Case Report

Long-term tapering regimen use of oclacitinib for the control of pruritus in an atopic dog

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Abstract

Canine atopic dermatitis (CAD) is a genetically predisposed inflammatory skin disease with a global distribution, yet it is incurable. A key clinical sign of CAD is pruritus. Oclacitinib has proven effective in managing pruritus in atopic dogs. This case report details the long-term administration of oclacitinib every other day for controlling pruritus in an atopic dog. An 8-year-old atopic Bangkaew dog presented with pruritus, alopecia, and recurrent Malassezia pachydermatis infection. To control the pruritus, the dog received oclacitinib at a dose of 0.4 mg/kg orally every 24 hours for 30 weeks. The pruritus visual analog scale (PVAS) decreased from 8/10 to 4/10 by week 2, and the skin lesions improved by week 18. After 30 weeks, with improved skin lesions and a stable PVAS at 2/10, the dosing frequency of oclacitinib was reduced to every other day, supplemented with hydroxyzine on the days without oclacitinib. This adjustment maintained the PVAS and skin condition at levels comparable to before the tapering of oclacitinib. No clinical abnormalities were observed during the 12 months of treatment under the tapered regimen of oclacitinib at 0.4 mg/kg orally every other day. This is the first report of successful pruritus management in an atopic dog using a tapering regimen of oclacitinib.

Keywords: atopic dermatitis, dogs, hydroxyzine, oclacitinib, pruritus

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Received: September 11, 2023
Accepted: October 26, 2023

Introduction

Canine atopic dermatitis (CAD) is one of the major skin diseases in veterinary practices. It is a common inherited chronic inflammatory and incurable skin disease worldwide. The age of onset of CAD usually starts between six months and three years but occasionally later (Saridomichelakis and Olivry, 2016). The diagnosis of CAD is based on the history, development of the disease and the pattern of lesions (Favrot *et al*., 2010). Pruritus is a specifically important clinical sign of CAD. The pruritic areas on the face, ears, paws, axillae, ventral chest, abdomen and perineum are typical for CAD (Saridomichelakis and Olivry, 2016). CAD is a lifelong disease that cannot be cured, but in most cases, it can be successfully controlled.

Pruritus in CAD is mainly mediated by a group of proinflammatory and proallergic cytokines (Gonzales *et al*., 2014). The main cause of pruritus relates to the over-expression of T-helper type 2 cytokines such as IL-2, IL-4, IL-6, IL-13, and IL-31. These cytokines bind to cytokine receptors that have Janus kinase (JAK) enzymes related to their cytoplasmic portion. The binding of these cytokines to their receptors leads to further cytokine production (Gonzales *et al*., 2014; Schindler *et al*., 2007.). Glucocorticoids (GCs) and cyclosporine (CsA) have been used to control pruritus and inflammation in CAD. However, the severity of the adverse drug reactions (ADRs) to these drugs limits their uses in some dogs. Although many other treatments, including antihistamines (hydroxyzine, diphenhydramine), fatty acids, vitamin E, and topical tacrolimus, have shown fair efficacy for CAD, their uses as monotherapy is not common (Olivry *et al*., 2015). The JAK inhibitor has become an important drug for the control of CAD–induced pruritus.

Oclacitinib is the first JAK inhibitor approved for the control of pruritus found in CAD and is the only one approved in veterinary medicine (Marsella *et al*., 2023). Oclacitinib is a selective JAK1 inhibitor targeting the signaling of cytokines involved in pruritus and inflammation like IL-2, IL-4, IL-6, IL-13, and IL-31. It has minimal effects against JAK2-dependent cytokines involved in hematopoiesis. Oclacitinib most potent effect is blocking the IL-31, indicated to have a major role in the pathophysiology of CAD. It, therefore, has been beneficial for the control of pruritus in atopic dogs (Gonzales *et al*., 2014). Pharmacokinetics of oclacitinib in dogs indicated rapid absorption and high absolute oral bioavailability (BA) ranging from 79% to 89% and not affected by food administration (Collard *et al*., 2014). The time to maximum concentration (Tmax) is less than 1 h, and the half-life ranges from 4.0 to 5.9 h. These properties support a twice-daily or once-daily dosing regimen in dogs (Collard *et al*., 2014). Twice a day dosing (up to 2 weeks) provides plasma concentration that inhibits JAK1-dependent cytokines relevant to the disease process throughout the dosing interval. A twice-daily regimen significantly improves pruritus and dermatitis and can be transitioned to a once-daily dosing for long-term management. Once-daily dosing generates plasma concentrations above the amount required to inhibit JAK1-dependent cytokines by 50% (IC50) and effectively inhibits proinflammatory JAK1-dependent cytokines (Collard *et al*., 2014).

