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Clinical Application of Oclacitinib in Dogs with Atopic Dermatitis

Eun-Hyung Hong, Seo-Jin Park, Dong-In Jung*, Ji-Houn Kang, Mhan-Pyo Yang and Byeong-Teck Kang[1]

Veterinary Medical Center, College of Veterinary Medicine, Chungbuk National University, Cheongju 28644, Korea
**Research Institute of Natural Science, College of Veterinary Medicine, Gyeongsang National University, Jinju 52828, Korea*

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Abstract : This study evaluated the efficacy and safety to determine the therapeutic responses of oclacitinib in canine atopic dermatitis (CAD) and identified factors related to the therapeutic response. Overall, 13 dogs with CAD were treated with oclacitinib for 56 days. Owners and veterinarians assessed visual analog scale (VAS) scores of pruritus and dermatitis. The examined dogs were grouped according to treatment success and failure based on changes in the VAS scores. To identify factors related to the therapeutic responses of oclacitinib, signalments (breed, sex, age, and body weight), mean progression time of CAD, mean Owner and Veterinarian VAS scores at day 0, and preexisting infection rate were compared between the two groups. Among the 13 dogs, 7 (53.8%) met the criteria of treatment success. In the success group, the Owner VAS scores were significantly lower from day 6 to 56 compared with the score at day 0 ($P < 0.05$). Additionally, the Veterinarian VAS scores were significantly decreased at days 14 and 42 compared with the score at day 0 ($P < 0.05$). There were no changes in hematological indices after the administration of oclacitinib. The most common abnormality reported was otitis externa (30.8%), followed by pyoderma (23.1%), and vomiting (7.7%). Factors related to responses of oclacitinib were not identified. This study demonstrated that oclacitinib was safe and moderately effective in dogs with CAD. This is the first report of the clinical application of oclacitinib in South Korea.

Key words **:** canine atopic dermatitis, oclacitinib, visual analog scale.

Introduction

In small animal practice, dermatological problems, especially pruritus, are frequent clinical complaints (10). Canine atopic dermatitis (CAD) is one of the most common chronic allergic skin diseases in dogs. CAD is defined as a genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with immunoglobulin E antibodies against environmental allergens (11).

Glucocorticoids are most commonly used to relieve pruritus of CAD, and they are highly effective (17,21). However, these drugs frequently have short- and long-term problems. Acute adverse effects include polyuria, polydipsia, and polyphagia. Chronic problems such as pancreatitis, gastrointestinal ulceration, lipidemia, diabetes mellitus, muscle wasting, and iatrogenic hyperadrenocorticism restrict prolonged administration (21). Although cyclosporin does not have this problem, its delayed onset of action prevents the immediate relief of pruritus and management of acute flares of CAD (17). Because of these limitations related to immunosuppressive drugs, targeted therapy for AD-specific pathways is considered a therapeutic alternative in humans (13).

Among numerous receptors, cytokines, and mediators related to AD development, pruritogenic cytokines, especially interleukin interleukin (IL)-31, are a major stimulus of pruritic behavior (9). In veterinary medicine, the Janus kinase (JAK) inhibitor, oclacitinib (Apoquel®; Zoetis, Florham Park, NJ, USA), has been approved in number of countries for the control of pruritus associated with allergic dermatitis and AD in dogs over 12 months of age. Oclacitinib selectively inhibits key pathways involved in pruritus and skin inflammation, by blocking JAK-1, which is involved in IL-31 signaling (6,8,9).

The current study evaluated the safety and efficacy of oclacitinib and identified factors related to the treatment responses of oclacitinib in CAD. To the best of our knowledge, this is the first report of the clinical application of oclacitinib in South Korea.

Materials and Methods

Case selection

Overall, 13 dogs were enrolled in this study among all dogs presented to the Veterinary Medical Center, Chungbuk National University between June 2015 and July 2016. CAD was diagnosed based on the fulfillment of at least five items from the eight items of the Favrot diagnostic criteria (1, onset of signs under 3 years of age; 2, dog living mostly indoors; 3, glucocorticoid-responsive pruritus; 4, pruritus without lesions at onset; 5, affected front feet; 6, affected ear pinnae; 7, unaffected ear margins; and 8, unaffected dorso-lumbar area) along with ruling out other possible pruritic causes such as microbial and fungal infection, parasite burdens, adverse food reactions, and endocrine diseases (5,15). Signalments, clinical history, and preexisting infection were recorded for

[1]Corresponding author.
E-mail : kangbt@chungbuk.ac.kr

13 dogs. Written client consent was obtained from all owners prior to the administration of oclacitinib.

