Review / *Derleme*

# Pharmacotherapy of canine atopic dermatitis - current state and new trends

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**Abstract:** This review offers a concise overview of current treatment options for canine atopic dermatitis and provide an outline of two promising new treatment options (phosphodiesterase 4 and histamine H4 receptor inhibitors). Glucocorticoids have been one of the first successful treatment options and are still part of the treatment regime. Ciclosporin was introduced more than 15 years ago and is also a main pharmacological treatment option. In 2013, the Janus kinase inhibitor oclacitinib was introduced as a first in class, which is then followed by the anti-canine IL-31 antibody lokivetmab in 2016. Thus, exciting new treatment options have found their way into clinical practice. Apart from these substance classes, antihistamines, essential fatty acids and lipid substitution will be discussed as add-on treatments.

**Keywords:** Atopic dermatitis, dog, pharmacotherapy.

## Introduction

Atopic dermatitis (AD) is a chronic recurrent inflammatory skin disease that is clinically characterized by extreme itching and a typical eczematous morphology and body distribution. AD is a common skin disease, particularly in dogs, as almost 10% of the dog population is affected by this hypersensitivity (15). In other species, such as horses and cats, it plays a less substantial role. In the following, we will therefore focus on atopic dermatitis in dogs, as the diagnosis and treatment outcome is best characterized for the dog. AD is a genetically predisposed disease that for the majority of dogs occurs for the first time between the ages of 6 months and 3 years. The symptoms in dogs are typically accompanied by localized dermatitis (face, ears, paws, abdomen, armpits, inner thighs) and often severe itching. The severe itching and cutaneous hyperreactivity lead to a vicious circle of self-injury due to scratching, destruction of the skin barrier, penetration of bacteria and allergens followed by a dysregulation of cytokine release (31). Complications include secondary pyoderma and dermatitis induced by Malassezia. The exact pathogenetic mechanisms that contribute to the establishment of this allergic disease are still only partially understood. Recent research indicates that genetic and environmental factors are involved in determining susceptibility to clinical disease. Dogs might be sensitized to environmental allergens but also to food allergens. However, microbial and even insect antigens might also be the source of trigger that leads to inflammatory cell infiltration into the skin. Due to their dominance in cellular infiltrates in lesioned skin, there are indications for an important role of antigen-presenting (dendritic) cells and T-cells (24). In addition, other pathogenetic factors such as keratinocyte dysfunction or skin barrier dysfunction play a role, as well. Intercellular lipids are important for an intact barrier function. The lipids extractable from normal skin are composed of ceramides, cholesterol and free fatty acids in nearly equimolar proportions. An imbalance of the lipid metabolism can lead to a deficiency of stratum corneum ceramides and the disturbance of the barrier function in atopic dermatitis. This has also been shown for the atopic dog (8). In the *stratum corneum* of atopic dogs, the contents of some ceramides are lowered, while the cholesterol content is increased. These lowered ceramide levels may also be responsible for a disturbed barrier function (8, 27), which might favor the penetration of typical AD triggering allergens (e.g. antigens from grass pollen or house dust mite). In this review, current treatment options for canine atopic dermatitis are summarized and updated for a former review in German (3).

## Pharmacotherapy of atopic dermatitis

*Glucocorticoids:* Although glucocorticoids are one of the oldest forms of therapy, they still play an important role in the pharmacotherapy of AD despite undesirable drug effects like polyuria, polydipsia, muscle atrophy, behavioral changes, bacterial and fungal infections and, especially after topical administration, skin atrophy. They are characterized by both anti-inflammatory and antipruritic effects, whereby the mechanism of action is mainly based on the anti-inflammatory effect. In addition, glucocorticoids also have an influence on the expression and secretion of a number of itching mediators. They are administered both topically and systemically and the clear advantage is their fast onset of action (31).

*Systemic glucocorticoid therapy:* Prednisolone has been the drug of choice for systemic therapy for decades. Initially the dosage should be 0.5 - 1 mg/kg. Once the itching is significantly reduced, the therapy interval is extended to every 48 hours. A maintenance dose of 0.25-0.5 mg/kg/48h can be achieved (varies in individuals), so that side effects can be reduced.

