

The frequency of urinary tract infection and subclinical bacteriuria in dogs with allergic dermatitis treated with oclacitinib: a prospective study

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Background – Oclacitinib is a selective Janus kinase inhibitor for the treatment of canine allergic pruritus and atopic dermatitis in dogs. Glucocorticoids and ciclosporin increase urinary tract infection (UTI) frequency in dogs with inflammatory skin disease.

Objective – Prospective study to evaluate the frequency of UTI and subclinical bacteriuria in dogs with allergic dermatitis receiving oclacitinib.

Methods – Client-owned dogs ≥ 2 years of age with a history of allergic dermatitis without apparent history of urinary tract disease or predisposition to UTI were included. Prior to enrolment, urinalysis and quantitative urine culture were performed after a washout period of at least 14 days from systemic antimicrobial drugs and 28 days for ciclosporin and systemic glucocorticoids. Dogs received oclacitinib at labelled dosing for an intended period of 180–230 days with a follow-up urinalysis and urine culture performed regardless of urinary tract signs. Systemic antimicrobial and immune-modulating drugs were not administered during the study.

Results – None of the 55 dogs in this study developed UTI while receiving oclacitinib based on follow-up urinalysis and urine culture performed during a range of 58–280 days (mean 195 days). Two dogs developed self-limiting abnormal urinary tract signs without urine culture or urinalysis findings consistent with UTI.

Conclusions and clinical importance – These findings indicate that bacteriuria is not an expected adverse effect in dogs treated with oclacitinib without a prior history of UTI or predisposing condition during this treatment period. Therefore, routine urine culture is not indicated for such dogs in the absence of abnormal urinalysis or clinical signs of urinary tract disease.

Introduction

Oclacitinib is a novel Janus kinase (JAK) inhibitor labelled, in some countries, for the treatment of pruritus associated with allergic dermatitis and control of atopic dermatitis (AD) in dogs.¹ Inhibition is selective for JAK 1 and JAK 3 receptors which are required for the activity of pro-inflammatory cytokines and pruritogenic cytokines.^{1,2}

An open label trial reported urinary tract infection/cystitis to occur in 28 of 247 (11.3%) oclacitinib-treated allergic dogs.³ Systemic antibiotic drugs were permitted during the study. Urinary tract infection (UTI) is a commonly diagnosed condition in dogs and is defined as a disruption in

host defence mechanisms leading to microbial adherence, multiplication and persistence within the urinary tract.^{4–7}

The diagnosis of UTI is based on the combination of appropriate clinical signs in addition to supporting urinalysis findings and, ideally, positive urine culture.^{4,8} In contrast to UTI, subclinical (or asymptomatic) bacteriuria is a term used to define the presence of bacteria in the urine determined by positive bacterial culture without concurrent cytological or clinical signs of urinary tract disease.⁸

An immunocompromised state can predispose patients to bacterial internalization of the uroepithelium with subsequent inflammation.⁴ In dogs predisposed to recurrent or persistent UTI, systemic glucocorticoids, chemotherapy or other immunosuppressive drugs are identified as the most common comorbidities.⁹ Dogs receiving ciclosporin and/or glucocorticoids for the control of inflammatory skin disease for a duration of 5 months–7 years were diagnosed with UTI in the absence of clinical urinary signs (subclinical bacteriuria) at frequencies of 13% and 18–27%, respectively.^{10–12} Only one of these studies described dogs actually showing clinical signs of urinary tract disease. These signs were noted in nine of 27 dogs with a positive urine culture.¹² Quantitative urine cultures

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were used in two of the studies, whereas a previous study utilized either positive urine culture or cytological evidence of bacteria on urinalysis to diagnose UTI.^{10–12} Baseline urinalyses and/or urine cultures were not required prior to drug administration in these retrospective studies to rule out pre-existing bacteriuria. The incidence of bacteriuria noted at a single time point in control dogs with chronic inflammatory skin disorders in the absence of immunomodulatory drugs ranged from 0 to 3%.^{10,11}

Studies involving the use of JAK inhibitors in humans, including tofacitinib and ruxolitinib, have reported an incidence of UTI in 2% and 6% of patients, respectively.^{13,14} Oclacitinib has been shown to block the effects of IL-6, a cytokine involved in the signalling pathway emanating from toll-like receptor 4 in bladder epithelial cells, along with IL-8, which in theory could lead to a decreased defence against urinary pathogens.^{2,15–17} Abnormal urinary tract signs described as “cystitis” in dogs receiving oclacitinib have been reported at a frequency of 0.5–11.3%.^{3,18,19} Quantitative urine cultures, the gold standard in confirming a UTI, were not evaluated in these studies to assess bacteriuria.^{5,8,20} The incidence of UTI or subclinical bacteriuria in allergic dogs receiving oclacitinib in the absence of concurrent antibiotic drugs and predisposing urinary or metabolic factors is unknown. Moreover, prospective studies evaluating the influence of immune-modulatory/immune-suppressant therapy on the development of UTI or subclinical bacteriuria by means of paired urinalysis and urine culture have not been performed. Therefore, the requirement for routine urinalysis and urine culture monitoring to assess for UTI or subclinical bacteriuria in dogs receiving long-term oclacitinib needs to be established.

The purpose of this study was to evaluate prospectively the frequency of UTI and subclinical bacteriuria in dogs treated chronically with oclacitinib for the management of allergic dermatitis.

Materials and methods

Study design

A prospective observational study design was used. Client-owned dogs were recruited through the Dermatology Service at the Colorado State University Veterinary Teaching Hospital from December 2014 to December 2015. Owners signed a written consent. Primary veterinarians involved in the referral setting were informed of their patients' enrolment and criteria for study withdrawal. The primary investigator was notified by the attending veterinarian or patient owner when adverse events occurred, or if patients developed conditions requiring nonpermitted drugs. All study protocols were approved by and conducted in accordance with the Colorado State University Institutional Animal Care and Use Committee.

Dogs were administered oclacitinib (Apoquel[®], Zoetis; Kalamazoo, MI, USA) by their owners according to label directions: 0.4–0.6 mg/kg given orally twice daily for 14 days, followed by once daily administration throughout the remainder of the study period. The intended study period was 180–230 days. All dogs received active drug; no placebo or control group was used due to difficulty in recruitment of dogs with allergic dermatitis without systemic immunomodulatory therapy for 180–230 days. For dogs that did not complete at least 180 days of the study, data were recorded regarding the number of days of study participation, in addition to urinalysis and urine culture findings prior to discontinuation of oclacitinib.