Drug administration

All dogs were treated orally with oclacitinib at a dose of 0.4-0.6 mg/kg, twice daily from day 0 to day 14, and then once daily until day 56. During the trial period, allergen-specific immunotherapy and systemic therapy (glucocorticoids or cyclosporin) were not allowed, whereas other infectious treatments, such as antimicrobial and antifungal therapy, were permitted. The owners and veterinarians were free to withdraw their dogs from the study at any point because of adverse effects and/or worsening of clinical signs of CAD.

Visual analog scale scoring

Owner performed a pruritus enhanced visual analog scale (VAS) assessment at home daily for the first 14 days. After 14 days, owners assessed the VAS score on days 21, 28, 42, and 56. Veterinarians performed a dermatitis VAS assessment at scheduled clinic visits on days 0, 14, 28, 42, and 56. Assessment was performed by the same owner and veterinarian at all points. Both owners and veterinarians assessed pruritus and dermatitis using a 10-cm VAS line to determine severity (12,20). The Owner Pruritus VAS had six descriptors of pruritus evenly spaced at 2-cm intervals with 'normal dog' at 0 cm and 'extremely severe itching' at 10 cm (Fig 1). Similarly, the Veterinarian Dermatitis VAS had six descriptors of dermatitis evenly spaced at 2-cm intervals with 'normal dog' at 0 cm and 'extremely severe dermatitis' at 10 cm (Fig 2).

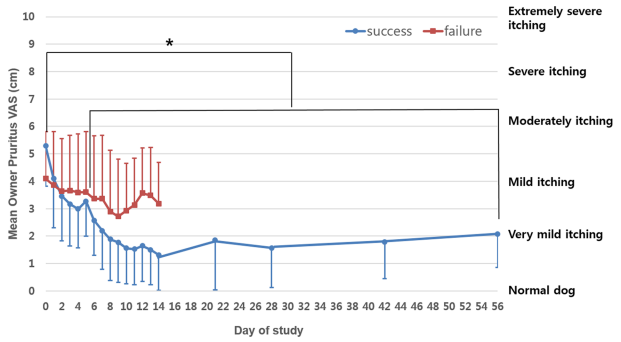

Fig 1. Temporal changes of the Owner pruritus VAS scores in the success and failure groups (mean, 95% confidence intervals). *$P < 0.05$ compared with day 0 in the success group. VAS, visual analog scale.

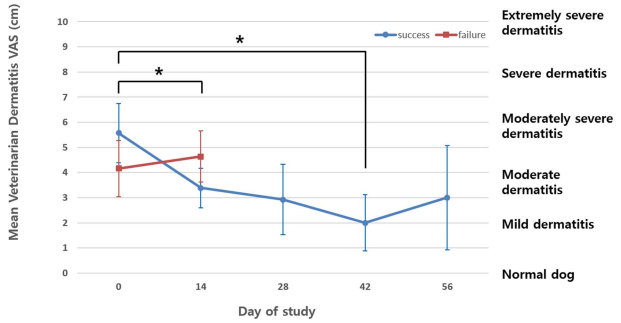

Fig 2. Temporal changes of the Veterinarian dermatitis VAS scores in the success and failure groups (mean, 95% confidence interval). *$P < 0.05$ compared with day 0 in the success group. VAS, visual analog scale.

Efficacy outcome measures

The variables for evaluating the effectiveness of oclacitinib were as follows: (1) the Owner VAS and Veterinarian VAS scores measured at each assessment time; (2) percentage of dogs with a ≥ 50% reduction of the Owner and Veterinarian VAS scores from baseline; and (3) the proportion of dogs with treatment success based on the Owner VAS assessment on day 56.

