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Clinical Efficacy of Oclacitinib and Lokivetmab in Dogs with Canine Atopic Dermatitis

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Abstract Canine atopic dermatitis (CAD) is a genetically predisposed inflammatory and pruritic skin disease presenting characteristic clinical features in dogs. Despite oclacitinib and lokivetmab being commonly used, no study has compared their efficacies in CAD. This study aimed to compare the efficacy, safety, and control of CAD-associated pruritus and skin lesions between oclacitinib and lokivetmab. It also investigated whether switching to lokivetmab from oclacitinib or prednisolone had any benefits. Twenty-five client-owned dogs, newly diagnosed with CAD, were allocated to the oclacitinib (n = 20) and lokivetmab (n = 5) groups and administered oclacitinib (0.4-0.6 mg/kg orally, twice daily for 14 days, then once daily) and lokivetmab (2 mg/kg subcutaneously, every month) for 8 weeks, respectively. The switching group included five dogs previously administered with oclacitinib (n = 4) or prednisolone (n = 1) who were switched to lokivetmab directly at the start of the study. The pruritus visual analog scale (PVAS) and Canine Atopic Dermatitis Extent and Severity Index (CADESI-04) values were surveyed at weeks 0, 4, and 8. Oclacitinib and lokivetmab significantly reduced the PVAS and CADESI-04 scores. Switching from oclacitinib or prednisolone to lokivetmab maintained the severity of pruritus (4 weeks: $p = 0.068$; 8 weeks: $p = 0.068$) and dermatitis (4 weeks: $p = 0.144$; 8 weeks: $p = 0.068$) at the levels measured at baseline. Thus, both oclacitinib and lokivetmab reduced CAD-associated pruritus by a similar degree. Switching to lokivetmab maintained the severity of pruritus and dermatitis at the same level as the previous treatment.

Key words canine, atopic dermatitis, oclacitinib, lokivetmab.

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Introduction

Canine atopic dermatitis (CAD) is a genetically predisposed inflammatory and pruritic skin disease presenting characteristic clinical features in dogs (10). There are several treatments available for CAD, including glucocorticoids, cyclosporine, oclacitinib, and lokivetmab, which reduce pruritus and inflammation (8,18).

Oclacitinib is a Janus kinase (JAK) inhibitor that selectively inhibits JAK 1-dependent cytokines involved in itching and inflammation associated with allergies, with minimal effects against JAK 2-dependent cytokines involved in hematopoiesis (1,6,22). It has been approved for the control and treatment of pruritus associated with allergic dermatitis.

Lokivetmab, a caninized, anti-canine interleukin (IL)-31 monoclonal antibody, binds specifically to circulating IL-31, thereby inhibiting the binding of IL-31 to the IL-31 receptor (4). IL-31 is considered an essential cytokine involved in pruritus associated with CAD in many species, including humans and dogs (7). Neutralization of IL-31 following subcutaneous administration of lokivetmab results in a dose-dependent reduction in IL-31-induced pruritus in dogs for up to 8 weeks following a single dose (23).

There are few studies illustrating the efficacy of oclacitinib compared with other known treatments, including cyclosporine and prednisolone (5,13). However, no prospective studies have compared the efficacy of oclacitinib and lokivetmab in dogs diagnosed with CAD. Therefore, this study aimed to evaluate the efficacy and safety of oclacitinib and lokivetmab and to compare their control of pruritus and skin lesions associated with CAD. Furthermore, this study investigated whether dogs receiving oclacitinib or prednisolone benefited from switching to lokivetmab.

Materials and Methods

Animals

This study recruited dogs diagnosed with CAD between 2017 and 2020. All dogs were client-owned, 12 months of age or older, and in overall good health, based on the initial physical examination (0 week/baseline). The eligibility criteria for this study was a minimum score of 3 on the pruritus visual analog scale (PVAS) as assessed by the dog owners or a minimum score of 30 out of a possible 180 points on the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-04 as assessed by clinicians (19,21).