For the purposes of this study, UTI was defined as the presence of appropriate clinical signs consistent with urinary tract disease in

conjunction with a positive quantitative urine culture.^{8,20} A positive urine culture was defined as a bacterial colony count of >1,000 colony forming units (cfu)/mL. Subclinical bacteriuria was defined as the presence of a positive urine culture in the absence of clinical signs consistent with UTI.

Inclusion criteria

Dogs were at least 24 months of age with a history of pruritus and a presumptive diagnosis of allergic dermatitis, including AD and/or cutaneous adverse food reaction (CAFR). Diagnosis was based on characteristic clinical features and exclusion of other pruritic dermatoses. Differential diagnoses for allergic dermatitis such as flea-allergy dermatitis, external parasitism, bacterial or fungal dermatitis, metabolic conditions or other inflammatory dermatoses were eliminated through an appropriate diagnostic regimen and thorough physical examination as determined by the attending veterinarian. Dogs were not required to undergo a restrictive diet trial for the purposes of diagnosing CAFR, because the study protocol was inclusive for AD and CAFR.

The study protocol required dogs to be at least 24 months of age not only to comply with label instructions (at least 12 months of age), but also to allow for the development of signs and/or a diagnosis of any congenital, metabolic or anatomical predisposition for urinary tract disease to emerge prior to enrolment.

Administration of antihistamines, fatty acids, allergen-specific immunotherapy, ophthalmic and otic medications (including steroids or ophthalmic ciclosporin), otic flushes, topical hydrocortisone and topical antimicrobials were permitted up until the time of enrolment and throughout the study. Dogs showing clinical signs consistent with otitis externa and/or superficial bacterial pyoderma were enrolled and remained in the study as long as their conditions were adequately treated with topical therapy.

Exclusion criteria

In order to avoid recruiting cases with conditions predisposing to UTI, dogs were excluded from enrolment if they had a history within the previous 24 months of UTI, other urinary tract disease/abnormality, or conditions that would predispose individuals to UTI, including, but not limited to: history of bacteriuria, positive urine culture, crystaluria, urolithiasis, congenital urogenital abnormalities, prostatitis, pyelonephritis, neoplasia of the urinary tract, diabetes mellitus and hyperadrenocorticism. Clinical signs of urinary tract disease, including pollakiuria, stranguria, dysuria, periuria, urinary incontinence or haematuria within the prior 24 months were also criteria for exclusion.

Dogs were withdrawn from systemic antibiotic therapy for 14 days prior to initial urine sampling. A 28 day withdrawal period was required for oral glucocorticoids, oral ciclosporin, oclacitinib or any other systemic immune-modulating drugs prior to study enrolment. A 56 day withdrawal period was required for injectable glucocorticoids. Lokivetmab (Cytopoint[™], Zoetis) administration was not permitted prior to inclusion or during the course of the study.

Other exclusion criteria included demodicosis, malignant neoplasia, deep bacterial infection or fungal infection. Bitches who were pregnant or lactating were also not considered for enrolment. These exclusion criteria are in accordance with precautions described on the product label.¹

All dogs meeting inclusion criteria were sampled for routine urinalysis and urine culture prior to oclacitinib therapy. Dogs were then excluded if urine sediment analysis revealed bacteriuria, pyuria, or crystaluria and/or if the urine culture showed growth within 48 h. Microscopic haematuria was not considered to be an exclusion criteria with an otherwise inactive sediment analysis, given the potential for iatrogenic haematuria due to the cystocentesis technique.

Sample collection

Urine samples were collected using sterile technique via ultrasound-guided antepubic cystocentesis.²¹ Study protocol required a baseline sample and a second sample for urinalysis and urine culture at the conclusion of the study between 180 and 230 days, or prior to study

withdrawal. All urine samples were evaluated at the Colorado State University Veterinary Diagnostic Laboratory.

Urinalysis

Urine samples were transferred to a conical tube and gently agitated prior to testing. Urine specific gravity (USG) was determined after placing one drop of urine on a temperature-compensated refractometer. Routine protocols and manufacturer instructions were used for dipstick measurements including: pH, protein, glucose, ketones, bilirubin and blood (Chemstrip 10 UA, Roche Diagnostics; Indianapolis, IN, USA). A urine chemical test strip was completely submerged into the urine for 1 s and evaluated within 60 s by matching the test strip against the colour block references. Quality control measures of the urine test strips and refractometer were performed daily in the laboratory.

Samples were then centrifuged for 5 min at 1500 rpm (403 g). Approximately 1–2 mL of supernatant was removed for the sulfosalicylic acid turbidimetric (SSA) test to evaluate for proteinuria if indicated by a positive protein result on dipstick. The remaining supernatant was decanted and the sediment pellet was resuspended by agitating the tube. A drop of mixed sediment was transferred with a pipette to a clean glass slide and a coverslip was placed over it. A Wright–Giemsa stained air-dried smear of the sediment was used to confirm the presence of bacteria or to distinguish between bacteria and crystals. All samples were evaluated with a microscope using low power magnification ($\times 10$) to count casts and high power field (hpf, $\times 40$) magnification to count erythrocytes, leucocytes and epithelial cells. A semi-quantitated method was used to evaluate crystals, bacteria, sperm and fat. Slides were considered positive for bacteriuria if there was ≥ 1 bacterium/hpf, and reported as negative if there were no bacteria observed in any field. Pyuria was considered if there was > 3 leucocytes/hpf identified.²² Microscopic haematuria was defined as ≥ 5 erythrocytes/hpf and positive haeme result found on urine dipstick.²² Proteinuria was reported if there was $\geq 1+$ protein on the SSA test.

Bacterial culture of the urine

Two separate Columbia plates (Becton, Dickinson and Company; Sparks, MD, USA) were inoculated, one with 1 μ L of urine and the other with 10 μ L of urine. A third plate consisting of MacConkey agar (Becton, Dickinson and Company) was inoculated with 1 μ L of urine from the same sample. The MacConkey plates were incubated in ambient air and Columbia plates in 10% carbon dioxide at 36°C for 18–24 h. All plates were observed after 18–24 h of incubation for growth and then reincubated for an additional 18–24 h. Colonies were counted on the plates and recorded as cfu/mL. Counts greater than 100 colonies were reported as $> 100,000$ cfu/mL.

Criteria for study withdrawal

Development of any clinical signs related to urinary tract disease during the study period required a urinalysis and quantitative urine culture, but not necessarily immediate withdrawal from the study. Dogs continued to receive oclacitinib during the intended study period despite urinary tract signs if there was no evidence for UTI on urine sediment analysis and/or urine culture. The presence of bacteriuria, pyuria, crystalluria and/or positive urine culture required study withdrawal. Dogs were withdrawn from the study if oclacitinib was stopped by the owner for a total of > 28 days during the study.

