

What's new in dermatology?

Interest of the association of dermo-cosmetics and drugs in the multimodal management of allergic dermatitis



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Dr. Marion Mosca and Pr. Didier Pin

Preface



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ACVD Award of Excellence 2010 & Frank Kral Award 2018, International speaker & former consultant dermatologist at VIN (Veterinary Information Network).

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« What can barrier repair bring to itchy skin? »

Canine allergic dermatitis, and in particular atopic dermatitis, is a chronic inflammatory disease requiring lifelong management. This disease is very frustrating to owners, and has a negative impact on the quality of life for the families as well as the dogs. The pathogenesis of the disease in dogs is slowly being elucidated, and these studies have provided new antipruritic and anti-inflammatory therapeutics that allow us to customize treatment for each patient, according to what is most effective. Canine atopic dermatitis is a multifactorial disease, associated with genetic and environmental inputs. A dysregulated immune response and a defective skin barrier contribute to the pathogenesis of this disease. While there is some controversy about whether skin barrier defects are primary or secondary (in fact individual and breed variation may contribute to this controversy), skin barrier repair is an excellent complementary approach to our current antipruritic and anti-inflammatory therapeutics. One of the aspects of allergic dermatitis, that we, as veterinarians, may have underestimated, is the distress

owners experience when their dogs' skin and coat are abnormal. Many of my clients have expressed embarrassment about taking their dogs in public, for fear of being judged as bad owners. Beyond the cosmetic impairment, barrier defects likely contribute to increased itch by virtue of absorption of allergens through the skin, as well as increased rates of infection. While the use of modern anti-inflammatory therapeutics will reduce the cytokines that aggravate the barrier defect, addressing the barrier defect specifically with appropriate topical remedies could accelerate healing and reduce infection rates. Evidence is accumulating that the use of these topicals can have additive effects on itch and inflammation control. These products are easy to use and appealing to pet owners, thus promoting compliance. Topical barrier repair is an appealing part of the multimodal approach to the treatment of this most frustrating disease. It is my hope that we will continue to see innovation in the field of skin barrier repair and its impact on canine skin health.

Performance of a natural complex in a reconstructed canine epidermis model stressed by cytokines



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Study conducted with an independent and specialized laboratory

INTRODUCTION

The recent development of reconstructed canine epidermis models (RCE) enables to mimic *ex vivo* canine atopic dermatitis and therefore study the efficacy of active ingredients at the epidermis level. In this study, a complex of natural active ingredients (vegetable oils rich in essential fatty acids, synergy of essential oils, phytoceramides, etc.) of a spot-on formula (ATOP 7® spot-on) was evaluated.

MATERIAL AND METHODS

Epidermis (RCE) were produced from keratinocytes collected from healthy dogs. A cocktail of cytokines is used to simulate barrier defects, thus creating epidermis similar to those seen in atopic dermatitis (RCE-AD). Epidermis were treated with the 0.02% complex of active ingredients and compared to untreated RCE and RCE treated with 0.5µM of tofacitinib, a selective Janus Kinase (JAK) inhibitor. Morphology of RCE was assessed by histological staining with Hemalun-Eosin and inflammation by ELISA dosage of the pro-inflammatory marker interleukin 8 (IL-8). Three epidermis were analyzed per condition.

RESULTS

Tolerance: The good tolerance of the complex was confirmed by histology since no morphological changes in the RCE models were observed.

Efficacy: RCE-AD showed structural disorganization with cell dissociation, spongiosis and a decrease in the number of keratohyaline grains (Figure 1). Treatment with the natural complex limits the impact of cytokines by reducing spongiosis and increasing the number of keratohyaline grains (Figure 1).

Figure 1: Hemalun-Eosine histological colorations

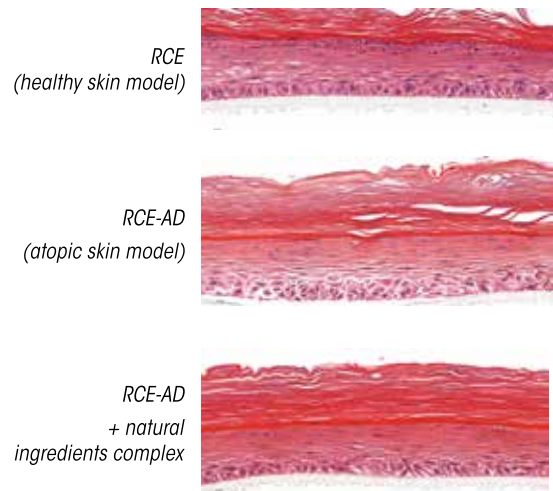
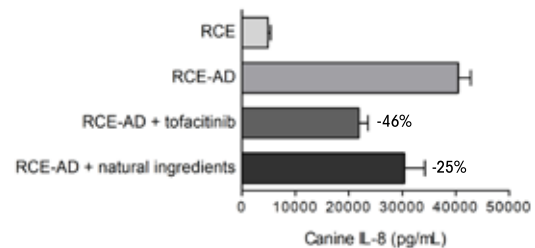