All dogs were diagnosed with CAD. The diagnosis was established based on the medical history, typical clinical signs according to the International Committee on Allergic Diseases of Animals guidelines, and fulfillment of more than five postulates of the Favrot's criteria (11,17). The possibility of other diseases such as bacterial or fungal dermatitis, flea allergy dermatitis, cutaneous adverse food reactions that can cause pruritus and skin lesions was ruled out through proper tests and treatments.

Study group

The dogs diagnosed with CAD were divided into two groups: oclacitinib group, treated with oclacitinib (Apoquel®, Zoetis; Florham Park, NJ, USA); and lokivetmab group, treated with lokivetmab (Cytopoint®, Zoetis; Parsippany, NJ, USA). The PVAS and CADESI-04 scores of the two groups were evaluated and compared. None of these dogs received any other medication for CAD.

Five dogs receiving oclacitinib (n = 5) or prednisolone (n = 1) were included in the switching group to evaluate the benefit of switching the treatment to lokivetmab. These dogs received oclacitinib or prednisolone for at least 2 months before the change in treatment.

Drug administration

The oclacitinib group was administered 0.4 mg/kg of oclacitinib, twice daily for 2 weeks, followed by 0.4-0.6 mg/kg, once daily until the end of the study. During the treatment period, allergen-specific immunotherapy and systemic therapy were not allowed, but other anti-infective treatments, such as antimicrobial, antifungal, and antiparasitic therapies, were permitted.

The lokivetmab and switching groups were administered 2 mg/kg of lokivetmab every month from 0 week (baseline) to 8 weeks.

The treatment of the dogs included in the switching group was switched from prednisolone or oclacitinib to lokivetmab directly at the start of the study.

Efficacy estimates

PVAS scoring

The severity of pruritus was graded using the PVAS on a scale of 0-10 (0, no pruritus; 10, most severe pruritus) (21). The PVAS values were determined based on history and evaluation by the owners. Treatment success for PVAS was defined as a 50% or greater score reduction on the assessment day as compared to the baseline score (3,18).

CADESI-04 scoring

The extent and severity of skin lesions were evaluated using the CADESI-04, which is designed to assess 20 different body parts (19). Clinicians assessed three skin lesions, includ-

ing erythema, lichenification, and excoriation/alopecia, based on a 4-point severity scale (0, none; 1, mild; 2, moderate; 3, severe). The clinicians assessed total 20 body sites, three types of lesions, and four grades of severity, thus generating a maximal score of 20 × 3 × 3 = 180. The CADESI-04 cut-off scores for mild, moderate, and severe AD were 10, 35, and 60, respectively (19). Treatment success for CADESI-04 was defined as a 50% or greater score reduction on the assessment day as compared to the baseline score (20).

Side effects

Clinicians recorded any abnormal health events reported by owners or those identified during physical examination throughout the study period. The adverse drug effects of oclacitinib include urinary tract infection, cystitis, vomiting, otitis, dermatitis, and diarrhea, while that of lokivetmab include vomiting, diarrhea, lethargy, dermatitis, and pruritus (2,16).

The abnormal health events were categorized as gastrointestinal, dermatological, urogenital, immunological, neurological, behavioral, and musculoskeletal problems.

Additionally, dogs administered lokivetmab were observed in the clinic for 30 min following each administration for signs of immediate hypersensitivity-like reactions, such as wheal, vomiting, or lethargy.

Study design and grouping

Baseline data (signalment and severities of pruritus and skin lesions) were collected for all dogs during enrollment. In the oclacitinib and lokivetmab groups, the PVAS and CADESI-04 scores were recorded every 4 weeks from weeks 0 to 8.

In the switching group, the PVAS and CADESI-04 scores were retrospectively collected at the initiation of the previous medication (oclacitinib or prednisolone) and then after 4 weeks and 8 weeks. At the start of the study, these dogs switched directly from oclacitinib or prednisolone to lokivetmab after obtaining consent from the owners. The PVAS and CADESI-04 scores were evaluated three times at weeks 0, 4, and 8 after the first injection of lokivetmab.