The use of systemic antimicrobial or immune-modulating drugs (such as systemic glucocorticoids) were criteria for withdrawal. Other withdrawal criteria included development of: pregnancy, demodicosis, malignant neoplasia, diabetes mellitus, hyperadrenocorticism, or deep bacterial or fungal infection.

Data analysis

This study used descriptive statistics. Statistical software (R® Statistical Program, Bell Laboratories; Murray Hill, NJ, USA) was used to

determine the median values of oclacitinib dosage, patient body weight and patient age, in addition to mean values of days receiving oclacitinib and time to second urine sampling.

Results

Sixty six dogs met the inclusion criteria. Results of preliminary urinalysis and urine culture led to the exclusion of six dogs: bacteriuria on urine sediment analysis in three dogs (4.5%), two of which had a positive urine culture (3%), and crystalluria in four dogs (6%). Bacterial growth on quantified urine cultures from dogs included *Escherichia coli* ($n = 1$) and *Staphylococcus aureus* ($n = 1$). The dogs with crystalluria did not have positive urine cultures nor bacteriuria on sediment analysis. Amorphous crystals were identified in two dogs (3%), whereas struvite crystals were found in two dogs (3%). None of the dogs with either crystalluria or bacteriuria (found on sediment analysis or urine culture) showed clinical signs of urinary tract disease.

Sixty dogs were enrolled in the study. Five of these dogs did not complete the study and did not return for follow-up urinalysis or urine culture for the following reasons: oclacitinib was not an effective treatment ($n = 1$), the owner discontinued oclacitinib for more than 28 days due to seasonal improvement in pruritus ($n = 1$) and three were lost to follow-up with no information regarding clinical response to oclacitinib, adverse effects or laboratory data.

A total of 55 dogs were available for a follow-up urinalysis and urine culture. Forty seven of these dogs achieved 180–230 days of oclacitinib therapy. Rationale for the early withdrawal of eight dogs included: severe superficial bacterial pyoderma requiring systemic antibiotic therapy ($n = 3$), metronidazole for the treatment of colitis ($n = 1$), soft tissue surgery requiring perioperative antibiotics ($n = 2$), discontinuation of oclacitinib due to decreased efficacy over time ($n = 1$) and urinary incontinence ($n = 1$). Those individuals treated for less than 180 days received 58, 86, 140, 140, 147, 161, 167 and 169 days of oclacitinib therapy prior to urine sample collection.

All dogs enrolled received oclacitinib 0.4–0.6 mg/kg (median 0.5 mg/kg) orally twice daily for 14 days, followed by administration once daily for the remainder of the study period. Fifty four of 55 (98%) of dogs received oclacitinib continuously until follow-up urine sample. One dog with seasonal AD was sampled 14 days after seasonal discontinuation of oclacitinib.

The ages of the 55 dogs with follow-up data ranged from 2 to 13 years (median 5 years). Of these, 31 were male (26 castrated and five intact) and 24 were spayed females. Body weight at enrolment ranged from 3.2 to 50 kg (median 24.2 kg). Dog breeds with more than one representation included mixed breed ($n = 20$), Labrador retriever (4), Jack Russell terrier (3), English bulldog (2), shih tzu (2), Australian shepherd dog (2) and Chesapeake Bay retriever (2). There was a single representation the following breeds: Scottish terrier, bloodhound, Swedish Vallhund, German shepherd dog, dachshund, Belgian Malinois, Rottweiler, silky terrier, boxer, Akbash, cocker spaniel, Yorkshire terrier, keeshond, Irish setter, soft-coated wheaten terrier, standard poodle, West Highland

white terrier, Alaskan malamute, Australian cattle dog and German short-haired pointer.

Among dogs with follow-up data, 29 of 55 (52.7%) were diagnosed with AD, two of 55 (3.6%) were diagnosed with CAFR (both had concurrent AD) and 26 of 55 (47.2%) were assigned a general diagnosis of allergic dermatitis because no restrictive diet trial had been performed to rule out cutaneous adverse food reaction.

Concurrent diseases at the time of enrolment

Dermatoses in addition to allergic dermatitis were reported in 14 of 55 (25.5%) of dogs at enrolment including otitis externa ($n = 8$), superficial bacterial pyoderma ($n = 3$), subcutaneous lipoma ($n = 2$), ear margin seborrhoea ($n = 2$), sebaceous adenoma ($n = 1$), sebaceous adenitis ($n = 1$), nasal philtrum arteritis ($n = 1$), chin furunculosis ($n = 1$), recurrent flank alopecia ($n = 1$) and discoid lupus erythematosus of the nasal planum ($n = 1$).

Nondermatological conditions were reported in 15 of 55 (27.3%) of dogs including osteoarthritis ($n = 5$), patellar luxation ($n = 3$), mitral valve disease ($n = 1$), tricuspid regurgitation ($n = 1$), heart murmur of undiagnosed aetiology ($n = 1$), gingival hyperplasia ($n = 1$), systemic hypertension ($n = 1$), brachycephalic airway syndrome ($n = 1$), blepharitis ($n = 1$), immune-mediated keratitis ($n = 1$), myelopathy ($n = 1$), keratoconjunctivitis sicca ($n = 1$) and entropion ($n = 1$).

Concurrent medications

None of the enrolled study dogs with follow-up ($n = 55$) received any drugs in accordance with the withdrawal criteria prior to their second urine sample collection for urinalysis and culture. Topical and systemic therapies were administered during the study period in 44 of 55 (80%) including topical antimicrobials (cutaneous, otic and ophthalmic), topically administered immune-modulatory/anti-inflammatory drugs (cutaneous, otic and ophthalmic), topical moisturizers and cleansers (cutaneous and otic), antihistamines, allergen-specific immunotherapy, analgesics, joint supplements, parasiticides, nutritional supplements, benazepril and fluoxetine (See Tables S1 and S2 in Supporting Information).

Urine culture results

No growth was reported on any urine sample submitted for culture at any time point. Urine from 55 dogs was sampled for culture after starting oclacitinib. The sampling time points ranged from 58 to 280 days (mean 195 days); 47 were sampled ≥ 180 days into treatment. Fifty three dogs were sampled once during oclacitinib treatment. Two were sampled twice after starting oclacitinib: Case 6 with clinical signs of pollakiuria (days 141 and 280) and Case 46 with proteinuria (days 113 and 219) found on yearly urinalysis performed by the referring veterinarian.

Urinalysis results

Urine from 55 dogs was sampled for urinalysis after starting oclacitinib at time points 58–280 days (mean 195 days), including 47 dogs sampled ≥ 180 days into treatment. An additional urinalysis was performed on two dogs. The dog exhibiting pollakiuria (Case 6) had a total of two urinalyses performed during oclacitinib administration (on days 141 and 280). Case 46, which developed

proteinuria, was sampled at five additional time points from Day 0 without discontinuing oclacitinib to monitor proteinuria (on days 107, 113, 143, 191 and 219). No bacteriuria was noted for any of the 55 dogs (0%) at any time point.