Treatment success for the Owner VAS was defined as achieving at least a 2 cm reduction from the baseline score on day 56. If dogs failed to meet this criteria or administration of oclacitinib was terminated because of worsening signs of CAD before day 56, they were considered treatment failure. Dogs with treatment success were categorized as the success group, whereas those corresponding to treatment failure were categorized as the failure group.

Safety outcome measures

To evaluate hematological abnormalities, complete blood count and serum chemical analysis were serially performed in 6 dogs at days 0, 14, 28, 42, and 56. Additionally, side effects such as pyoderma, otitis externa, vomiting, diarrhea, and cystitis were monitored.

Statistical analysis

To identify factors related to the therapeutic responses of oclacitinib, signalments (breed, sex, age, and body weight), mean progression time of CAD, mean Owner and Veterinarian VAS scores on day 0, and preexisting infection (bacterial or fungal) rate were compared between the two groups by Wilcoxon rank sum test or Fisher's exact test. To evaluate therapeutic efficacy, Owner and Veterinarian VAS scores were analyzed by Wilcoxon signed rank test or Wilcoxon rank sum test. The frequency of side effects and hematological changes following oclacitinib administration were compared between the success and failure groups by Fisher's exact test and Wilcoxon signed rank test, respectively. Statistical significance was considered when $P < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Efficacy outcome measures

Among the 13 dogs with CAD, 7 dogs (53.8%) were included in the success group (Table 1). At day 14, administration of oclacitinib was stopped in 6 dogs because of worsening dermatitis and pruritus, and these were categorized as the failure group.

At day 0, the Owner VAS scores were not different between the success (5.3 cm) and failure (4.1 cm) groups ($P > 0.05$, Fig 1). At 14 days after the administration of oclacitinib, the Owner VAS score of the success group (1.3 cm) was significantly decreased ($P < 0.05$), while the score of the failure group (3.2 cm) was unchanged from the initial score at day 0 ($P > 0.05$). In the success group, a relatively low score was

Table 1. Comparison of signalments and clinical features between the success and failure groups

Parameters	Total (13 dogs)	Success group (7 dogs)	Failure group (6 dogs)
Purebred status			
Yes [n (%)]	13 (100)	7 (100)	6 (100)
No [n (%)]	-	-	-
Sex distribution			
Male [n (%)]	7 (53.8)	3 (42.9)	4 (66.7)
Female [n (%)]	6 (46.2)	4 (57.1)	2 (33.3)
Mean age [years (range)]	8.2 (4-12)	7.9 (4-12)	8.5 (5-12)
Mean body weight [kg (range)]	8.1 (4.7-12.3)	8.8 (5.8-11.4)	6.8 (4.7-12.3)
Mean progression time of CAD [years (range)]	4.4 (1-8)	4.3 (1-8)	4.5 (2-7)
Mean Owner pruritus VAS on day 0 [cm (range)]	4.7 (2-9.5)	5.3 (4-9.5)	4.1 (2-7.5)
Mean Veterinarian dermatitis VAS on day 0 [cm (range)]	4.9 (1.5-7.5)	5.6 (3.5-7.5)	4.2 (1.5-6)
Preexisting infection rate			
Yes [n (%)]	7 (53.8)	4 (57.1)	3 (50)
No [n (%)]	6 (46.2)	3 (42.9)	3 (50)

No significant differences in parameters between the two groups ($P > 0.05$)
VAS, visual analog scale; CAD, canine atopic dermatitis

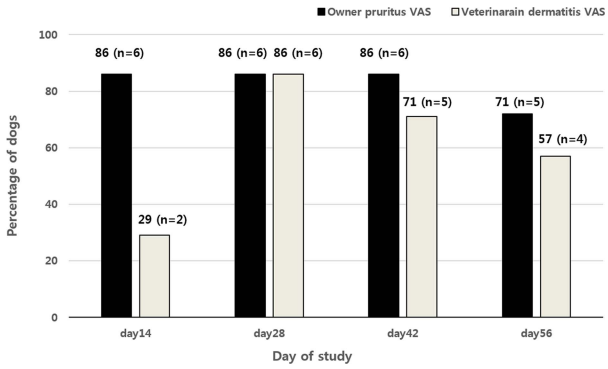

Fig 3. Percentages of dogs with a ≥ 50% reduction of the Owner and Veterinarian VAS scores from baseline in the success group. VAS, visual analog scale.

maintained from day 6 to 56 in comparison with the score at day 0 ($P < 0.05$).

