Nutrafoods (2023) 1:505-511 DOI 10.17470/NF-023-0059

Original Research

Attenuation of canine atopic dermatitis pruritus through a novel complementary feed

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Abstract

Canine atopic dermatitis (cAD) is a complex and multifaceted disease in which pruritus represents the main concern for owners. In recent years, non-pharmacological therapeutic alternatives for the long-term management of dermatological disorders and related symptoms are being explored. The aim of the present study was to assess the aptitude of a novel complementary feed containing bioactive molecules such as flavonoids, stilbenes and cannabinoids in the control of pruritus in cAD. Twelve dogs affected by cAD received oclacitinib for six weeks followed by supplementation with a complementary feed for 24 weeks. Canine Atopic Dermatitis Extent and Severity Index (CADESI-4) and Pruritus Visual Analogue Scale (PVAS) scores were recorded every two weeks for 28 weeks in total.
Results obtained showed a statistically significant decrease of pruritus after treatment with oclacitinib in the first four weeks (oclacitinib discontinued at week six) and was maintained by complementary feed supplementation for six months. The data obtained suggest that the investigated complementary feed may help to control itching caused by cAD after an adequate period of oclacitinib administration.

Keywords: Atopic dermatitis, dog, complementary feed, pruritus

Introduction

Canine atopic dermatitis (cAD) is a chronic, multifactorial allergic and pruritic disorder of dogs caused by immunological imbalance and disruption of skin barrier defence mechanisms [1, 2]. In the pathogenesis of cAD, many studies have looked at cytokines as indicators of disease severity and response to treatments [3]. More recently, interleukin 31 (IL-31), a T helper 2 cytokine, has attracted the attention of researchers for its role in pruritus and atopic inflammation [4–6]; this cytokine can directly activate the peripheral nerve endings and induce pruritus, as well as stimulate other additional cells to express its specific receptor [7]. Being chronic in nature, cAD can be managed with different approaches, mainly anti-inflammatory and/or immunomodulatory drugs; the application of epidermal barrier treatments is mostly considered supportive [8].

Pharmacological treatments and complementary feeds to control pruritus quickly and for the long-term are in great demand and have attracted the attention of many researchers and stakeholders [9]. Consequently, nutritional supplementation has been applied to the management of dermatological disorders [10].
In fact, it has been proposed by some studies that several ingredients and complementary feeds have the potential to ameliorate canine dermatopathies [11].

Dietary supplementation with polyunsaturated fatty acids (PUFA) is a strategy that is widely used to improve pruritus and lower dosages of glucocorticoids and cyclosporine needed to control clinical signs [11]. Polyphenols, organic compounds found primarily in fruits and vegetables, have been widely studied for their anti-inflammatory properties and there is evidence to support the use of certain classes of polyphenols in allergic diseases [12,13]. Examples of molecules belonging to different polyphenol classes, including flavonoids, stilbenes, phenolic acids and hydroxycinnamic acid lignans include resveratrol, quercetin, and curcumin [14].

Cannabis sativa plants contain cannabinoids, a unique group of chemical compounds that has been employed medicinally throughout history [15]. Cannabidiol (CBD) is the predominant non-psychotropic cannabinoid found in the cannabis plant [16] and cannabidiolic acid (CBDA) is the precursor carboxylic acid form of CBD [16]. Recent studies showed immunomodulatory and anti-inflammatory actions in mammals [17,18]. Of late, CBD/CBDA have been tested as an adjunct therapy to decrease pruritus in canine atopic dermatitis while having no effect on skin lesions associated with cAD.

A mixture of bioactive molecules including flavonoids, stilbene, and cannabinoids, has recently been reported to be able to reduce the expression of IL-31 in in-vitro experimental model of atopic dermatitis [19].

The aim of the present study was to assess the ability of a novel complementary feed containing polyphenols and cannabidiol to ameliorate pruritus in the long-term management of cAD in dogs.