The antipruritic efficacy of oclacitinib has been reported in a large number of studies associated with allergic skin diseases (Crosgrove *et al*., 2013). The recommended dose is 0.4 to 0.6 mg/kg orally (PO) every 12 h (q 12 h) for 14 days and then q 24 h thereafter (Marsella *et al*., 2023). Although the long–term use of oclacitinib administered q 24 h is relatively safe, the long–term safety of other dosing regimens is not known (Olivry *et al*., 2015). Moreover, in cases where a complete remission of signs is obtained, further tapering of drug use should be attempted with the dose adjusted to maintain the remission of clinical signs (Olivry *et al*., 2015).

Because CAD is a chronic disease, attempts should be made to limit the use of drugs for CAD. This is to prevent harmful effects on other body systems from long–term treatment and to make the treatment sustainable. In clinical practice guidelines for CAD, GCs (prednisolone) and CsA should be prescribed every day for the control of pruritus in acute flares until complete remission of the signs. The drugs should be subsequently tapered by either reducing the frequency of dosing or by reducing the daily dose to maintain clinical remission (Olivry *et al*., 2015). Therefore, it is important to reconsider the treatment protocols following clinical examination of the patient to prescribe proper drug use in each individual case.

In this case report, we described the long-term use of oclacitinib for the control of pruritus in an atopic dog after clinical signs remission using an oclacitinib once-daily regimen followed by an every-other-day regimen combination with hydroxyzine. This is the first report on the successful management of pruritus in an atopic dog using an oclacitinib tapering regimen.

Case description

A 30 kg, 8-year-old neutered male Bangkaew dog with a history of CAD was presented at the Animal Hospital Bangkok, Thailand. Its skin problem started at five years of age. Severe pruritus was the first symptom. The dog met Favrot's diagnostic criteria for CAD, and other pruritic skin diseases were ruled out. The dog was treated with a variety of drugs such as antimicrobials, GCs, CsA, skin supplements, and topical shampoo therapy on separate occasions for approximately three years. A food allergy test was also done, and there was no response to an 8-week food trial using a commercial and home–cooked novel protein or hydrolyzed hypoallergenic diet.

Physical examination of the dog revealed alopecia, erythema, hyperpigmentation, and epidermal collarettes on the entire body, especially the four legs, under the neck, thoracic areas, axillar areas, and inguinal areas (Fig. 1a). The level of pruritus graded by the dog's owner was 8 / 10 using the pruritus visual analog scale (PVAS) on a scale of 0 – 10 (0, no pruritus; 10, most severe pruritus) (Rybnicek *et al*., 2009; Young

et al., 2019). Otitis externa was found in both ears. Multiple skin scrapings were taken for skin cytological examination and examined microscopically in both paraffin oil and with Gram's staining. The microscopic examinations revealed a number of *Malassezia pachydermatis* and a number of cocci bacteria.

