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Impact of Monthly Afoxolaner Administration on Relapse Frequency in Dogs with an initial diagnosis of Atopic Dermatitis

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Abstract

This prospective multicentric study evaluated whether regular monthly administration of afoxolaner reduces relapse frequency in dogs with an initial diagnosis atopic dermatitis (CAD). One hundred dogs diagnosed based on Favrot's criteria were enrolled and allocated to two groups: one receiving monthly afoxolaner treatment and one untreated. Relapses were defined as worsening pruritus or skin lesions requiring medical intervention. The primary outcome was the number of relapses over a 12-month period, while secondary outcomes included flea infestations, treatment types, and occurrence of secondary infections. The study is not intended to determine the cause of relapses, but simply to measure the reduction in the number of such relapses. Ninety-six dogs completed the study, including 65 treated and 31 untreated individuals. The median number of relapses was significantly lower in the treated group compared to the untreated group (2 vs 3; $p = 0.04$). In addition, flea-related relapses occurred less frequently in treated dogs ($p = 0.01$), and untreated dogs more often required long-term antipruritic therapy ($p = 0.03$). These findings indicate that monthly administration of afoxolaner significantly reduces relapse frequency and flea-associated flare-ups in dogs with an initial diagnosis of CAD, while also decreasing the need for prolonged antipruritic treatment. Ectoparasite prevention should therefore be considered an integral component of the multimodal management of canine atopic dermatitis.

Introduction

Canine atopic dermatitis (CAD) is a common, chronic, inflammatory and pruritic skin disease with a multifactorial pathogenesis involving genetic predisposition, epidermal barrier dysfunction, immune dysregulation and environmental factors.(Nuttall et al. 2019) The disease is characterized by recurrent flares and relapses that often require long-term management and multimodal therapeutic approaches. (Marsella and Benedetto 2017; Marsella 2021a; Marsella 2021b) Despite appropriate control strategies, many atopic dogs experience periodic worsening of clinical signs, leading to repeated medical interventions and a significant impact on animal welfare and owner quality of life. (Olivry et al. 2015; Olivry and Banovic 2019)

Flea allergy dermatitis (FAD) and CAD are regarded as distinct conditions in many reference works. (Miller et al. 2023) This is justified by the fact that the causative allergens are different, that clinical signs may differ, and that the pathophysiology has long been considered distinct, with one being primarily T-cell-mediated whilst the other was thought to be mainly IgE-mediated.

Whilst the allergens causing the two diseases are different, it should be noted that cross-reactions between insects (fleas) and arachnids (house dust mites) occur between highly conserved proteins such as tropomyosins, for example, suggesting that a single component carried by two different allergens could induce the clinical signs of both conditions. (Cantillo et al. 2018; Gier and Verhoeckx 2018)

With regard to clinical signs, even though some differences may be detected, (Bruet et al. 2012) it is widely accepted that the two conditions may resemble one another, that neither has pathognomonic

signs, and that each forms part of the differential diagnosis for the other. (Hensel et al. 2015)

FAD is often regarded as a cell-mediated disease, but it has been widely demonstrated that immediate reactions to flea extracts are frequently observed and that dogs with FAD often have specific anti-flea IgE. (Wilkerson et al. 2004; Wuersch et al. 2006) The role of allergen-specific IgE in the pathogenesis of CAD is well established, but it is also known that some atopic dogs test negative in all allergy tests. (Pucheu-Haston et al. 2015b; Pucheu-Haston et al. 2015a; SUTO et al. 2015)Similarly, the role of IgE does not rule out the possibility that a cellular component plays a part, and it should be remembered here that human atopic dermatitis is considered a mixed IgE/cell-mediated condition. (Boothe et al. 2017)It may also be added that food allergies associated with CAD symptoms are probably rarely linked to IgE-mediated reactions, and that sarcoptic mange, for its part, induces IgE. (Moog et al. 2021; Fernandez-Lozano et al. 2024) Even from a pathogenic perspective, therefore, the hypersensitivity dermatitis are much closer than the somewhat arbitrary distinctions in textbooks might suggest.

It is also important to note that the populations of dogs with AD and FAD overlap considerably, suggesting either common predispositions, or that sensitization to a primary allergen may lead to secondary sensitization, or that the two phenomena overlap in certain cases. (Carlotti and Cosatrgent 1994; Sousa and Halliwell 2001) Additionally, Halliwell and coworkers showed that non atopic dogs exposed to fleas did not develop detectable sensitization while atopic dogs do, one more time suggesting common development pathways. (Halliwell and Longino 1985)

All these points explain why the guidelines for atopic dermatitis identify the identification of fleas and their treatment as the first and most important step in the diagnosis and management of AD [5].