Findings noted on follow-up urinalysis included: proteinuria, crystalluria, haematuria, casts and leucocytes (Table 1). Six of 55 dogs (10%) developed proteinuria during the study, measured as the following on SSA: 1+ ($n = 4$), 2+ ($n = 1$) and 3+ ($n = 1$). Prior to oclacitinib administration, four of six were negative for proteinuria based on dipstick and SSA, whereas the other two dogs measured trace protein or 1+. Cases 23, 44 and 47 had 1+ protein [urine protein: creatinine (UPC) ratio not evaluated due to clients' financial concerns] and USG values of 1.065, 1.057 and 1.040, respectively. Urine protein: creatinine ratios were evaluated in three dogs (cases 4, 18 and 46) with proteinuria. Those results paired with SSA findings were as follows: (Case 4) 3+ protein, UPC ratio of 7.95 (reference interval 0.0–0.19), (Case 18) 2+ protein, UPC ratio of 1.04 and (Case 46) 1+ protein, UPC ratio of 1.29. The USG values for those dogs were 1.049, 1.035 and 1.006, respectively. Case 18 began the study with trace protein on SSA. After the study period, oclacitinib was discontinued a month later due to decreased efficacy. A follow-up UPC performed 1 month after discontinuing oclacitinib showed continued proteinuria (1.09). In the case of the highest proteinuria value (Case 4), a UPC was declined by the client and therefore not performed at the final study day despite the detection of 3+ proteinuria on SSA. A follow-up visit 5 months after study completion showed persistent proteinuria (3+ on SSA) and a UPC of 7.95. At the time of this follow-up, the patient developed renal azotaemia and was diagnosed with multicentric lymphoma.

Crystalluria was detected on follow-up urine sediment analysis in nine of 55 (16.4%) dogs. None displayed any abnormal urinary tract signs. Crystal types identified at the conclusion of the observation period included amorphous (six of nine) and struvite (three of nine), all reported as few/hpf. Two of the dogs with amorphous crystals (cases 6 and 18) had urinalysis performed after the study period (days 280 and 368 of treatment, respectively), with no crystalluria. Diagnostic imaging to assess for urolithiasis was not performed for any of the dogs.

Granular casts were found in low numbers in three of 55 (5.5%) dogs. The urinalysis from one of these three dogs (Case 42) was found to have increased leucocyte numbers (6–10/hpf) on urine sediment analysis (normal ≤ 3 /hpf). The remainder of the urinalysis was unremarkable. The other two dogs with granular casts (cases 1 and 43) had otherwise inactive sediment. Serum biochemistry was performed on cases 1 and 42 with blood urea nitrogen and creatinine values within normal limits. Repeat urinalysis was not performed on any of these dogs after the study.

Seven of 55 (12.7%) dogs were positive for haematuria on follow-up urinalysis. No clinical signs of haematuria were noted by the owners and the laboratory classified the urine colour of all samples as "yellow" on gross examination. The interval of erythrocyte counts was 10 to >150 /hpf and detection of blood from the urine dipstick was as follows: 1+ ($n = 1$ dog), 2+ ($n = 3$) and 3+ ($n = 3$). In comparison to pre-study values, haematuria was

Table 1. Dogs receiving oclacitinib-abnormal findings on follow-up urinalysis

	Protein on SSA test	Crystalluria	Haematuria [†]	Casts	Pyuria
Case Number					
1	—	—	—	Granular	—
4	3+	—	—	—	—
6	—	Amorphous	—	—	—
8	—	—	2+ (10–20 RBC/hpf)	—	—
13	—	—	3+ (50–100 RBC/hpf)	—	—
15	—	Struvite	—	—	—
18	2+	Amorphous	1+ (10–20 RBC/hpf)	—	—
22	—	Amorphous	—	—	—
23	1+	—	—	—	—
27	—	Struvites	—	—	—
29	—	—	3+ (50–100 RBC/hpf)	—	—
30	—	—	2+ (20–50 RBC/hpf)	—	—
32	—	Amorphous	—	—	—
37	—	—	2+ (>150 RBC/hpf)	—	—
39	—	—	3+ (20–50/hpf)	—	—
42	—	—	—	Granular	6–10 WBC/hpf
43	—	—	—	Granular	—
44	1+	—	—	—	—
46	1+	—	—	—	—
47	1+	—	—	—	—
49	—	Amorphous	—	—	—
51	—	Amorphous	—	—	—
54	—	Struvites	—	—	—

SSA sulfosalicylic acid, RBC red blood cells, WBC white blood cells, hpf high power field, — not present.

[†]Haematuria is expressed as the dipstick measurement followed by the microscopic findings.

detected in two (cases 18 and 29) of the seven dogs prior to oclacitinib administration without any additional clinically relevant findings on urinalysis. The cause of haematuria was not determined for any dog. Iatrogenic haematuria due to the cystocentesis technique was suspected in most cases. However, a naturally voided urine sample was collected from case 29 who was continued on oclacitinib beyond the study period to rule out iatrogenic causes for haematuria. This repeated sample revealed 1+ blood on the urine dipstick as well as 5–15 erythrocytes/hpf. An ultrasonographic evaluation of the urinary tract including kidneys, ureters, bladder and urethra did not reveal abnormalities. Diagnostic imaging (besides an ultrasound-guided antepubic cystocentesis) was not completed on any other patients found to have microscopic haematuria.

Abnormal urinary events

Two of the 55 (3.6%) dogs were reported to have abnormal urinary behaviour. A urinalysis and urine culture were performed in both dogs and urinalyses were normal and urine cultures were negative. Case 6 developed pollakiuria 141 days after starting oclacitinib. This was described by the owner as making multiple postural attempts to urinate. The dog remained in the study after not finding any criteria for withdrawal on urinalysis and urine culture. No further urinary investigation was performed. Her abnormal urinary behaviour resolved within 2 months of initial onset. Oclacitinib administration was continued until study completion on Day 280. Case 26 developed urinary incontinence on Day 167 of oclacitinib therapy. The behaviour was described as multiple episodes of suspected involuntary urination during sleep over the course of 3 weeks. The owner elected to withdraw the dog from

the study. Signs of urinary incontinence resolved after discontinuation of oclacitinib.