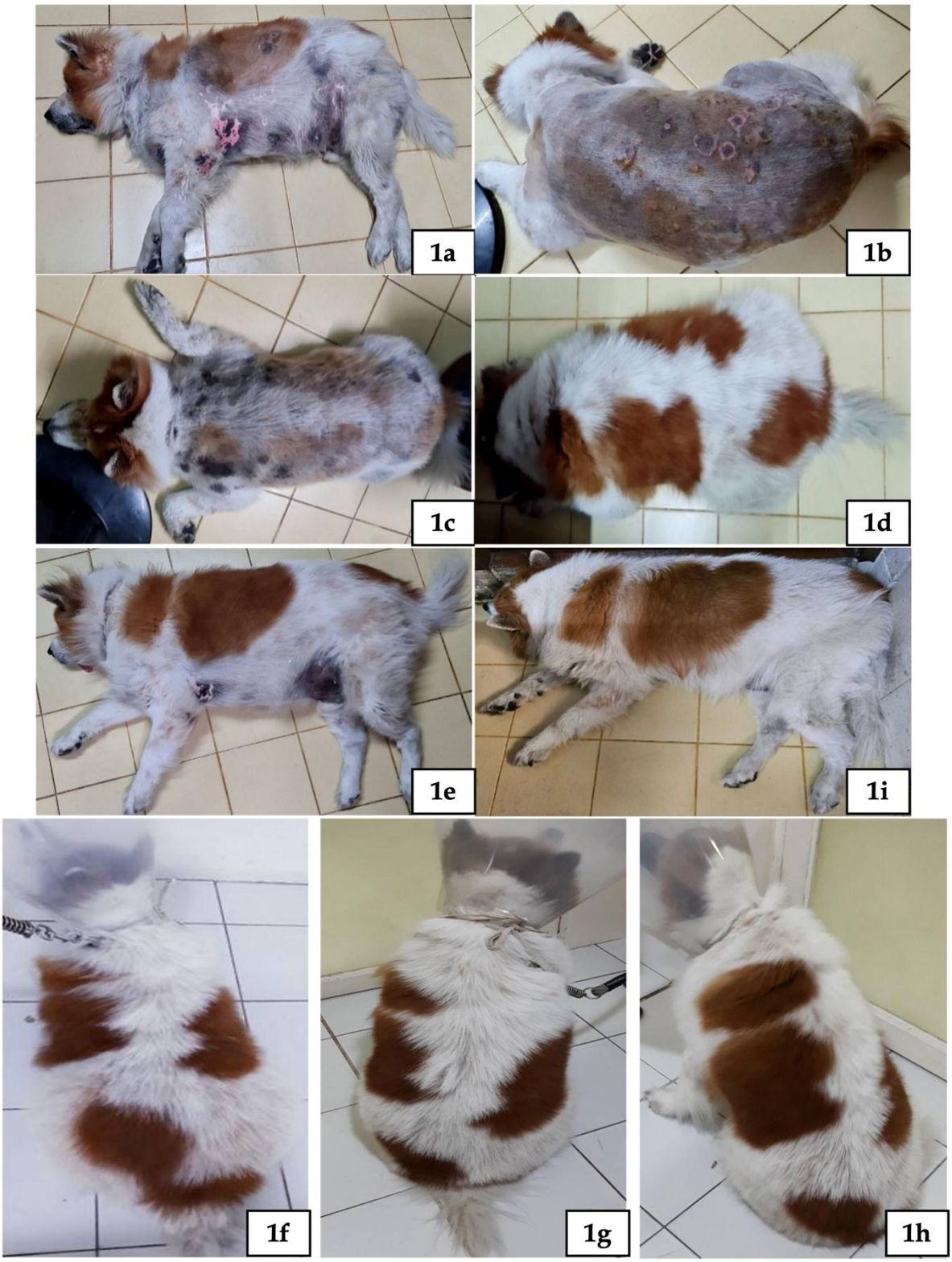

Figure 1 Macroscopic skin lesions in an atopic dog following treatment. (1a) week 0, (1b) week 2, (1c) week 4, (1d) and (1e) week 12, (1f) week 18, (1g) week 26, (1h) week 48, (1i) week 78.

Incisional skin punch biopsies of the dog's skin lesions were collected for histopathological study. The specimens were fixed in 10% neutral buffered formalin, then histologically processed and finally stained with Hematoxylin and Eosin (HE). Microscopic results showed severe diffuse epidermal hyperplasia, increased 8 - 10 layers of the epidermis, and moderate parakeratotic hyperkeratosis (Fig. 2a). Moderate diffuse infiltration of macrophages, lymphocytes, and plasma cells, occasionally segmented neutrophils, and eosinophils beneath the epidermis and upper dermis and some areas of deep dermis were also found

(Fig. 2b and 2c). Infundibular epidermal inclusion cyst, multiple follicular keratosis, multifocal sebaceous glandular hyperplasia with increased dense interlacing bundles of collagen fibers and reactive fibroblasts and increased some small capillaries in deep dermis were observed (Fig. 2d). These histopathological findings were similar to those reported in recent studies on skin lesions of atopic dermatitis (Bizikova *et al*., 2015). Hematology, blood chemistry, and urinalysis were in normal ranges (Tables 1 and 2). The diagnosis of CAD was made for the dog based on the treatment histories and clinical findings.