Figure 2 : IL-8 dosage in the culture medium of RCE



In addition, RCE-AD showed an increase in IL-8 secretion while the reference molecule (tofacitinib) allows a 46% decrease in IL-8 level, and the natural complex resulted in a remarkable decrease of 25% (Figure 2).

CONCLUSION

The tested natural complex has a good tolerance and shows a beneficial effect on the morphology of stressed epidermis, limiting spongiosis and thus promoting cellular cohesion. In addition, the complex allows an obvious reduction in the level of the dosed pro-inflammatory marker. These results will need to be confirmed *in vivo*.

Use of natural topicals with essential fatty acids in combination with lokivetmab in the management of canine atopic dermatitis

«Topical therapy with a spot-on and a shampoo containing essential fatty acids and other natural extracts increases the efficacy of lokivetmab in canine atopic dermatitis and delays disease flares: a single-blinded, randomized, controlled study»

Poster at the 2020 World Congress of Veterinary Dermatology (WCVD)



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BACKGROUND

Canine Atopic Dermatitis (CAD) is a chronic pruritic inflammatory dermatosis. This complex condition is associated with a skin barrier defect and an inappropriate immune response involving the cytokine IL-31, which is responsible for pruritus. This leads to a vicious circle that exacerbates the symptoms (Figure 1). New therapeutic approaches have changed the management of CAD in recent years. The monoclonal antibody lokivetmab, commercially available in dogs, specifically targets IL-31 and enables a rapid disruption of the pruritus vicious circle to lead to improvement in clinical signs of CAD. However, in order to better control atopic dermatitis, concomitant restoration of the skin barrier remains critical.

OBJECTIVE

The aim of this prospective study is to evaluate the effect of combining dermo-cosmetic products (ATOP 7[®]; Dermoscent[®], LDCA) with the administration of lokivetmab (Cytopoint[®]; Zoetis, 1 mg/kg SC) to promote a better improvement in clinical signs of CAD and help prolong the period between episodes.

MATERIAL AND METHODS

The study was simple-blinded, randomized and controlled.

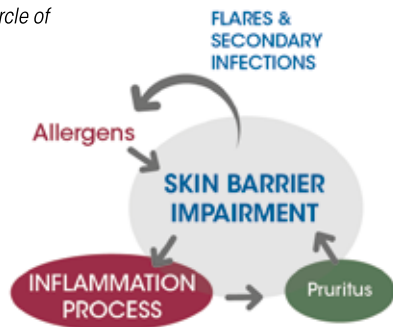
Thirty atopic dogs were included in the study and randomly divided into two groups:

- > One group received an injection of lokivetmab (Cytopoint[®]; Zoetis, 1 mg/kg SC)
- > One group received an injection of lokivetmab (Cytopoint[®]; Zoetis, 1 mg/kg SC) as well as ATOP 7[®] spot-on and ATOP 7[®] Shampoo (Dermoscent[®], LDCA), composed of essential fatty acids, ceramides and soothing active ingredients extracted from plants, once a week for 4 weeks.

The evaluation is based on 3 indexes: a pruritus score using a visual analogue scale, a CADLI (Canine Atopic Dermatitis Lesion Index) score and a cosmetic score comprising a scale for evaluating the coat appearance, skin dryness/moisture, dandruff and odor. Finally, the satisfaction of the owner and that of the investigator were evaluated.

Dogs were followed up at 10, 17, 31 days after the 1st injection and a final follow-up visit was made when relapse occurred requiring a second injection of lokivetmab (Cytopoint[®]; Zoetis, 1 mg/kg SC).

Figure 1 : Vicious circle of atopic dermatitis



RESULTS

Twenty-eight dogs completed the study, two dropped out due to the COVID-19 lockdown. No side effects were reported. At day 31, the evolution was positive in both groups with a significant improvement ($p < 0.001$) of the 3 scores: pruritus, CADLI and cosmetic compared to DO.