Abnormal health events (nonurinary)

Abnormal health events were reported in 16 of 55 (29%) enrolled dogs during the study period. Cutaneous events included histiocytomas ($n = 2$), focal deep bacterial pyoderma secondary to trauma ($n = 1$), superficial bacterial pyoderma ($n = 2$), perivulvar dermatitis ($n = 1$), otitis externa ($n = 1$), *Malassezia* pododermatitis ($n = 1$) and worsening pruritus ($n = 1$). With the exception of the dog (Case 49) that developed worsening pruritus and the one that developed perivulvar dermatitis (Case 35), the cutaneous adverse events did not require study withdrawal. The histiocytoma of Case 10 resolved spontaneously within 3 weeks, whereas the histiocytoma of Case 12 present for 2 months was removed by the referring veterinarian after the conclusion of the study.

Gastrointestinal events were noted in four of 55 (7.3%) dogs and included vomiting ($n = 3$), colitis ($n = 1$) and anorexia ($n = 1$). Case 11 experienced both vomiting and colitis, requiring withdrawal from the study due to the administration of metronidazole. The cause of the vomiting and colitis was not determined and did not require discontinuation of oclacitinib for resolution despite withdrawal from the study. The vomiting noted from Case 48 was attributed to foreign body ingestion requiring a gastrotomy and perioperative antibiotics, leading to withdrawal from the study. Vomiting and anorexia resolved in the other two dogs without discontinuation of oclacitinib from the study.

Other adverse clinical signs included lethargy ($n = 1$), keratoconjunctivitis sicca with concurrent corneal ulcer ($n = 1$), apocrine gland anal sac adenocarcinoma ($n = 1$) and a

fractured tooth requiring extraction under general anaesthesia ($n = 1$). There were no perioperative antibiotics administered for the extraction of the fractured tooth and the individual remained in the study. Development of malignant neoplasia in addition to perioperative cefoxitin prior to surgical biopsy in Case 42 required withdrawal from the study in the case of apocrine gland anal sac adenocarcinoma. The other dogs showing adverse signs listed above did not require discontinuation of oclacitinib nor withdrawal from the study to manage their conditions.

Discussion

The presence of bacteriuria based on urine sediment analysis and urine culture was not detected from any dog enrolled in this study. To the best of the authors' knowledge, this is the first prospective study using urine culture paired with urinalysis to evaluate the incidence of urinary tract infection in a population of dogs diagnosed with presumptive allergic dermatitis receiving long-term (≥ 180 days) immune-modulatory therapy.

The study protocol intended for all dogs to be evaluated after at least 180 days of oclacitinib administration. However, eight of 55 dogs required an earlier withdrawal from the study primarily because of a need for systemic antimicrobial therapy ($n = 6$) or due to a decreased efficacy of the drug over time ($n = 1$) or the development of urinary incontinence ($n = 1$). Forty seven of 55 (85.5%) of dogs were evaluated after 180 days (6 months). Fifty three of 55 (96.4%) completed ≥ 140 days (4.5 months) of therapy. Nineteen of 55 (34.5%) received oclacitinib for 210–280 days (7–9 months) prior to their follow-up urinalysis and urine culture.

In order to assess statistically the increased risk for UTI during the study period, a control group consisting of dogs diagnosed with allergic dermatitis but not receiving any systemic antimicrobials or systemic immune-modulatory therapy (i.e. glucocorticoids, ciclosporin, lokivetmab) was needed. However, acquiring the numbers of dogs for a control group that would achieve statistical power was not available within the Dermatology Service population. Additionally, many dogs in our service diagnosed with allergic dermatitis do not achieve reasonable quality of life in the absence of these interventions. Based on urinalysis and urine culture data acquired during the recruitment phase of this study, prior to starting oclacitinib, subclinical bacteriuria was detected in two of 66 (3%) of dogs diagnosed with allergic dermatitis. Both of these dogs had no exposure to any immune-modulating drugs, including glucocorticoids or ciclosporin within 2 years prior to urine sample collection. This incidence of subclinical bacteriuria is similar to the control group evaluated in a previous study describing the frequency of UTI in dogs treated with ciclosporin with or without concurrent glucocorticoid therapy.¹¹ The control group in that study consisted of canine patients with inflammatory skin disorders that had not been administered ciclosporin or glucocorticoids for 6 months or antibiotics for 3 months. Dogs were sampled at one time point and the authors reported UTI without clinical signs in two of 59 (3%) of dogs.

It is estimated that 14% of dogs will be affected by UTI during the course of their lifetime.²³ Urinary tract infection has been shown to occur in 17% of dogs presenting for necropsy for various reasons not necessarily related to

urinary tract disease.²⁴ The prevalence of subclinical bacteriuria has been reported in healthy female dogs (8.9%), dogs presenting for elective surgical procedures (8.9%) and morbidly obese dogs (25%).^{25–27} These data support the necessity of quantitative urine cultures as an indicator of bacteriuria in dogs without urinary tract signs. Subclinical bacteriuria has been reported in dogs with inflammatory skin disease treated chronically with ciclosporin in which nine of 71 (13%) dogs had positive urine cultures at a single time point of sample collection.¹¹ In addition, the long-term use of systemic glucocorticoids in dogs with chronic skin disease has been associated with a positive urine culture in 23 of 127 (18%) dogs to 27 of 71 (38%) dogs.^{10,12} Considering the reported frequencies of UTI as well as subclinical bacteriuria that occur naturally or under the influence of immune-modulatory therapy, the 0% incidence in this present study suggests that oclacitinib does not increase the frequency of UTI in dogs with no other predisposing conditions or recent UTI history.

Five prospective studies evaluating the safety of oclacitinib have described urinary events and/or the results of urinalyses during drug administration.^{3,18,19,28,29} None of these studies identified previous urinary tract disease as an exclusion criteria or required urine culture screening prior to prescribing oclacitinib. Only two of these studies excluded dogs with abnormal urinalysis findings prior to study enrolment.^{3,19} Urinalysis as a means of monitoring changes within the urinary tract during the course of oclacitinib therapy was performed in four of the studies.^{3,19,28,29} Two studies did not describe any results from the urinalyses.^{28,29} One other study reported no significant differences in urinalyses compared to placebo.¹⁹ A fifth study reported a one of 179 (0.5%) incidence of "cystitis," although urinalyses were not performed while dogs were administered oclacitinib.¹⁸ The study investigating the long-term use of oclacitinib in dogs with allergic skin disease noted 13 of 247 (5.3%) dogs having abnormal urinalyses during the observation period.³ These changes included proteinuria, haematuria, bacteriuria, hyposthenuria and microalbuminuria. This was also an open-label study design which allowed antimicrobial therapy when warranted. In addition, 28 of 247 dogs (11.3%) in that study were documented as having "urinary tract infection/cystitis" with 37 unique reported occasions in which an abnormal clinical sign was observed. None of these occasions were classified as serious adverse events. It is important to note that urine culture results were not reported in either study describing cystitis, and that samples collected for urinalysis were acquired either via cystocentesis or from natural voiding in the long-term study.