Data analysis

Data were analyzed using GraphPad Prism 6 software (GraphPad Software Inc., San Diego, CA, USA) and Statistical Package for the Social Sciences (SPSS 22.0 for Windows, IBM, New York, NY, USA). Signalments (sex, age, and body weight) were compared between the two groups using Fisher's exact test to identify factors related to the therapeutic response of oclacitinib and lokivetmab. The Wilcoxon test was used to compare the PVAS and CADESI-04 scores at different time points in each of the three groups. The differences in values between the two groups were analyzed using the non-parametric Mann-Whitney U test. Signalment data were expressed as mean and range, and PVAS and CADESI-04 data were expressed as mean ± standard deviation (SD). Differences were considered statistically significant at p-value <0.05.

Results

Evaluation and comparison for the efficacy of oclacitinib and lokivetmab

Twenty-eight dogs fulfilling the CAD diagnosis criteria were allocated to the oclacitinib group (n = 20) and lokivetmab group (n = 8). However, three dogs in the lokivetmab group were unable to complete the 2-month study period due to the occurrence of side effects such as pruritus, Malassezia infection, and generalized lymphadenopathy. Finally, the lokivetmab group included five dogs. The signalment (age, sex, and breed) in the oclacitinib and lokivetmab groups are shown in Table 1. In both groups, the most common breed was Maltese (oclacitinib: n = 7; lokivetmab: n = 2). There were no significant differences between the dogs of the

Table 1. Summary of signalments and clinical features in the oclacitinib and lokivetmab groups at the start of the study

	Oclacitinib group (n = 20)	Lokivetmab group (n = 5)	Total (n = 25)	p-value
Breed distribution, % (n)				
Pure-bred	95% (19)	100% (5)	96% (24)	0.804
Mixed breed	5% (1)	0% (0)	4% (1)	
Sex distribution, % (n)				
Male/neutered	40% (8)	20% (1)	36% (9)	0.62
Female/spayed	60% (12)	80% (4)	64% (16)	
Mean age, years (range)	6.1 (1-15)	11.2 (4-18)	7.12 (1-18)	0.05
Mean weight, kg (range)	6.96 (2.64-16.6)	4.53 (3.6-5.5)	6.87 (2.64-16.6)	0.30

oclacitinib and lokivetmab groups with respect to sex, age, breed, and body weight ($p > 0.05$).

The serial changes, reductions, and percentage of dogs with more than 50% reduction in the PVAS and CADESI-04 scores in the oclacitinib and lokivetmab groups are shown in Fig. 1.

At the start of the study, there were no significant differences in the PVAS scores between the oclacitinib and lokivetmab groups (5.5 ± 2.14 vs. 6 ± 1.41; $p = 0.40$); however, the CADESI-04 score in the lokivetmab group was significantly higher than that in the oclacitinib group (46.8 ± 15.64 vs. 21.4 ± 16.37; $p = 0.01$).

There was a significant decrease in the PVAS scores at weeks 4 and 8 when compared to week 0 in both the oclacitinib ($p < 0.01$) and lokivetmab ($p < 0.05$) groups. At each time point (0, 4, and 8 weeks), no significant differences were observed between the two groups ($p > 0.05$) (Fig. 1A). Similarly, the decrease in the PVAS scores did not differ significantly between the oclacitinib and lokivetmab groups (0-4 weeks: 3.75 ± 1.71 vs. 3.4 ± 1.67; 0-8 weeks: 3.9 ± 1.77 vs. 4.2 ± 1.3) ($p > 0.05$) (Fig. 1B). In the oclacitinib group, 85% of the dogs achieved more than 50% reduction in the PVAS scores after 4 weeks and 8 weeks as compared to the baseline scores. In the lokivetmab group, 80% of the dogs achieved more than 50% reduction in the PVAS scores after 4 weeks and 100% reduction after 8 weeks as compared to the baseline scores (Fig. 1C).

