 육안적 병변이나 소양감의 정도를 변화시킬 만큼 두드러진 영향을 미치지 않았다. Oclacitinib 치료 효과에 대해 대부분의 보호자들은 긍정적인 평가를 내렸으며, 대부분의 개에게 심각한 부작용을 유발하지 않으며 안전하게 사용되었다. 따라서 본 연구는 oclacitinib이 개 알레르기성 피부염을 조절하는데 있어 효과적이고 안전한 약제임을 확인하였다.

주요단어: 알레르기성 피부염, oclacitinib, 피부장벽 기능, 소양감, 개

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