However, this should not lead us to believe that it is easy, or even necessary from a practical point of view, to distinguish between the two conditions and, generally speaking between all hypersensitivity dermatitis. For example, keeping a dog on continuous flea control does not rule out the possibility of a or few bite or bites triggering a reaction in sensitized individuals. (Gross and Halliwell 1985)

On the contrary, it seems more reasonable to consider hypersensitivity dermatitis in dogs from a holistic perspective. This would prevent CAD from being separated from other hypersensitivity dermatitis in the minds of some clinicians and ensure that anti-flea treatment is not, all too often, overlooked.

Isoxazolines, such as afoxolaner (NexGard®, Boehringer Ingelheim), are widely used for the prevention and treatment of flea and tick infestations in dogs and have demonstrated high efficacy and high safety profiles.(Beugnet et al. 2014; Dumont et al. 2014; Shoop et al. 2014; Petersen et al. 2024) While their role in preventing ectoparasitic diseases is well established,(Beugnet et al. 2014; Dumont et al. 2014; Six et al. 2016) limited data are available on their potential impact on the long-term clinical course of CAD, particularly regarding relapse frequency and the need or the reduction of additional antipruritic treatments.

This study is based on this decidedly practical and holistic approach and has the sole aim of demonstrating—something that has never been done before—that anti parasitic treatment is an integral part of the treatment for dogs diagnosed with CAD. Our aim is not to determine whether a dog experiences a relapse due to fleas, but simply to show that a dog diagnosed with CAD has fewer relapses when treated with afoxalaner, which is obvious to specialists but not to all practitioners.

Materials and methods

Dogs with atopic dermatitis were included in this prospective, multicentric study by several veterinarians with a special interest in dermatology, some but not all being board certified. The diagnosis was based on the fulfilment of at least five out of eight Favrot's criteria (i.e., affected ear pinnae, affected front paws, age of onset < 3 years, chronic or recurrent yeast infections, glucocorticoid-responsive pruritus, mostly indoor lifestyle, nonaffected dorso-lumbar area, pruritus without skin lesions at onset)(Favrot et al. 2010) Differential diagnoses, including ectoparasitic infestations, were ruled out using standard diagnostic procedures as recommended in published guidelines.(Hensel et al. 2015) Food allergy was not excluded but pyoderma and yeast infections were controlled before inclusion. Ongoing dietary management and topical treatments (except those containing glucocorticoids and calcineurin inhibitors) were allowed throughout the study, provided they remained unchanged and not started in the last four weeks before inclusion. Dogs were allocated to one of two study groups based on owner preference and were therefore not randomized: approximately one third of the dogs were not treated with any antiparasitic treatments while two third received monthly treatment with afoxolaner (NexGard®, Boehringer Ingelheim) according to the label recommendations. Dogs were followed for one year and any treatment of allergy was authorized, including allergen-specific immunotherapy provided it was started at least 12 months before inclusion. At inclusion, the disease was adequately controlled. It was also allowed to change any treatment of the atopic dermatitis during the study if the previous one was not effective or not effective anymore. These changes had to be approved by the Investigator and were recorded. Owners were instructed to inform the Investigator of any relapse of the atopic dermatitis or pruritus. Relapses were defined as a clinically relevant worsening of pruritus and/or skin lesions requiring medical intervention, in order to reflect routine clinical practice. A conscious decision was made to abandon the use of traditional criteria such as PVAS or CADESI, as the use of cores by multiple investigators and owners significantly reduces the reliability of the measurements.(Mulsant et al. 2002) Owners were instructed to report any relapse of pruritus or skin lesions to the Investigator. In the absence of reported relapses, monthly follow-up contacts were conducted to ensure completeness of data collection. The primary outcome was the total number of relapses recorded over the 12-month follow-up period.

When a relapse was attributed to ectoparasites, defined by the detection of fleas or flea faeces on visual inspection and flea combing, or by identification of parasites through skin scrapings, appropriate antiparasitic treatment was administered and recorded.

When a suspicion of sarcoptic mange was made and the mites were not found, serology was used to confirm or rule out the suspicion.

As well, when the cause of the relapse was identified, i.e. pyoderma, *Malassezia* dermatitis, otitis, it was treated appropriately and recorded. Symptomatic treatment of the pruritus was applied in any other cases. Treatments were recorded as short term (oral prednisolone, topical hydrocortisone aceponate, oclacitinib…) or long-term treatment (lokivetmab). Side effects and adverse events occurring after the administration of afoxolaner were recorded.

As mentioned above, the primary outcome measured was the number of relapses during the 12-month follow-up period. Secondary outcomes included the recording of other parameters such as flea infestations, otitis, pyoderma and *Malassezia* dermatitis. As well, treatments of the relapses were recorded and classified in two groups (Long-term treatment of pruritus (LTT= lokivetmab) or short term-treatments (STT).