The Veterinarian VAS score of the success group (5.6 cm) was not different with the score of the failure group (4.2 cm) at day 0 ($P > 0.05$, Fig 2). At day 14, the score of the failure group was unchanged (4.6 cm), whereas the score of the success group (3.4 cm) was significantly decreased from the initial score at day 0 ($P < 0.05$). In the success group, the lowest score was noted at day 42 (2 cm), and this was significantly lower than the score at day 0 ($P < 0.05$).

When the percentage of dogs showing a ≥ 50% reduction of the Owner and Veterinarian VAS scores from baseline was evaluated in the success group, the highest rates (86%) were observed in the Owner VAS score at days 14, 28, and 42, whereas the highest rate (86%) in the Veterinarian VAS score was at day 28 (Fig 3). Generally, the percentage had a tendency to be higher in the Owner VAS score than the rate in the Veterinarian VAS score except for day 28.

Safety outcome measures

Following the administration of oclacitinib, there were no changes in hematological indices (Table 2). All values were within reference ranges except for an elevated level of alkaline phosphatase (ALP). The most common abnormality was otitis externa (30.8%), followed by pyoderma (23.1%), and vomiting (7.7%; Table 3). There were no differences in the

Table 2. Temporal changes of hematological indices following the administration of oclacitinib in six dogs (mean, 95% confidence interval)

Indices	Day of study				References
	0	14	28	56	
WBC ($\times 10^3$ /μL)	7.81 (5.53-10.09)	8.23 (5.74-10.73)	7.84 (6.36-9.32)	8.04 (6.04-10.04)	5.05-16.76
Neutrophils ($\times 10^3$ /μL)	5.57 (3.76-7.37)	5.67 (4.04-7.30)	5.37 (4.56-6.17)	5.63 (3.98-7.28)	2.95-11.64
Monocytes ($\times 10^3$ /μL)	0.36 (0.27-0.44)	0.29 (0.16-0.41)	0.33 (0.22-0.43)	0.32 (0.14-0.50)	0.16-1.12
Lymphocytes ($\times 10^3$ /μL)	1.69 (1.20-2.19)	1.83 (1.28-2.37)	1.93 (1.19-2.67)	1.82 (1.16-2.49)	1.05-5.10
Hematocrit (%)	56.1 (47.7-64.5)	56.7 (53.4-60.0)	53.2 (49.1-57.3)	53.2 (45.4-61.1)	37.3-61.7
Total protein (g/dL)	6.7 (6.31-7.09)	6.53 (6.02-7.05)	6.08 (5.06-7.11)	6.63 (5.76-7.51)	5.4-7.1
Globulin (g/dL)	3.42 (2.90-3.93)	3.47 (2.93-4.00)	3.12 (2.67-3.57)	3.23 (2.50-3.97)	2.7-4.4
ALP (IU/L)	594 (205-983)	1257 (281-2233)	1031 (126-1935)	864 (157-1572)	29-97

No significant differences of hematological indices between day 0 and days 14, 28, and 56 ($P > 0.05$)
WBC, white blood cell; ALP, alkaline phosphatase

Table 3. Incidence rates of abnormalities following the administration of oclacitinib in 13 dogs (number, percentage)

Abnormalities	Total	Success group	Failure group
Otitis externa	4 (30.8%)	2 (28.6%)	2 (33.4%)
Pyoderma	3 (23.1%)	1 (14.3%)	2 (33.4%)
Vomiting	1 (7.7%)	-	1 (16.7%)
Diarrhea	-	-	-
Cystitis	-	-	-

No significant differences of incidence rates between the two groups ($P > 0.05$)

incidence rates of abnormalities between the success and failure groups ($P > 0.05$).

Identification of factors related to the therapeutic responses of oclacitinib

There were no significant differences in signalments (breed, sex, age, and body weight), mean progression time of CAD, mean Owner and Veterinarian VAS scores on day 0, and preexisting infection rate between the success and failure groups (Table 1).

Discussion

This study demonstrated the moderate efficacy of oclacitinib in 13 dogs with CAD. However, factors related to the treatment responses of oclacitinib were not identified.