In comparison with the CADESI-04 scores at week 0, significant reductions were noted at both 4 weeks and 8 weeks in the oclacitinib group ($p < 0.01$), whereas the lokivetmab group showed a significant reduction only at 8 weeks ($p < 0.05$) (Fig. 1D). At each time point, the CADESI-04 scores were significantly higher in the lokivetmab group as compared to the oclacitinib group ($p < 0.01$). However, the decrease in the CADESI-04 scores did not differ significantly between the oclacitinib and lokivetmab groups (0-4 weeks: 10.05 ± 9.68 vs. 6.8 ± 7.92; 0-8 weeks: 10.05 ± 9.68 vs. 10.2 ± 9.55) ($p > 0.05$) (Fig. 1E). In comparison with the CADESI-04 scores at week 0, 45% of the dogs in the oclacitinib group achieved more than 50% reduction after 4 weeks and 40% reduction after 8 weeks. However, none of the dogs in the lokivetmab group achieved a reduction greater than 50% in the CADESI-04 scores until 8 weeks (Fig. 1F).

Evaluation of switching to lokivetmab treatment

In this study, four dogs receiving oclacitinib or prednisolone were included in the switching group. The signalment (age, sex, and breed) and clinical features (CADESI-04 and PVAS scores) in the switching group are shown in Table 2. Among these dogs, three had received oclacitinib and one had received prednisolone until the first injection of lokivetmab.

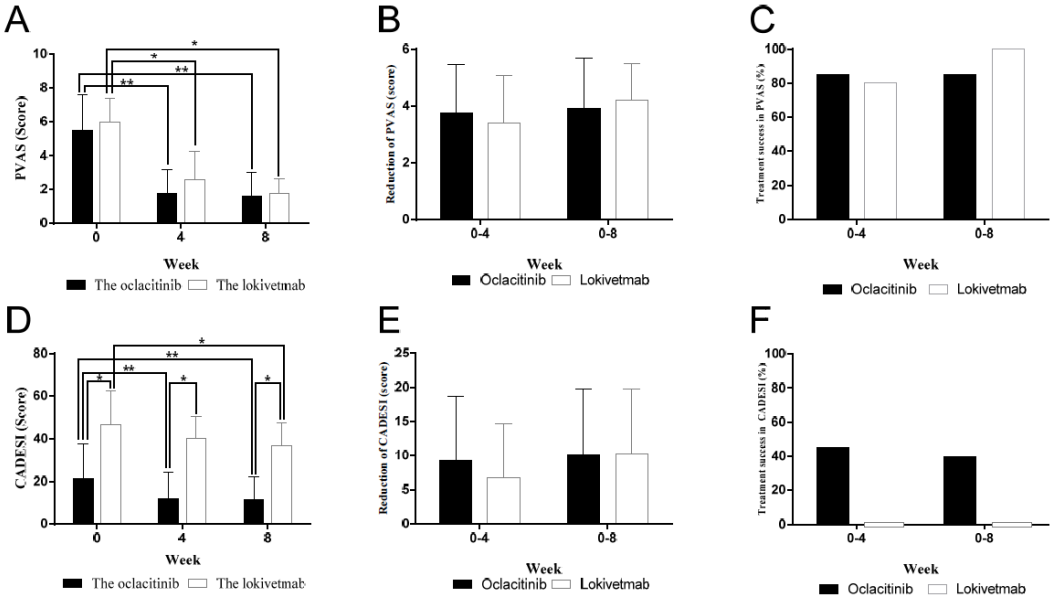

Fig. 1. Time-course changes in the PVAS scores (A), the reduction of PVAS scores (B), and percentage of dogs with more than 50% reduction in the PVAS scores (C), the CADESI-04 scores (D), the reduction of CADESI-04 scores (E), and percentage of dogs with more than 50% reduction in CADESI-04 scores (F) in the oclacitinib and lokivetmab groups. *significantly different from week 0 ($p < 0.05$); †significantly different from week 0 ($p < 0.01$). Error bars indicate the mean ± standard deviation. PVAS, pruritus visual analog scale; CADESI, canine atopic dermatitis extent and severity index.