Statistics

The sample size was calculated assuming a mean number of relapses of 2 in the treated group and 3 in the untreated group over a 12-month period, with a power of 80% and a two-sided alpha level of 0.05. Based on these assumptions, a total of 107 dogs (71 treated and 36 untreated) were included. Statistical analyses were performed on a per-protocol population and included only dogs that completed the 12-month follow-up to allow a consistent assessment of relapse frequency over the entire observation period, which represented the primary outcome of the study. As the data were not normally distributed, statistical analyses were made using the non-parametric Mann-Whitney U test. Categorical variables, including sex distribution and the causes of relapses or treatments administered, were compared using Fisher's exact test. All analyses were conducted using GraphPad Prism (GraphPad Software, USA). The statistician performing the analyses was blinded to group allocation.

Animal Ethics and Consent to Participate

The study was approved by the competent cantonal veterinary authorities (approval number ZH166/2021/34145). Written informed consent to participate was obtained from all dog owners prior to enrolment.

Results

Animals

One hundred dogs were enrolled in the study, of which ninety-six completed the 12-month follow-up and were analysed per protocol. Three dogs were excluded due to poor owner compliance, and one dog was withdrawn after three months because of diarrhoea occurring immediately following afoxolaner

(NexGard®) administration. Sixty-five dogs were allocated to the treated group and thirty-one to the untreated group. The mean age was 6.1 years in the treated group and 4.9 years in the untreated group, with no significant difference between groups (Mann–Whitney test, p = 0.12). The male-to-female ratio was 37:18 in the treated group and 18:13 in the untreated group, respectively, with no significant difference between groups (Fisher's exact test, p = 0.99).

The median number of relapses over the 12-month follow-up period was 2 (25th percentile: 1; 75th percentile: 3) in the treated group and 3 (25th percentile: 1; 75th percentile: 4) in the non-treated group, with a statistically significant difference between groups (Mann–Whitney test, p = 0.04).

The causes of relapses and the concurrent treatments are summarized in Table 2. For this analysis, each dog was counted only once per category, even if the same cause of relapse or treatment occurred multiple times during the study period. Statistical comparisons between groups were performed using Fisher's exact test.

Table 1
Number of dogs that experienced at least one relapse during the 12-month follow-up period, grouped according to the cause of relapse or the type of treatment required (short-term: oral prednisolone, topical hydrocortisone aceponate, oclacitinib). One count per dog per category.

Treated	**Pulicosis**	**Pyoderma**	**Otitis**	**Malassezia dermatitis**	**Short-term treatment**	**Lokivetmab**
	1/65	**17/65**	**13/65**	**2/65**	**29/65**	**10/65**
Non-treated	5/31	8/31	6/31	2/31	16/31	11/31
p value	**0.01**	0.99	0.99	0.59	0.65	**0.03**

Additionally, the total number of occurrences for each item was recorded and analyzed using medians, with comparisons made via the Mann-Whitney test.

Table 2
Total number of relapse events and treatment episodes recorded during the 12-month follow-up period, grouped according to the cause of relapse and the type of treatment required, reflecting the overall burden of relapses and treatments in the two groups.

Treated	**Fleas**	**Pyoderma**	**Otitis**	**Malassezia**	**Short-term treatment**	**Lokivetmab**
	1	**25**	**16**	**2**	**85**	**31**
Non-treated	12	10	10	2	63	57
P value	**0.007**	0.85	0.94	0.58	0.17	**0.007**

Discussion

This study is the first to investigate the effect of regular, systematic ectoparasite control on relapse frequency in dogs with an initial diagnosis of atopic dermatitis. Our results demonstrated that untreated dogs experienced a higher number of relapses compared with those receiving treatment. Although fleas were identified as a cause of relapse in some treated dogs, the number of dogs for which flea infestations were observed was significantly higher in the untreated group. Furthermore, long-term treatment of flares was required more frequently in the untreated dogs.

When a dog experiences a flare-up of symptoms after previously having a disease that was in full or nearly full remission, veterinarians should investigate and, if possible, remove the trigger of the exacerbation. Known triggers of flares in canine atopic dermatitis (AD) include fleas, food, and environmental allergens such as dust mites and pollens. (Olivry et al. 2015)

In cases of acute AD flare-ups, particularly in regions where flea infestations are common, clinicians should first assess whether fleas might be responsible for the worsening of symptoms. (Olivry et al. 2010; Olivry et al. 2015)