Materials and methods

Twelve pet owners referred to the Veterinary Teaching Hospital of University of Camerino for investigation of pruritic disease were enrolled in this open-label, non randomized, non controlled exploratory trial. Investigational protocol was successfully submitted to the University of Camerino Institutional Animal Care and Use Committee (number 10/2021) and pet owner informed consent was obtained before enrolment. To diagnose cAD and to exclude other diseases responsible for pruritus, each dog underwent the following tests: complete blood count, serum biochemistry, serum protein electrophoresis; leishmaniasis serodiagnosis; urinalysis; copromicroscopic examination; microscopic examination of superficial and deep skin scrapings; trichoscopic examination

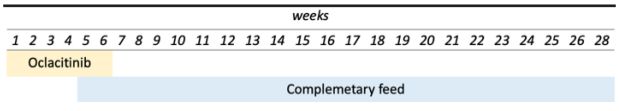
and skin biopsy. Prior to enrolment, dogs received an appropriate ectoparasite control to rule out the presence of flea bite hypersensitivity and underwent a hydrolyzed diet trial to rule out presence of food allergy.

In addition, dogs were scored using the Canine Atopic Dermatitis Extent and Severity Index (CADESI-4) [20] and were enrolled if they scored at least 35 points (corresponding to moderate cAD). Dogs were excluded if they were diagnosed with poor general health or the presence of any current, recent or previous history of systemic diseases such as diabetes mellitus, hypothyroidism, hyperadrenocorticism, hyperestrogenism, hyperprogesteronism, growth hormone deficiency, leishmaniasis, renal dysfunction, skin neoplasia, which, even if well controlled, alter the interpretation of the data. Dogs receiving oclacitinib, cyclosporine, lokivetmab or oral steroid therapy or slow-release steroid therapy within two and four weeks, respectively, were excluded. Pregnant bitches were not enrolled.

Upon enrolment, dogs received oclacitinib (Apoquel®, Zoetis) at a dosage of 0.4mg/kg body weight, administered orally twice daily for 14 days (two weeks), reduced to once daily, at the same dosage, for four weeks. Starting from week five, the dogs' diet was supplemented with the investigated complementary feed containing polyphenols and cannabidiol (Ancaria®, C.I.A.M. s.r.l., Ascoli Piceno Italy) at a dosage of one tablet/10kg body weight, administered orally twice daily for 14 days (two weeks) and then only once a day, at the same dosage, for 22 weeks.

Oclacitinib dosing was discontinued at week six and dogs were only supplemented with complementary feed until week 28, as per the following scheme:

Figure 1: Timeline of the pharmacological and dietary interventions.



Upon enrolment and every other week until the end of the study (week 28), dogs received general clinical and specialist dermatological examinations. The dog owners were asked to score the itch of their dogs using a Pruritus Visual Analogue Scale (PVAS) [21], in which the extent of the pruritus is evaluated on a scale of 0–10 points. At the same timepoints, CADESI-4 was repeated in each dog.

CADESI-4 and PVAS scores were statistically evaluated between the various time points using one way analysis of variance (ANOVA) and Tukey's multiple comparisons test. A *p*-value less than or equal to 0.05 was considered significant.

Results

Signalment data of enrolled dogs (breed, age, sex and weight) are detailed in **Table 1**.

Table 1: Breed, age, sex and weight of enrolled dogs.

	Breed	Age (years)	Sex	Weight (Kg)
1	German Shepherd	4	Intact male	31
2	German Shepherd	3	Intact male	31
3	Italian Bracco	10	Neutered female	30
4	Rhodesian Ridgeback	2	Intact male	40
5	Cocker Spaniel	3	Neutered female	22
6	Labrador Retriever	2	Neutered female	25
7	Golden Retriever	7	Intact male	32
8	Labrador Retriever	4	Intact male	40
9	Labrador Retriever	2	Intact male	35
10	German Shepherd	5	Intact male	40
11	Weimaraner	3	Intact male	40
12	Italian Bracco	2	Intact male	35

All dogs enrolled completed the study. The average age of the dogs was 3.91 ± 2.43 years while the average weight was 33.42 ± 6.07kg. The average scores relating to pruritus and CADESI-4 index are reported in **Table 2** and **Table 3**, respectively. **Fig. 2** and **Fig. 3** report CADESI-4 and PVAS mean values observed in the study population.

Table 2: CADESI-4 scores for each dog and time point.