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Table 2. Summary of signalments, clinical features, and history of previous medication of the switching group (n = 4)

Patient no.	Sex	Age (years)	*Initial PVAS score	*Initial CADE-SI-04 score	†Baseline PVAS score	†Baseline CADE-SI-04 score	Previously prescribed drugs	Previous medication period
ID-1	SF	8	9	2	4	8	Oclacitinib 0.6 mg/kg sid	471 days
ID-2	IF	11	7	56	4	36	Oclacitinib 0.4 mg/kg sid	59 days
ID-3	SF	9	6	78	5	50	Oclacitinib 0.4 mg/kg sid	389 days
ID-4	CM	4	8	44	4	43	Prednisolone 0.1-0.5 mg/kg sid	1,248 days

*Initial: at the time point of initiation of previous medication for CAD.

†Baseline: at the time of first lokivetmab injection.

PVAS, pruritus visual analog scale; CADESI, Canine Atopic Dermatitis Extent and Severity Index; CM, castrated male; IF, intact female; SF, spayed female; sid, once a day.

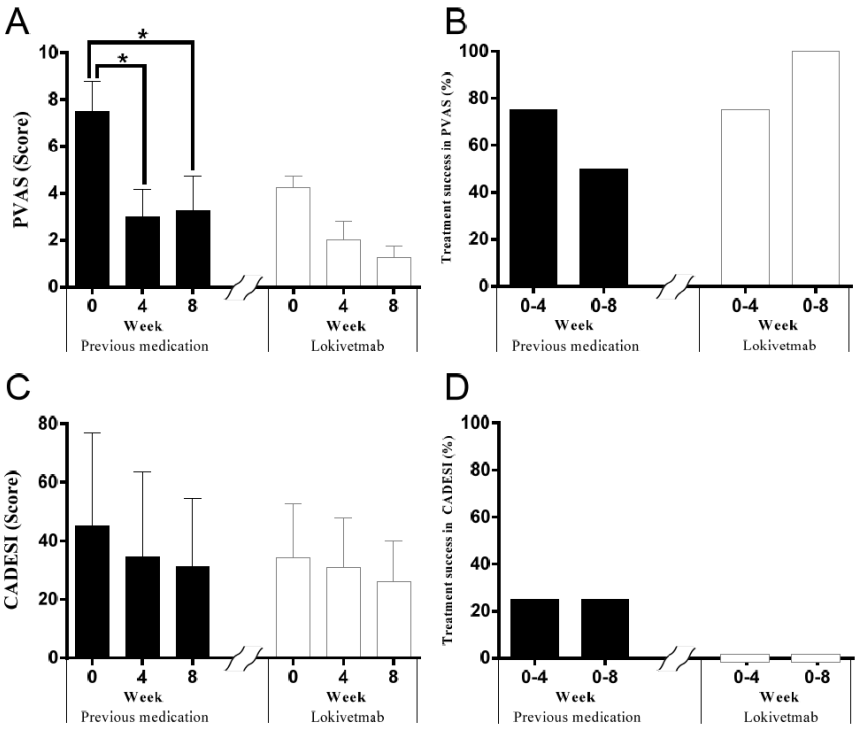

Fig. 2. Time-course changes in the PVAS scores (A), percentage of dogs with more than 50% reduction in the PVAS scores (B), the CADESI-04 scores (C), and percentage of dogs with more than 50% reduction in CADESI-04 scores (D) in the switching group. *Significantly different from week 0 ($p < 0.05$). Error bars indicate the mean ± standard deviation. PVAS, pruritus visual analog scale; CADESI, canine atopic dermatitis extent and severity index.

The mean ± SD duration of the previous medication prior to baseline/week 0 was 541.75 ± 503.38 days (range: 59-1,248).