A greater and significant improvement of all parameters was noted in the group having received ATOP 7[®] topicals (Dermoscent[®], LDCA) associated with the injection of lokivetmab. Indeed, a 69% decrease in CADLI score was measured in this group vs. 47% in the group with lokivetmab alone ($p < 0.05$, Figure 2); pruritus score was reduced by 72% versus 55% in the group with lokivetmab alone ($p < 0.05$, Figure 3); cosmetology score was improved by 67% vs. 35% in the group with lokivetmab alone ($p < 0.001$). This difference is confirmed by the perception of the owners and investigators with higher satisfaction scores in the group that received lokivetmab combined with topical care.

In addition, the time span between two lokivetmab injections was extended by 4.3 days in the group having received the topical care associated with the injection: 37.5 days vs. 33.2 days in the group with lokivetmab alone ($p < 0.05$).

CONCLUSION

In this study, treatment with lokivetmab in combination with a spot-on and a shampoo containing essential fatty acids and other natural ingredients promoted skin barrier repair, which may have contributed to improved pruritus and CADLI scores compared to using lokivetmab alone. In addition, the study suggests a sparing effect. Thus, combining lokivetmab with topical cares that contribute to skin barrier repair could be interesting in a multimodal approach to CAD management. Such results confirm the value of complementary skin care in dogs, as what has been widely recommended in the management of human atopic dermatitis since decades^{1,2}.

DISCUSSION

CAD is a chronic condition involving three factors: skin barrier, immune system and environment (ranging from skin microbiota to aeroallergens). Atopic skin presents an alteration of the cutaneous barrier with a modification of its composition³. This tends to increase water loss and facilitates the penetration of environmental allergens into epidermis. The inadequate immunological response induces an exaggerated production of aeroallergen-specific IgE and activates signaling pathways leading to pruritus which would worsen skin barrier defects. Such reaction has led to the «outside-inside-outside» theory that currently prevails (Figure 1)^{4,5,6}. A combination of antipruritic treatment and topical care to promote hydration and repair cutaneous barrier is therefore essential.

This study suggests the interest of combining topicals since they helped better improve clinical signs of CAD compared to lokivetmab when used alone. It is interesting to note that this positive effect was shown after only one month of treatment. Further studies would be necessary to confirm a potentially more pronounced effect over a longer term.

In addition, the lead time between 2 injections of lokivetmab was significantly extended by 4.3 days in the group with the association of topical cares suggesting a sparing effect thanks to the combination of topicals. Further studies will be useful to confirm the clinical relevance of such sparing effect over a longer term.

Figure 2: CADLI score

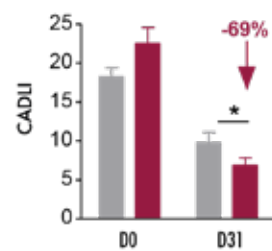
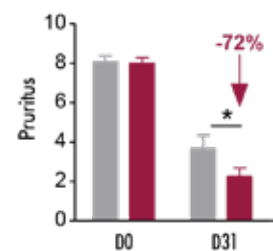


Figure 3: Pruritus score



Legend:
■ Cytopoint
■ Cytopoint + ATOP 7[®] spot-on & Shampoo

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Interest of using ATOP 7[®] spot-on in the management of canine atopic dermatitis

From « Case series of five atopic dogs treated with ATOP 7[®] spot-on »
Poster presented at the 2020 Southern European Veterinary Conference (SEVC)



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Photo 1: Evolution of the lesions at D0 and D90.



D0



D90

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HISTORY

Bella is a 5-year-old Yorkshire terrier female and has been followed for several years for canine atopic dermatitis. She presents a moderate form of CAD dominated by podal, labial and auricular pruritus. It is relatively well stabilized with local treatments such as shampoos (chlorhexidine 3%, every 8 to 10 days) and dermocorticoids (hydrocortisone aceponate spray, once or twice a week). However, Bella has phases of very pruritic episodes associated with greasy back seborrhea and bacterial surface infections. During these episodes, the owner is reluctant to use systemic antipruritic and immunomodulating treatments.

Upon the first consultation Bella is presented for marked pruritus and a greasy coat. A strong odor is also reported by the owner.

CLINICAL EXAMINATION AND MANAGEMENT

The clinical examination at D0 reveals no abnormalities. Skin examination shows a CADESI-4 score of 22 (max 180) and pruritus is estimated at 10.2 (max 15.6) on a visual analogue scale. The lesions are mostly abdominal (Photo 1) and podal and are characterized by erythema. The dog has a greasy dorsal seborrhea.