In the present study, oclacitinib diminished dermatitis and pruritus in 53.8% of dogs with CAD, which was slightly lower than a previous study (76%) (3). This might be explained by the difference in population size and severity of CAD between the studies. Because of a limited inventory, oclacitinib was prescribed to 13 dogs with resistance to long-term glucocorticoid therapy. The mean age of the 13 evaluated dogs and progression time of clinical signs were 8.2 and 4.4 years, respectively. In the previous study, oclacitinib was administered to atopic dogs regardless of chronicity and tolerance to previous treatments (3), whereas most dogs in the present study suffered from chronic CAD. Therefore, the severity and chronicity of AD-related signs might explain the relatively low efficacy in this study.

The trend of change in the Owner VAS score following the application of oclacitinib was similar to previous studies (2,7,14). The Owner VAS score of examined dogs was decreased until 14 days after therapy. During this period, oclacitinib was prescribed twice daily, and then the frequency was decreased to once daily. Interestingly, the Owner VAS score was slightly increased at day 21 and this elevated score was maintained until the end of study. However, the Veterinarian VAS score had a continuous downward trend from day 0 to day 42.

Because dog owners are generally satisfied with the treatment for CAD once their dog experiences a 50% reduction of pruritus scores compared to baseline, this threshold has been used as the standard for evaluating the efficacy of pruritus treatment (16,19). In the current study, the percentage of dogs with a ≥ 50% reduction of the VAS scores had a tendency to have a higher Owner VAS score compared with the Veterinarian VAS score. Therefore, veterinarians tended to assess the VAS scoring more strictly compared with the dog owners.

In the failure group, one dog was withdrawn from the study at day 33 because of worsening AD signs, and then prednisolone (0.1 mg/kg once daily) was added to oclacitinib. To date, this dog is well and without side effects. Further evaluation is required to identify the efficacy of combination therapy using prednisolone and oclacitinib.

Similar to previous studies (1,2,4,7), there were no changes in hematological indices following the administration of oclacitinib. Hematology and serum chemistry values remained within the reference ranges except for the elevation of ALP levels. Because this abnormality was already noted at day 0 and most of the dogs had a history of long-term glucocorticoid therapy, the increased level of ALP may result from steroid-induced hepatotoxicity rather than oclacitinib administration.

Previously, urinary tract infection/cystitis (11.3%), vomiting (10.1%), otitis (9.3%), pyoderma (9.3%), and diarrhea (6.1%) were reported as abnormal signs (1). In the present study, otitis externa (30.8%), pyoderma (23.1%), and vomiting (7.7%) were observed during therapy with oclacitinib. The relatively high rate of otitis and pyoderma may be related to defects in the antimicrobial immune defense caused by severe AD in the evaluated dogs.

Because the efficacy of oclacitinib was moderate in this study, identification of the factors related to therapeutic responses might be useful to determine initiation of therapy with oclacitinib. Therefore, various parameters such as signalments, mean progression time of CAD, mean Owner and Veterinarian VAS scores on day 0, and preexisting infection rate were compared between the two groups; however, meaningful factors could not be found. Considering oclacitinib blocks JAK-1 and IL-31 signaling (6,8,9), the evaluated factors might not be involved in this pathway. To identify which factors are related to therapeutic responses, other factors should be investigated in future studies.

This study had some limitations. First, the efficacy of oclacitinib might be influenced by other adjunctive therapies, including medicated shampoos, essential fatty acids, and antimicrobials. Second, the clinical evaluation of AD patients depended on VAS scoring only. Because the Canine Atopic Dermatitis Extent and Severity Index has been validated in a previous study (18), this scoring system is needed to examine the severity of clinical signs of CAD. Finally, the small number of cases and short study period restricted the accurate investigation of drug efficacy. Therefore, more dogs should be monitored in a long-term study.

To the best of our knowledge, this report is the first to describe the clinical application of oclacitinib in South Korea. The present study shows that oclacitinib is safe and effective in dogs with CAD. Because the therapeutic responses of oclacitinib was not related to signalments, mean progression time of CAD, mean Owner and Veterinarian VAS scores on day 0, and preexisting infection, additional investigation of other parameters is needed.

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