The serial changes and percentage of dogs showing more than 50% reduction in the PVAS and CADESI-04 scores in the switching group are shown in Fig. 2. During the previous medication period with oclacitinib or prednisolone, significant reduction in the PVAS scores was noted at 4 weeks and 8 weeks when compared with the initial therapy (week 0) ($p< 0.05$). Although the PVAS scores consistently decreased

after the first injection of lokivetmab, the differences were not significant between before and after lokivetmab therapy ($p = 0.066$) (Fig. 2A). During the previous medication period, 75% of the dogs achieved more than 50% reduction in PVAS scores after 4 weeks and 50% reduction after 8 weeks when compared to the initial therapy (week 0). After the first lokivetmab injection, 75% of the dogs achieved more than 50% reduction in PVAS scores after 4 weeks and 100% reduction after 8 weeks when compared to the first lokivetmab injection (week 0) (Fig. 2B). The CADESI-04 scores gradually decreased during the period of the previous medication, but the changes were not significant ($p > 0.05$). After the lokivetmab injection, the CADESI-04 scores did not significantly change until 8 weeks ($p > 0.05$) (Fig. 2C). In comparison with the CADESI-04 scores during initial therapy (week 0), 25% of the dogs achieved more than 50% reduction in the scores during the period of previous medication after 4 weeks and 8 weeks. However, none of the dogs achieved more than 50% reduction in CADESI-04 scores until 8 weeks after the first lokivetmab injection (Fig. 2D).

Side effects

No adverse effects were reported during the study period in the oclacitinib group. However, one immunological and two dermatological adverse effects occurred in three dogs of the lokivetmab group, and they were withdrawn from the study.

The first dog had pre-existing pruritus that became more severe 3 days after the first lokivetmab injection as reported by the owners. The pruritus was relieved without any specific treatment. The second dog was diagnosed with *Malassezia* dermatitis by a clinician at 4 weeks. The third dog had generalized lymphadenopathy identified on physical examination at 4 weeks. Although fine needle aspiration and polymerase chain reaction for antigen receptor rearrangements were performed, there was no significant finding to suspect inflammation or neoplasia.

Other problems, such as gastrointestinal, urogenital, neurological, behavioral, and musculoskeletal side effects, were not identified during the study period. Until the end of the study, there were no hypersensitivity-related reactions immediately after injection.

Discussion

This study evaluated and compared the efficacy of oclacitinib and lokivetmab treatment for pruritus and skin lesions associated with CAD. The results demonstrate that oclacitinib and lokivetmab significantly improve pruritus and skin lesions in dogs diagnosed with CAD. There was no significant difference in the anti-pruritic effect between the two groups. This study also found that switching from prednisolone or oclacitinib treatments to lokivetmab maintained the severity of pruritus and dermatitis at the same level as that during the previous treatment.

A previous study on oclacitinib performed using PVAS and CADESI-02 (an older clinical assessment system) followed up with the studied dogs for 8 weeks, and a 60.3% reduction in PVAS scores and 55.6% reduction in CADESI-02 scores was reported (3). This study has obtained similar findings in the mean percentage reduction of PVAS (74.5%) and CADESI-04 (54.0%) scores in the oclacitinib group.

In this study, lokivetmab improved pruritus and skin lesions in 75% of the dogs administered lokivetmab, which was consistent with a previous study (72%) (15). A previous study reported a reduction in the PVAS and CADESI-03 scores after lokivetmab administration, and it was most apparent with a single administration of 2 mg/kg dose (15). In another study, there was a significant reduction in the mean PVAS (from 7.4 to 3.0; 60% reduction) and mean CADESI-03 (from 184 to 60; 67% reduction) scores after 8 weeks of lokivetmab treatment (16). Similarly, this study also showed PVAS score reduction at 8 weeks after therapy (from 6.9 to 1.8; 61% reduction). However, the reduction in CADESI-04 scores in this study is lesser than that in the previous study (from 46.8 to 36.6; 22% reduction). The CADESI-04 has higher correlation coefficients with the subjective owner and investigator global assessments of lesions as compared to the CADESI-03, suggesting improvement from the previous version (19). Because CADESI-03 was used in the previous study and CADESI-04 in this study, the clinical severity cannot be compared directly between them. The mean age of the dogs in this study (11.2 years) was higher than the mean age of the dogs in the previous study (5.3 years). Moreover, most of the dogs in this study presented highly lichenified lesions rather than acute lesions. Therefore, it is possible that the chronic skin lesions reduced the therapeutic effect of lokivetmab in this study.