Oclacitinib (Apoquel®, Zoetis, USA) at a dosage of 0.4 mg/kg PO q 24 h was prescribed for two weeks to control pruritus in the dog. Antimicrobial drugs, including itraconazole (Spornar®, Charoen Bhaesaj Lab. Co., LTD., Thailand) at a dosage of 5 mg/kg PO q 24 h and amoxicillin–clavulanic acid (Clavaceptin®, Vetoquinol, UK) at a dosage of 15 mg/kg PO q 12 h were prescribed for eight weeks to control Malassezia and bacterial skin infection, respectively. Medicated shampoo composed of hydrolyzed oatmeal, ceramide complex, and safflower seed oil (Dermallay®, Dechra, USA) was used as a topical therapy. Topical ear drugs consisting of marbofloxacin, clotrimazole, and dexamethasone (Aurizon®, Vetoquinol, UK) were used to treat otitis externa for 14 days.

After two weeks of treatment, the level of pruritus was decreased, and the skin lesions were improved. Oclacitinib was continuously prescribed at the same dosage until week 30 of the treatment, when the skin lesions were resolved. The frequency of dosing of oclacitinib was decreased from q 24 h to every other day after that. Another drug, hydroxyzine (Atarax®, OLIC, Thailand), was used at the dosage of 2 mg/kg PO q 12 h on the day that oclacitinib was omitted. Oclacitinib and hydroxyzine were still prescribed to control pruritus in this dog. Other antipruritic drugs were not allowed, but anti-infective drugs (antimicrobials and antiparasitic drugs) were permitted during the treatment. The dog's health was monitored at the interval of 8 - 16 weeks. The skin scrapings were performed monthly.