Urine culture via cystocentesis with bacterial quantification is the gold standard for diagnosing UTI definitively.^{5,8,20} Previous studies have reported a 46–64% incidence of UTI diagnosed by urine culture in dogs displaying clinical signs of urinary tract disease.³⁰ Thus bacterial infection is not the only cause for urinary tract signs and other aetiologies could have been playing a role in the previous reports (i.e. urolithiasis, neoplasia, cysts and prostatitis).³¹ Therefore, our exclusion criteria in addition to the use of urine culture as a required diagnostic may account for the lower reported incidence of UTI in our study population compared with the aforementioned

studies. Interestingly, two dogs in our study exhibited abnormal urinary behaviours 141 and 167 days after starting oclacitinib. These behaviours manifested as pollakiuria in Case 6 and urinary incontinence in Case 26. Although an aetiology for these events was not determined, UTI was not present. Both demonstrated resolution of clinical signs without antibiotic intervention.

General risk factors for UTI have been reported, although prospective studies are lacking. Urinary tract infection appears to occur more commonly in female dogs, and spayed female dogs are noted to be at higher risk as oestrogen might have a protective effect.^{4,7,32} Older age also appears to be a risk factor.^{7,9,24,33,34} Dog breeds more commonly reported to have persistent or recurrent UTI were present in our study, including retrievers, a German shepherd mixed breed dog and spaniels.^{6,7} Females were not over-represented in our study and all females (24 of 55) enrolled were spayed. The median age of enrolled dogs was 5 years. Thus, we conclude that the low incidence of UTI noted in the present study is unlikely due to gender, reproductive status, age or breed.

Proteinuria was found in six of 55 (10%) dogs in this study, none of which had a UTI or subclinical bacteriuria. None of these dogs was treated with topical glucocorticoids (cutaneous, otic or ophthalmic). This is a higher incidence compared to a previous report wherein four of 247 (1.6%) dogs treated long term with oclacitinib developed proteinuria.³ In our study, three dogs had a UPC performed. Cases 18 and 46 had no identifiable systemic cause for proteinuria and otherwise showed no abnormal clinical signs. Case 4 was later diagnosed with multicentric lymphoma, which was proposed to be the most likely cause for the proteinuria. Nonurinary tract inflammatory disease may result in a transient, mild renal proteinuria.^{35–37} Significant correlation between proteinuria and skin disease (including AD) is documented in humans; however, the incidence of proteinuria in dogs affected by dermatitis has not been established.^{38,39} Future prospective, controlled studies using UPC ratios are needed to investigate the significance and frequency of proteinuria in allergic dogs treated with oclacitinib.

Previous studies of oclacitinib-treated dogs described clinical signs of haematuria in two of 61 (3.3%) dogs and transient haematuria as a urinalysis finding in four of 247 (0.8%) dogs, all of which resolved spontaneously.^{3,28} None of the dogs in the present study exhibited clinical signs of haematuria, however, microscopic haematuria was detected in seven of 55 (12.7%) dogs in the absence of urinary clinical signs and with an otherwise normal urinalysis. A repeated urinalysis was available for Case 29 sampled 1 week after the study from naturally-voided urine. The dog was found to have microscopic evidence of haematuria despite lack of clinical signs. A follow-up ultrasonographic evaluation of the urinary tract showed no evidence of disease. With the exception of this particular case of microscopic haematuria of unknown aetiology, it was assumed that the cystocentesis technique for the other six dogs was most likely responsible for these changes.

Other findings in the present study included granular casts, crystalluria and pyuria. Given the lack of lower urinary tract signs, negative bacterial culture from the urine and the low numbers of crystals and casts found, these

findings were not considered clinically significant and oclacitinib was continued.

At least one form of topical antimicrobial was applied to the skin of 21 of 55 (38.2%) dogs at some time point during the study. It is feasible that routine application of a chlorhexidine-based product might help prevent an ascending bacterial infection originating from the perianal or external urogenital tract in comparison to dogs that were not treated with a topical antimicrobial in the perineal region.

The types of nonurinary adverse events reported in this population of dogs undergoing treatment with oclacitinib were similar to those reported previously.^{3,29}

The strengths of this study include a baseline urinalysis and culture screening of all dogs prior to study enrolment and oclacitinib administration in order to ensure no pre-existing UTI or subclinical bacteriuria. In addition, we prospectively evaluated the urine of all dogs with chronic oclacitinib administration regardless of any clinical sign of urinary tract disease. Systemic antibiotics also were prohibited during the study to avoid confounding assessment of bacteriuria via urine sediment analysis and urine culture. These exclusion factors selected for a population of dogs with no pre-existing history of urinary tract disease, no anatomical/congenital predispositions for urinary tract disease, or other known factors that might impair immunocompetence (i.e. immune-modulatory drugs, malignant neoplasia, hyperadrenocorticism or diabetes mellitus). When compared to previous studies, the more stringent selection criteria in this prospective study allowed for a better assessment of the true impact of oclacitinib on UTI/subclinical bacteriuria and helped to reduce confounding factors inherently present in retrospective study designs.

Future prospective studies are required to evaluate the impact of oclacitinib in patients with risk factors for UTI, a history of UTI, or active UTI. The findings from this study suggest that neither clinical UTI nor subclinical bacteriuria is an expected finding in dogs treated with oclacitinib without a prior history of UTI or predisposing condition during this treatment period. Therefore, routine urine cultures are not warranted for such dogs in the absence of abnormal urinalysis or clinical urinary signs, during this treatment period.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Concurrent topical therapy used during the study period.

Table S2. Concurrent systemic medications used during study period.

Résumé

Contexte – L'oclacitinib est un inhibiteur sélectif de Janus kinase indiqué dans le traitement du prurit allergique du chien et de la dermatite atopique canine. Les corticoïdes et la ciclosporine augmentent la fréquence des infections du tractus urinaire (UTI) chez les chiens atteints de dermatoses inflammatoires.

Objectifs – Une étude prospective pour évaluer la fréquence des UTI et des bactériuries subcliniques chez les chiens atteints de dermatites allergiques recevant de l’oclacitinib.

Méthodes – Les chiens de propriétaires ≥ 2 ans avec des commémoratifs de dermatite allergique sans antécédents de maladie urinaire ou de prédisposition aux UTI ont été inclus. Avant l’inclusion, une analyse et une culture urinaire quantitative ont été réalisées après une période de sevrage d’au moins 14 jours d’antibiotiques systémiques et de 28 jours de ciclosporine et de corticoïdes systémiques. Les chiens recevant de l’oclacitinib aux doses recommandées pendant une période de 180-230 jours avec un suivi d’analyses urinaires et de cultures urinaires réalisées en fonction des symptômes d’atteintes du tractus urinaire. Les antimicrobiens systémiques et les médicaments immunomodulateurs n’ont pas été administrés au cours de l’étude.