	# 1	# 2	# 3	# 4	# 5	# 6	# 7	# 8	# 9	# 10	# 11	# 12	Mean values	Standard deviations
Enrolment	129	71	163	99	62	41	72	122	59	75	48	63	83.67	36.96
week 2	57	21	38	14	18	13	23	41	16	16	28	12	24.75	13.89
week 4	79	5	12	6	0	0	5	8	0	0	0	0	9.58	22.22
week 6	16	5	5	0	0	0	0	0	0	0	0	0	2.17	4.76
week 8	13	5	0	0	0	0	0	0	0	0	0	0	1.50	3.90
week 10	6	0	0	0	0	0	0	0	0	0	0	0	0.50	1.73
week 12	2	0	0	0	0	0	0	0	0	0	0	0	0.17	0.58
week 14	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 16	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 18	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 20	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 22	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 24	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 26	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 28	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00

Table 3: PVAS scores for each dog and time point.

	# 1	# 2	# 3	# 4	# 5	# 6	# 7	# 8	# 9	# 10	# 11	# 12	Mean values	Standard deviations
Enrolment	10	8	9	8	8	9	9	10	8	9	8	8	8.67	0.78
week 2	5	4	2	4	4	5	4	5	3	3	4	3	3.83	0.94
week 4	7	0	1	3	0	0	2	2	0	1	2	0	1.50	2.02
week 6	7	2	0	0	0	0	0	0	3	0	0	0	1.00	2.13
week 8	4	2	0	0	0	0	1	2	1	0	0	0	0.83	1.27
week 10	2	0	0	0	0	1	0	0	0	0	0	0	0.25	0.62
week 12	2	0	0	1	0	0	0	0	0	0	0	0	0.25	0.62
week 14	0	0	0	1	0	0	0	0	0	0	0	0	0.08	0.29
week 16	0	0	1	0	0	0	1	0	0	0	0	0	0.17	0.39
week 18	0	0	0	0	0	0	2	2	0	0	0	0	0.33	0.78
week 20	0	0	0	0	0	1	1	0	0	0	0	0	0.17	0.39
week 22	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 24	0	0	0	1	0	0	0	0	0	0	0	0	0.08	0.29
week 26	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00
week 28	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00

Figure 2: CADESI-4 average score variation over time.

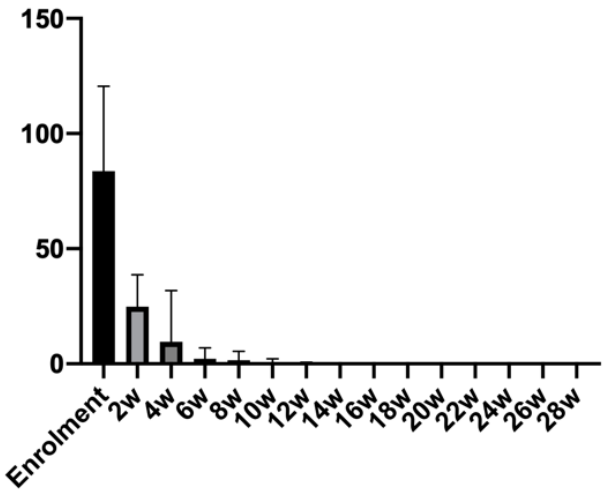
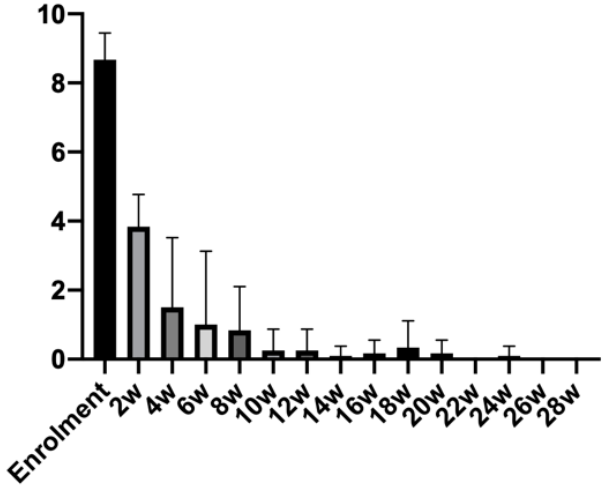


Figure 3: PVAS average score variation over time.