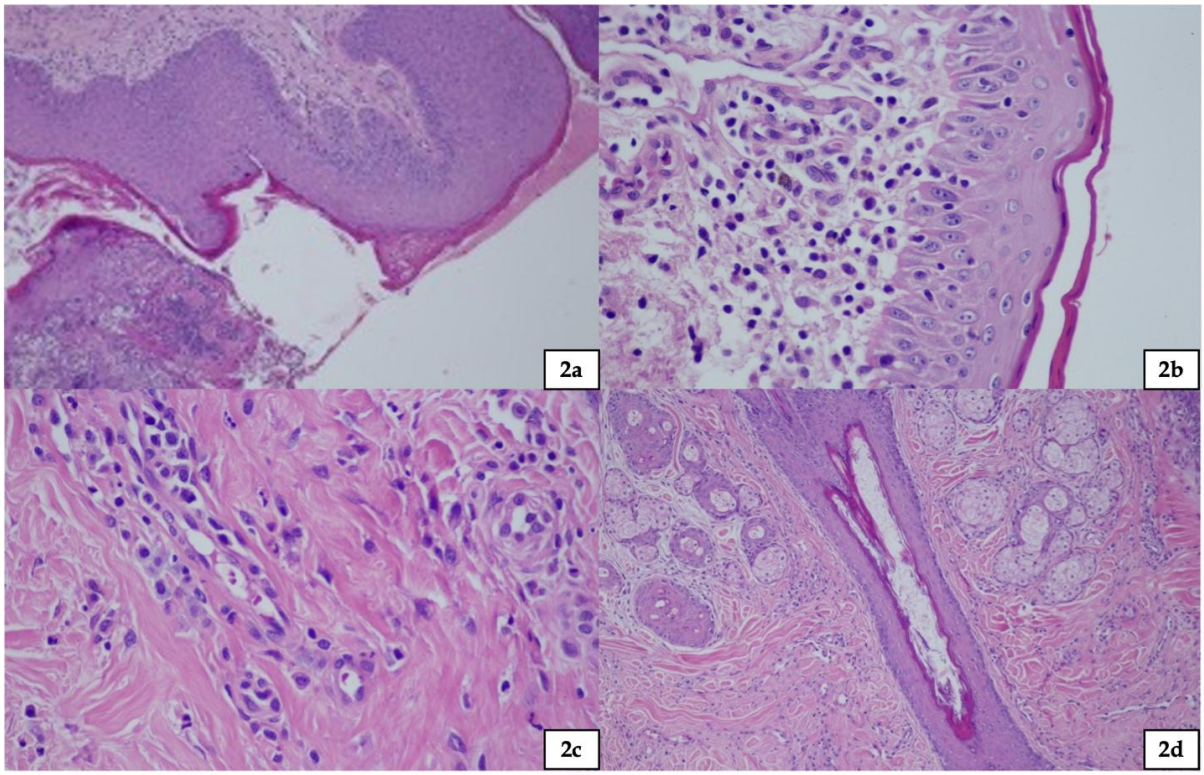

Figure 2 Histopathological findings before clinical remission of an atopic dog. (2a) epidermal hyperplasia and hyperkeratosis, (2b) and (2c) mixed dermal inflammatory cell infiltration, (2d) follicular keratosis and sebaceous gland hyperplasia.

Table 1 Haematology and blood chemistry profiles in an atopic dog on Wk0, Wk4, Wk16, and Wk82 of treatment.

Parameters	Wk0	Wk4	Wk16	Wk82	Reference*
RBC (x 10^6 /µl)	7.56	7.14	6.84	7.4	4.48 – 8.53
Hb (g/dl)	15.4	16.8	16.2	17.4	10.5 – 20.1
Hct (%)	47.5	52.1	46.4	52	33 – 58.7
WBC (x 10^3 /µl)	10.2	11.3	10.4	8.2	4 – 18
Neutrophil (x 10^3 /µl)	7.5	6.1	6.7	5.7	2.5 – 15.7
Eosinophil (x 10^3 /µl)	0	0	0	0	0 – 1.3
Lymphocyte (x 10^3 /µl)	2.5	0.84	0.56	0.54	0.3 – 3.9
ALT (U/L)	61	37	19	24	14 – 151
Creatinine (mg/dl)	1.23	0.59	0.8	0.8	0.4 – 2
BUN (mg/dl)	18.6	16	21	18	8 – 30
ALP (U/L)	1058	124	84	87	13 – 289

*Plumb, 2015

Table 2 Urinalysis profiles in an atopic dog on Wk0, Wk4, and Wk82 of treatment.

Parameters	Wk0	Wk4	Wk82	Reference*
Specific gravity	1.05	1.02	1.02	1.001 – 1.007
pH	6.0	6.5	7.0	5.5 – 7.5
Glucose	0	0	0	0
Ketone	0	0	0	0
Bilirubin	0	0	0	0 - Trace
RBC	0	0	0	0 – 5
WBC	1.5	1	1	0 – 5
Crystals	0	0	0	0

*Plumb, 2015

Discussion

The long-term administration of the oclacitinib tapering regimen for the control of pruritus appeared to be well tolerated in an atopic dog. The findings indicated the possibility of using oclacitinib every other day in cases where complete remission of clinical signs was obtained to maintain the skin condition. Since CAD has a life-long, chronic relapsing course with periods of remission and exacerbation, the treatment should be aimed at both controlling acute flares as well as having a long-term plan to decrease new flares. (Olivry *et al*., 2015). One of the key therapeutic goals when treating CAD is to terminate the itching quickly for the quality of life of both the dog and the owner. This is necessary to use appropriate antipruritic drugs in atopic cases (Favrot *et al*., 2010).

The treatment protocol should be revised for each case to prevent the ADRs following long–term drug uses. GCs such as prednisolone are the most frequently and effectively prescribed drugs for antipruritus in CAD cases, but they can cause severe ADRs. CsA is approved for use in the control of CAD but is limited by its long-term onset of action (Olivry *et al*., 2015). Oclacitinib is a JAK inhibitor approved for the control of pruritus associated with allergic dermatitis in dogs over 12 months of age (Cosgrove *et al*., 2015). The recommended dosage is 0.4 – 0.6 mg/kg PO q 12 h, administered for the first two weeks, followed by 0.4 – 0.6 mg/kg q 24 h as a maintenance dosage (Olivry *et al*., 2015). Oclacitinib is an effective control of pruritus in CAD and causes lower ADRs than GCs and CsA. Moreover, long-term use of oclacitinib has also been shown to be effective and safe in previous reports (Chansiripornchai and Chansiripornchai, 2019; Cosgrove *et al*., 2015).