Résultats – Aucun des 55 chiens de cette étude n’ont développé d’UTI pendant l’administration d’oclacitinib sur 58-280 jours (moyenne 195 jours) basé sur les analyses et les cultures urinaires. Deux chiens ont développés des signes anormaux d’atteinte du tractus urinaire sans culture urinaire ou analyse correspondant à une UTI.

Conclusion et importance clinique – Ces données indiquent que la bactériurie n’est pas un effet secondaire attendu chez les chiens traités à l’oclacitinib sans antécédent d’UTI ou de conditions prédisposantes au cours de cette période de traitement. Ainsi, Une culture de routine n’est pas indiquée pour ces chiens en l’absence d’analyse urinaire anormale ou de signes cliniques d’atteinte du tractus urinaire.

Resumen

Introducción – Oclacitinib es un inhibidor selectivo de Janus quinasa para el tratamiento del prurito causado por alergia y la dermatitis atópica en perros. Los glucocorticoides y la ciclosporina aumentan la frecuencia de la infección del tracto urinario (UTI) en perros con enfermedad inflamatoria de la piel.

Objetivo – Estudio prospectivo para evaluar la frecuencia de UTI y bacteriuria subclínica en perros con dermatitis alérgica tratados con oclacitinib.

Métodos – Se incluyeron perros ≥ 2 años de edad con historia de dermatitis alérgica, pero sin historia de aparente enfermedad urinaria o predisposición a UTI. Antes de la inclusión en el grupo de estudio, se realizaron análisis de orina y cultivo cuantitativo de orina después de un período de lavado de al menos 14 días sin antimicrobianos sistémicos y 28 días para ciclosporina y glucocorticoides sistémicos. Los perros recibieron oclacitinib a las dosis recomendadas durante un período previsto de 180-230 días con análisis de orina de seguimiento y cultivo de orina realizado independientemente de los signos de las vías urinarias. Durante el estudio no se administraron fármacos antimicrobianos sistémicos ni inmunomoduladores.

Resultados – Ninguno de los 55 perros en este estudio desarrolló UTI mientras recibía oclacitinib basado en los resultados del análisis de orina y el cultivo de orina realizados como seguimiento durante un periodo de 58-280 días (media 195 días). Dos perros desarrollaron signos clínicos de enfermedad del tracto urinario auto-limitantes sin resultados de cultivo de orina o de análisis de orina indicativos de ITU.

Conclusiones e importancia clínica – Estos hallazgos indican que la bacteriuria no es un efecto adverso esperado en perros tratados con oclacitinib que no tuviesen antecedentes previos de UTI o condiciones predisponentes durante este período de tratamiento. Por lo tanto, el cultivo de orina de rutina no está indicado para tales perros en ausencia de análisis de orina anormal o de signos clínicos de enfermedad del tracto urinario.

Zusammenfassung

Hintergrund – Oclacitinib ist ein selektiver Januskinase Inhibitor zur Behandlung von allergischem Juckreiz beim Hund, sowie der atopischen Dermatitis des Hundes. Glucocortikoide und Ciclosporin erhöhen die Häufigkeit von Harnwegsinfektionen (UTI) bei Hunden mit entzündlicher Hauterkrankung.

Ziel – Durchführung einer prospektiven Studie zur Evaluierung der Häufigkeit von UTI und subklinischer Bakteriurie bei Hunden mit allergischer Dermatitis, die Oclacitinib erhalten.

Methoden – Es wurden Hunde in Privatbesitz im Alter von ≥ 2 Jahren mit der Anamnese einer allergischen Dermatitis ohne offensichtliche Anamnese einer Harnwegsinfektion oder Prädisposition für UTI inkludiert. Vor Aufnahme in die Studie wurde nach einer Wash-Out Periode von mindestens 14 Tagen für systemische Antibiotika und 28 Tagen für Ciclosporin und systemischen Glucokortikoiden eine Urinanalyse und eine quantitative Urinkultur durchgeführt. Die Hunde erhielten Oclacitinib in der vorgegebenen Dosierung für eine beabsichtigte Zeitspanne von 180-230 Tage. Unabhängig von Zeichen des Harntraktes wurde eine Follow-Up Urinanalyse und eine Urinkultur durchgeführt. Es wurden während der Studie keine systemischen Antibiotika und immunmodulierenden Medikamente verabreicht.

Ergebnisse – Aufgrund der Follow-Up Urinanalyse und der Harnkultur, die während einer Spanne von 58-280 Tagen (Durchschnitt 195 Tage) durchgeführt wurde, konnte festgestellt werden, dass keiner der 55 Hunde in der Studie eine UTI während er Oclacitinib erhielt, entwickelte. Bei zwei Hunden traten selbstlimitierende abnormale Zeichen des Harntraktes auf ohne dass die Harnkultur oder die Befunde der Urinanalyse auf eine UTI hingewiesen hätten.

要約

背景 – オクラシチニブは犬のアレルギー性掻痒症およびアトピー性皮膚炎の治療のための選択的ヤーヌスキナーゼ阻害剤である。グルココルチコイドおよびシクロスポリンは、炎症性皮膚疾患を有する犬に対して尿路感染症(UTI)の頻度を増加させる。

目的 – オクラシチニブを投与されたアレルギー性皮膚炎の犬におけるUTIおよび無症候性の細菌性尿症の発生頻度を評価するための前向き研究。

方法 – 尿路疾患の明らかな病歴がなく、UTIの発症素因のない、アレルギー性皮膚炎の病歴を有する2歳以上の飼い犬が組み入れられた。組み入れ前に、全身性抗菌薬については少なくとも14日間の休薬期間後、シクロスポリンおよび全身性グルココルチコイドについては28日間の休薬期間後に、尿検査および定量尿培養を実施した。犬は予め設定された180-230日の期間中(平均195日)に、推奨量のオクラシチニブを内服することとし、尿路症状に関係なく尿検査および尿培養を追跡検査した。調査期間中、全身性抗菌薬および免疫調節薬は投与されなかった。

結果 – 58-280日(平均195日)の調査期間中、オクラシチニブ治療を受けた55頭に、追跡検査された尿検査および尿培養の結果に基づいて、UTIと診断された犬はいなかった。2頭の犬が、自然治癒性の異常な尿路症状を示したが、尿培養および尿検査所見はUTIと一致しなかった。