The results of the present study indicate that fleas and other ectoparasites may act as a trigger for disease flare-ups as observed in the untreated group, with a significant difference compared with treated dogs. When administered according to label instructions, afoxolaner, an isoxazoline-class ectoparasiticide has been shown to provide a high level of control of ticks and fleas infestations in dogs. (Beugnet et al. 2014; Six et al. 2016) Nevertheless, our findings highlight that antiparasitic prevention may not guarantee complete protection against infestation. Successful flea eradication requires not only the appropriate choice of products (ideally those with prolonged residual activity) but also full compliance with the treatment regimen, treatment of all in-contact animals, and adequate environmental control.(Carlotti and Jacobs 2000) A deficiency in any of these components can result in reinfestation and may account for the presence of fleas in some treated dogs. The significantly increased prevalence of ectoparasite-associated relapses in the untreated group reinforces the role of ectoparasites as major triggers of atopic dermatitis exacerbations and supports previous studies identifying effective flea control as a cornerstone of CAD management.(Olivry et al. 2010; Olivry et al. 2015)

From a clinical perspective, these findings support the systematic use of ectoparasite prevention as part of the baseline management of dogs with atopic dermatitis, even when the disease appears well controlled.

Other well-known triggers for acute AD flares are pyoderma, otitis or *Malassezia* dermatitis.(Olivry et al. 2010; Olivry et al. 2015) Ectoparasitic infestations are recognized as significant predisposing factors for secondary bacterial skin infections in dogs, likely due to barrier compromise and inflammatory changes that facilitate pathogen invasion.(Seckerdieck and Mueller 2018) Consequently, a higher risk of disease flares may be anticipated in patients more heavily exposed to or affected by ectoparasites. Nevertheless, no significant differences were observed between groups for these factors. This may suggest that while ectoparasite control specifically targets flea-induced flares, it does not directly influence relapses caused by secondary bacterial infections or other causes.

A clinically important finding of this study was that dogs in the untreated group required long-term symptomatic therapy (e.g., lokivetmab) significantly more often than dogs receiving regular ectoparasite control with monthly afoxolaner administration. This observation suggests that early and consistent ectoparasite prevention may contribute to improved disease stability by reducing the need for prolonged pharmacological therapy. By minimizing the need for long-term treatment, preventive ectoparasite control may reduce the risk of drug-related adverse effects and **simplify** disease management for owners, potentially improving compliance and lowering overall treatment costs.(Spitznagel et al. 2021) These results highlight the importance of incorporating regular ectoparasite prophylaxis into a comprehensive management plan for dogs prone to allergic flare-ups.

This study has several limitations. Dogs were not randomly allocated to treatment groups, which may have introduced selection bias and unrecognized baseline imbalances between groups. Relapses were defined pragmatically according to the requirement for medical intervention rather than by standardized disease severity scores, potentially leading to inter-investigator variability. (Mulsant et al. 2002) Concomitant treatments and therapeutic adjustments were permitted during the follow-up period and were based on individual clinical judgment, which may have influenced relapse management and outcomes. Moreover, analyses were performed on a per-protocol basis, raising the possibility of attrition bias.

Additional limitations include potential compliance issues within the treated group and a relatively small sample size, particularly in the untreated cohort, which may have reduced statistical power. Although the study was multicentric, all dogs were recruited from a single geographic region, potentially limiting the generalizability of the findings, as ectoparasite prevalence and exposure can vary considerably across regions. Furthermore, flea exposure outside the household environment and the risk of environmental reinfestation were not fully controlled, which may have affected relapse occurrence.

Nevertheless, these limitations are inherent to the pragmatic nature of the study design, which aimed to reflect routine clinical management of canine atopic dermatitis. Accordingly, the findings should be interpreted as associations observed under real-world conditions rather than as evidence of a direct causal relationship.

Conclusion

The regular monthly administration of afoxolaner significantly reduced the frequency of relapses in dogs with controlled atopic dermatitis compared to untreated dogs. It also lowered the incidence of flea-related flare-ups and decreased the need for long-term antipruritic therapy. These findings highlight the importance of integrating ectoparasitic prevention into the multimodal management of canine atopic dermatitis to improve clinical outcomes and reduce treatment burden.

Declarations

Conflict of interest

Eric Tielemans and Loïc Antoine are employees of Boehringer Ingelheim Animal Health.

The study was funded by Boehringer Ingelheim.

The other authors declare that they have no competing interests

Competing Interests

Eric Tielemans and Loïc Antoine are employees of Boehringer Ingelheim Animal Health. The study was funded by Boehringer Ingelheim. The other authors declare that they have no competing interests.

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Author Contribution

F.M., N.F., and E.M. contributed to the conception and design of the study. F.M., L.A., E.T., S.A., S.B., C.F., N.F., and E.M. contributed to data acquisition, analysis, and/or interpretation. F.M. drafted the manuscript. L.A., E.T., S.A., S.B., C.F., N.F., and E.M. critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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