The antiseptic shampoo is maintained, and ATOP 7[®] spot-on, designed specifically to restore the skin barrier of CAD by providing essential fatty acids and ceramides extracted from plants, is then prescribed. A pipette is applied once a week between the shoulder blades but also near the most affected areas (a few drops on the legs and abdomen and the rest on the upper back) and the dog is monitored for 3 consecutive months.

FOLLOW-UP

At the 1-month control, an improvement is noted with a CADESI-4 score of 12 and an estimated pruritus of 9. The same treatment is maintained and the improvement persists. Three months after application of the spot-on, the improvement is satisfactory. The CADESI-4 score is 4 and the pruritus is estimated at 0.5. ATOP 7[®] spot-on was very well tolerated.

DISCUSSION

This case illustrates the interest of ATOP 7[®] spot-on as a complement to treat mild to moderate forms of canine atopic dermatitis. The use of topicals such as this spot-on is interesting and can help in the management of dermatitis, especially when animals cannot receive systemic antipruritic or immunomodulating treatments. Skin barrier repair is essential for an optimal management of atopic skin in which specific ceramides is deficient and lipid composition is altered^{1,2}. The topical supplementation of essential fatty acids and specific ceramides extracted from plants through a spot-on like ATOP 7[®] is therefore of great interest in this context. The presence of essential oils, some of them having anti-infectious properties, can also help to regulate more efficiently atopic skins which are prone to bacterial or fungal secondary infection³.

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Evaluation of the protective effect of a spot-on in a model of cutaneous barrier altered by tape stripping



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INTRODUCTION

This case was extracted from a pilot study through a skin model specifically designed to evaluate the effect of a spot-on (Dermoscent® ATOP 7® spot-on) on the cutaneous barrier with a non-invasive method of acute barrier rupture by delamination of the *stratum corneum* (tape stripping).

MATERIAL AND METHODS

A healthy 3.5-year-old Beagle dog with no skin problems and who has not received any systemic or topical treatment in the previous 3 months (excluding internal parasiticides) was used. The model of disruption of the skin barrier by delamination of the *stratum corneum* is based on the repeated application of a fixed number of pieces of adhesive tape, each week, to 4 skin zones, where hair was clipped at the back, one area each week (Z1-4). The study method is controlled and the dog is its own control (Z1). The spot-on was applied once a week for 3 weeks on the same spot, at the center of the 4 tape-stripping sites (Figure 1). The intensity of the alteration of the cutaneous barrier induced by the tape stripping is evaluated by measuring the transepidermal water loss (TEWL, AF200Aquaflux®) each week, after delamination, successively on 3 zones (Z2, Z3, Z4) and compared to the control zone (Z1, before application of the spot-on) and to a zone of non-delaminated skin on the abdomen.

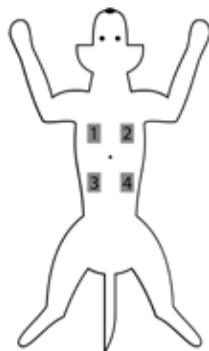
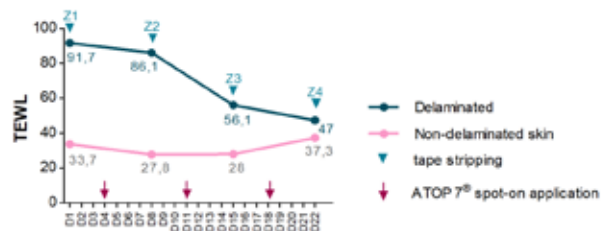


Figure 1: Schematic representation of the 4 tape-stripping zones. The spot-on is applied in the middle, at an equal distance from the 4 zones.

RESULTS

Whereas tape stripping induced a strong increase in the TEWL (1st week), the application of the spot-on progressively limits TEWL after delamination, with a TEWL close to that of the healthy area after the 3rd application (Figure 2). In addition, the spot-on demonstrates in parallel its efficacy of diffusion on different zones, at distance from the point of application.

Figure 2: Evolution of the transepidermal water loss in tape-stripping model.



CONCLUSION

This case shows that the topical care applied during 3 weeks limits transepidermal water loss in case of alteration of the cutaneous barrier, maintaining it almost to the level of healthy skin a few days after the 3rd application. The results suggest that repeated and regular use of this spot-on helps hydrate the skin and protect the skin barrier, giving it a better resistance to the aggression caused by the tape stripping.



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