結論および臨床的な重要性 – これらの知見は、UTIの既往歴または素因がない犬では、本治療期間中においては、細菌尿症はオクラシチニブの予期される副作用ではないと示唆する。したがって、異常な尿検査または尿路疾患の臨床徴候がない犬では、定期的な尿培養は必要ないことが示唆される。

摘要

背景 – 奥拉替尼是一种选择性Janus激酶抑制剂,可以治疗犬的过敏性瘙痒和异位性皮炎。糖皮质激素和环孢素治疗犬的炎性皮肤病,尿道感染的发病率较高。

目的 – 用奥拉替尼治疗犬过敏性皮炎,前瞻性研究评估其尿道感染和亚临床细菌尿的发病频率。

方法 – 大于2岁有过敏性皮炎的家养犬,未见尿道疾病病史,也无尿道感染易感性。停用抗生素14天,停用环孢素和全身性糖皮质激素28天后,在加入本研究前,进行尿液分析和定量尿培养。按照说明书剂量给予犬预期180-230天的奥拉替尼,随后不论是否出现尿道症状,都进行尿液分析和尿培养。在研究期间,不使用全身性抗微生物药和免疫调节剂。

结果 – 参与研究的55只犬,给予时长为58-280天(平均195天)的奥拉替尼,基于尿液分析和尿培养,未见任何犬出现尿道感染。两只犬出现自限性异常尿道症状,但培养或尿液分析未发现尿道感染。

结论和临床意义 – 这些发现说明,对于无尿道感染病史和不易感的犬来说,奥拉替尼治疗犬没有细菌尿的副反应。因此,如果这类犬,如果未见异常的尿道症状,无须进行常规的尿液培养。

Resumo

Contexto – O oclacitinib é um inibidor seletivo de Janus Kinase usado no tratamento de prurido alérgico e dermatite atópica em cães. Os glicocorticoides e a ciclosporina aumentam a frequência de infecções do trato urinário (ITU) em cães com dermatopatias inflamatórias.

Objetivo – Avaliar prospectivamente a frequência de ITU e bacteriúria subclínica em cães com dermatite alérgica recebendo oclacitinib.

Métodos – Foram incluídos cães de proprietários, com mais de dois anos de idade, histórico de dermatite alérgica e sem histórico aparente de doenças do trato urinário ou predisposição a ITU. Antes da inclusão, foram realizadas urinálise e cultura de urina quantitativa. Os cães deveriam estar sem antibióticos sistêmicos por pelo menos 14 dias e sem ciclosporina ou glicocorticoides por pelo menos 28 dias antes da inclusão. Os animais receberam oclacitinib na dose recomendada na bula, por um período desejado de 180-230 dias, com acompanhamento através de urinálise e urocultura independente da presença de sinais clínicos de ITU. Antimicrobianos sistêmicos e drogas imunomoduladoras não foram realizadas durante o estudo.

Resultados – Nenhum dos 55 cães do estudo desenvolveu ITU durante a terapia com oclacitinib baseado na urinálise e urocultura realizadas durante um período entre 58-280 dias (média de 195 dias). Dois cães desenvolveram sinais clínicos autolimitantes de alterações de trato urinário, mas sem alterações na urinálise ou urocultura consistentes com ITU.

Conclusões e importância clínica – Estes resultados indicam que a bacteriúria não é um efeito adverso esperado em cães tratados com oclacitinib, sem histórico ou predisposição à ITU, durante o tempo de tratamento. Portanto, a urocultura de rotina não é indicada para estes cães na ausência de alterações na urinálise ou sinais clínicos de doença do trato urinário.

Functional Use Term	Ingredient	Number of Patients (%)
Topical antimicrobials		
	4% chlorhexidine + TrisEDTA shampoo	5 (9)
	2% chlorhexidine + 1% ketoconazole wipes +2% acetic acid	8 (14.5)
	2% chlorhexidine + 2% miconazole shampoo	4 (7.3)
	2% chlorhexidine + 1% ketoconazole	1 (1.8)
	4% chlorhexidine + TrisEDTA spray	2 (3.6)
	1% Acetic acid + 1% boric acid wipes	1 (1.8)
	Silver sulfadiazine cream	1 (1.8)
	2% mupirocin ointment	1 (1.8)
Ophthalmic medications		
	0.2% ciclosporin ointment	3 (5.5)
	Oxytetracycline hydrochloride	1 (1.8)
	Ketotifen	1 (1.8)
Otic flushes		
	0.15% ketoconazole + 0.15% chlorhexidine + trisEDTA	3 (5.5)
	0.02% phytosphingosine	4 (7.3)
Otic medications		
	1% miconazole + 4 mg/ml dexamethasone SP (1:1 mixture)	6 (10.9)
	Gentamicin/Clotrimazole/Betamethasone	1 (1.8)
Topical moisturizers/anti-seborrheics		
	Phytosphingosine spray (0.1%)	1 (1.8)
	Phytosphingosine spot-on (1%)	1 (1.8)
	Pramoxine (1%) + colloidal oatmeal shampoo	2 (3.6)
	Colloidal oatmeal shampoo	1 (1.8)
	Lactic acid spray	1 (1.8)
	Pramoxine (1%) + colloidal oatmeal rinse	1 (1.8)
Topical anti-inflammatories/immune-modulators		
	1% hydrocortisone cream	1 (1.8)
	0.1% tacrolimus ointment	1 (1.8)

Supplementary Table S1 Concurrent topical therapy used during the study period

Functional Use Term	Ingredients	Number of Patients (%)
Parasiticides		
	Selamectin	1 (1.8)
	Fipronil	2 (3.6)
	Fluralaner	2 (3.6)
	Imidacloprid/permethrin	1 (1.8)
	Ivermectin/pyrantel pamoate	3 (5.5)
NSAIDs/Analgesics/joint supplements		
	Amantadine	1 (1.8)
	Gabapentin	4 (7.3)
	Polysulfated glycosaminoglycan	1 (1.8)
	Glucosamine + chondroitin	5 (9)
	Carprofen	6 (10.9)
Antihistamines		
	Chlorpheniramine	3 (5.5)
	Diphenhydramine	1 (1.8)
	Fexofenadine	3 (5.5)
	Loratadine	3 (5.5)
	Hydroxyzine	1 (1.8)
	Cetirizine	1 (1.8)
Allergen-specific immunotherapy		
	Subcutaneous or sublingual	7 (12.7)
Nutritional supplements		
	Vitamin A	1 (1.8)
	Fish oils	12 (21.8)
Others		
	Benazepril	1 (1.8)
	Fluoxetine	1 (1.8)

Supplementary Table S2 Concurrent Systemic Medications Used During Study Period