Despite the common use of oclacitinib and lokivetmab, there is a relative paucity of data comparing the efficacy of these drugs in clinical patients. This study shows that there are no significant differences in the PVAS scores between the two groups. Furthermore, the reductions in the PVAS scores are not significantly different between the two groups. These findings indicate that both oclacitinib and lokivetmab reduce pruritus associated with CAD to a similar degree. Although the CADESI-04 score in the lokivetmab group is significantly higher than that in the oclacitinib group at all time points, the reductions in CADESI-04 scores are not significantly dif-

ferent between the two groups. These results suggest that lokivetmab shows the same amount of CADESI-04 score reduction as oclacitinib.

Treatment response may be inversely related to the severity of skin lesions in CAD (9,14,24). Because the skin lesions in the lokivetmab group were more severe than those in the oclacitinib group at the start of the study, it may be difficult to compare the clinical efficacy of these drugs in improving skin lesions. Further studies with dogs presenting a similar degree of skin lesions are warranted.

Switching from prednisolone or oclacitinib to lokivetmab maintains the severity of pruritus and dermatitis at the same level as the previous treatment until 2 months after the first injection of lokivetmab. Although there is no statistical difference in the PVAS and CADESI-04 scores after switching to lokivetmab, their values in all dogs tended to decrease gradually during the study period. Moreover, all dogs in the switching group achieved a 50% or greater reduction in the PVAS score after 8 weeks since the first injection of lokivetmab. A 50% reduction in the PVAS scores from baseline can be defined as treatment success, representing a clinically relevant threshold above which owners are satisfied with treatment (18). It is suggested that switching to lokivetmab not only maintained clinical severity, but also improved the pruritus during the study period. A larger population of animals can reveal some significant variations between the different time points.

Previously, urinary tract infection/cystitis (11.3%), vomiting (10.1%), otitis (9.3%), pyoderma (9.3%), and diarrhea (6.1%) were the reported adverse effects in dogs treated with oclacitinib; however, no adverse effects were observed in this study (2).

Lokivetmab treatment has reportedly shown side effects such as vomiting (15.5%), diarrhea (13.4%), lethargy (9.9%), anorexia (4.9%), bacterial skin infection (7%), pruritus (5.6%), and otitis externa (5.6%) (16). In this study, three dogs presented temporary pruritus, *Malassezia* dermatitis, and generalized lymphadenopathy, respectively, during lokivetmab treatment. Notably, generalized lymphadenopathy has not been reported as a side effect of lokivetmab. This side effect has been reported in humans as an anaphylactic reaction to omalizumab, a humanized anti-immunoglobulin (Ig) E monoclonal antibody. Fever, arthralgia, and rash, sometimes accompanied by lymphadenopathy, occur in some patients 1-5 days after omalizumab injections (12). It was noted that 78% of reactions occurred within the administration of the first three doses of omalizumab. The mechanism of omalizumab anaphylaxis is not well understood. A previous study suggested that because omalizumab is composed of 5% mouse polypeptide, it is certainly possible that IgE-mediated reactions occur against murine sequences (13). Similar to omalizumab, lokivetmab is also composed of 5% mouse polypeptide. Therefore, generalized lymphadenopathy is possibly caused by an anaphylactic reaction to lokivetmab.

This study had some limitations. First, comparison of the control of skin lesions between the two groups was difficult because the CADESI-04 scores indicating severity were significantly higher in the lokivetmab group as compared to the oclacitinib group. Second, the small number of cases and short study period restricted the accurate investigation of drug efficacy. Finally, there was no placebo group for comparison with other CAD medication groups. Therefore, future long-term studies with large sample size and placebo groups should be conducted.

In conclusion, the present study shows that both oclacitinib and lokivetmab are effective in dogs with CAD, and both show a similar degree of anti-pruritic effect. Furthermore, switching to lokivetmab may be considered in dogs with CAD, when there is discomfort with the routes or frequency of administration of other CAD medications, such as oclacitinib or prednisolone.

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Conflicts of Interest

The authors have no conflicting interests.

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