At enrolment, the average CADESI-4 score was 83.67 ± 36.96. After two weeks of oclacitinib this decreased to 24.75 ± 13.89. At week four, the average CADESI-4 score reduced further to 9.58 ± 22.22. At week six, the average CADESI-4 score was 2.17 ± 4.76 and for the following weeks the CADESI-4 score did not rise above 2.

Upon enrolment the average PVAS score was 8.67 ± 0.78. After two weeks of oclacitinib, this decreased to 3.83 ± 0.94. At week four, the average PVAS score reduced further to 1.50 ± 2.02. At week six, the average PVAS score was 1.00 ± 2.13 and did not change for the following weeks.

ANOVA revealed a significant difference over time in CADESI-4 and PVAS scores (p<0.0001 for both). Tukey's multiple comparison test revealed that CADESI-4 and PVAS scores at enrolment and at week two were significantly different to those recorded for the other time points (p<0.001 and p<0.0001 respectively). CADESI-4 scores at week two when compared with those of week four and six had a p-value of 0.0891 and 0.0007 respectively. Compared to PVAS scores of week two, p-values for week four and six were 0.0376 and 0.0247 respectively.

Discussion

The results of the present study showed that the complementary feed was able to maintain the oclacitinib-related amelioration of pruritus in atopic dogs without concurrent administration of other treatment, neither topical nor systemic. In experimental models of pruritus, abrupt discontinuation of oclacitinib has resulted in a return of the pruritus, as can often happen when tapering a dose of the drug [22].

The complementary feed administered to the dogs of the present study was able to prevent such a phenomenon mainly due to its formulation. Polyphenols, including flavonoids, stilbenes and phenolic acids are natural compounds that have been widely studied for their anti-inflammatory properties in canine dermatological disease [23, 24]. Cannabidiol and cannabinoid extracts have been reported to exert antinociceptive, immunomodulatory and anti-inflammatory properties [25]. In a recent study, cannabidiol and cannabidiolic acid have been tested to reduce pruritus and cutaneous lesions in dogs with atopic dermatitis [26]. In a previous work from Massimini *et al.*, the same formulation was shown to reduce the expression of IL-31 in an experimental model of atopic dermatitis [19].

This uncontrolled, open-label clinical trial demonstrates that substantial clinical improvement as assessed by both pet owners and veterinarians can be achieved by feeding a complementary feed formulated to support skin barrier function and reduce inflammation.

The research of other non-pharmacological therapeutic alternatives is an expanding field [27] and several target diets containing bioactive lipids, aliamides, botanical extracts, vitamins and minerals are available for the management of pruritus.

Utilizing diet to manage cAD is a safe and easy therapeutic strategy for pet owners that may accompany other treatments. Feeding polyphenols and cannabidiol alone resulted in a reduction of skin inflammation and thus pruritus [25, 26], allowing clinicians to reduce the dosages or the number of medications used for cAD. Our results, although preliminary, suggest significant improvement in cAD pruritus seen within four weeks of feeding the complementary feed and oclacitinib discontinuation. Such improvement was maintained throughout the 22 weeks of dietary supplementation. It would have been interesting to assess if the dogs continued to improve over the supplementation period. While more efforts are needed to confirm the results of this study, the polyphenols and cannabidiol merged in the tested formu-

lation hold promise for cAD pruritus management.

The major limitations of the present study are represented by the open-label design without a control group and the small sample size. Pet owners and veterinarians may have scored dogs more favourably because they were aware of receiving a target complementary feed formulated to improve cAD. Additionally, seasonal allergies may play a role in the severity of pruritus. All the dogs were enrolled during late summer/autumn when seasonal allergies are often improving. To improve this, extending the timeline of the trial to a 12-month period or performing trials in different seasons could help to investigate possible seasonal effects.

Conclusions

In an open-label, uncontrolled clinical trial of 12 dogs of various breeds, pet owners and veterinarians reported marked improvements in cAD when the dogs were fed a dermatological supplementary feed.

Conflict of interest

This research was funded by C.I.A.M. s.r.l., Ascoli Piceno, Italy.
BB, EDV, MM and CR, at the time of study period, were employees of C.I.A.M. s.r.l.. They were involved in the design of the study only and had no role in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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