Severe pruritus in an atopic dog was successfully controlled with oclacitinib in 2 weeks of treatment in this report. The PVAS score decreased from level 8 to 4 within 12 h of the first administration of oclacitinib. It was then decreased from level 4 to 2 within 24 h. The dog's skin lesions were reduced and its hair regrowth by week 3. The skin lesions were entirely resolved by week 12 (Fig. 1). The condition resolution was complete by week 18, during which the ADRs did not occur. Oclacitinib was proved to be effective in controlling CAD, decreasing pruritus within 24 h after the first administration of the drug, and improving the skin condition within two weeks of treatment. This report is in agreement with a previous study that oclacitinib provided relief from itching within the first two weeks of administration (Marsella *et al*., 2020).

Complete remission of skin lesions in the dog was observed from week 18 to week 30. The frequency of dosing of oclacitinib was then decreased from q 24 h to every other day. The main purpose for this adjustment of the oclacitinib regimen was to prescribe proper drug use in each case, both for treatment outcome and treatment cost. An alternating drug (hydroxyzine at a dosage of 2 mg/kg PO q 12 h) was used to prevent itching recurrence on oclacitinib omission day. Hydroxyzine is a type 1 antihistamine beneficial in dogs with a mild degree of atopic dermatitis (Olivry *et al*., 2015). After using this alternate-day regimen, the level of pruritus and skin lesions were similar to those when oclacitinib was administered PO q 24 h. The results are consistent with the recommendation that type 1 antihistamines, such as hydroxyzine, are appropriate for pruritus prevention before a flare occurs and should be given on a continuous daily basis (Olivry *et al*., 2015). There were no severe skin lesions throughout the 12 months of the oclacitinib tapering regimen. These results indicated the likelihood of an oclacitinib tapering regimen, as previously recommended to maintain the remission of clinical signs (Olivry *et al*., 2015).

On the other hand, the skin of atopic dogs is often colonized with *M. pachydermatis* and cocci bacteria such as *Staphylococcus pseudintermedius*. The treatment of both microbials is in need. Itraconazole and amoxicillin–clavulanic acid was prescribed as suitable drugs for the treatment of Malassezia and bacterial infection, respectively (Olivry *et al*., 2015). In our report, the number of *M. pachydermatis* and cocci bacteria found on the skin of the dog decreased by week two after antimicrobial dosing. The severity of otitis externa was also decreased by week 2 of the treatment. Hematology, blood chemistry, and urinalysis were also in the normal ranges. These findings were consistent with the previous data that ADRs of oclacitinib were less than 5 % in dogs. The ADRs that could be found were urinary tract infection, vomiting, otitis, pyoderma, diarrhea, and neoplasia (Cosgrove *et al*., 2015; Marsella *et al*., 2023).

In conclusion, CAD is a complicated disease that requires a multifarious approach and long–term management. Therefore, veterinarians should endeavor to inform the dog owner of the treatment plan and especially the benefits of each treatment protocol, the ADRs, and the cost of treatment. The results of this current report support the efficacy and

safety of long–term use of oclacitinib, both q 24 h regimen for 30 weeks and a tapering regimen for up to 12 months.

Acknowledgements

The authors would like to thank the dog' s owners for their kind cooperation during the data collection. We thank Professor Dr. Anudep Rungsipipat, Faculty of Veterinary Science, Chulalongkorn University for the histopathological evaluation and Assistant professor Simon Jeremy Peter Wright, Faculty of Arts, Chulalongkorn University for English language editing.

Ethical approval: No ethical approval was obtained because this study did not involve laboratory animals and only involved non - invasive procedures.

Authors contribution: **P. Chansiripornchai** contributed to the design, performed clinical studies, collected animal patient data, analysed the data and prepared the manuscript. **P. Sukanan** collected animal patient data.

Conflict of interest: The author (s) declared no potential conflicts of interest with respect to the research, authorship, and/ or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

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