*Topical glucocorticoids:* As a topical therapeutic option, a 0.0584% hydocortisone aceponate spray has been approved in Europe for the treatment of canine AD. A published clinical study on efficacy in the treatment of AD showed a significant reduction in inflammation (skin lesions) and itching 28 days after treatment compared to the placebo group. The treatment was well-tolerated and there were no stronger adverse effects (e.g. cortisol suppression), suggesting low absorption and/or rapid metabolism of hydocortisone aceponate (21). More recently, it has been demonstrated that the topical treatment with hydocortisone aceponate is suitable for long-term maintenance therapy (18) in a pro-active manner, i.e. the glucocorticoid is administered in lesion free periods (e.g. twice a week) and time to relapse is significantly extended by this treatment schedule.

*Ciclosporin:* The calcineurin inhibitor ciclosporin was originally used in human medicine as an immunosuppressant to prevent transplant rejection. In human medicine, ciclosporin is also approved for the treatment of severe forms of atopic dermatitis that is otherwise therapy-resistant. Cyclosporin works by binding to cyclophilin in the cytoplasm of lymphocytes (and keratinocytes) and thus inhibits the translocation of the nuclear factor of activated T cells (NF-AT) to the nucleus. This ultimately leads to a reduced synthesis of cytokines like IL-2 and IFN-γ. Apart from its effect on the function of lymphocytes, it also leads to a modulation of dendritic cell function (especially Langerhans cells). In addition, the function of other inflammatory cells (mast cells, macrophages) is impaired and the activation of keratinocytes is inhibited (2).

Ciclosporin has been successfully used in veterinary medicine for the treatment of canine AD for several years now. In clinical studies, ciclosporin A shows an anti-inflammatory and itch-reducing effect comparable to that of prednisolone (23, 25). Ciclosporin is administered orally at a dose of 5 mg/kg/day until the symptoms are controlled, then reduced to the lowest effective maintenance dose. Compared to glucocorticoids, the onset of action is delayed and the patient owner has to be informed that an optimal reduction of lesions (and itch) might take up to 4 to 6 weeks. Although ciclosporin is generally considered safe for long-term administration, adverse effects, including nausea, vomiting and diarrhoea as well as gingiva hyperplasia can occur (31). Often, side effects are observed especially during the initiation of treatment and might be controllable in the long term.

*Antihistamines:* The first generation of H1 antihistamines is currently used for the treatment of canine AD, because they have a pronounced sedative effect and often also an anticholinergic effect. In dogs, diphenhydramine (p.os 2-5 mg/kg 1-2x daily) or chlorphenamine (p.os 4-8 mg/kg 2-3x daily) are used. Diphenhydramine might not work in the recommended doses, as we did not see an inhibition of histamine-induced weal or flare reactions in laboratory dogs (11). For hydroxyzine, a reliable PK/PD modelling exists for histamine and anti-IgE induced skin reactions. It was demonstrated that 2 mg/kg hydroxyzine can reduce the skin reaction significantly (6). If ineffective, a change of antihistamine can be successful. Nevertheless, the data on efficacy (reduction of itching) vary from 10% to a maximum of 50% (23, 25). Therefore, the administration of H1 antihistamines can only be supportive but can be encouraged, as side effects are rare and tolerable (e.g. sedation after administration of first generation antihistamines). Often, there is at least a drug sparing effect (e.g. reduction in prednisolone dose by co-administration of an anti-histamine).

*Essential fatty acids:* Numerous studies on the supplementation of essential fatty acids in dogs with AD have now been published. Many studies indicate that the clinical progression (itching and inflammation) can be positively influenced. The n-6 fatty acids, such as linoleic acid, are naturally present in the epidermis, where they are incorporated into ceramides. Since ceramides are important for epidermal barrier function, n-6 fatty acid supplementation may be preferable, at least for the restoration of barrier function. Many studies recommend a ratio of 6- and 3-fatty acids between 5:1 and 10:1. However, essential fatty acids are rather not suitable as a monotherapy of AD, since a randomized cross-over study also comes to the conclusion that, despite a significant improvement in clinical signs, supplementation can only be a supportive measure in most cases (5). Furthermore,

the ideal fatty acid composition of these supplements and the dosage regimen required to achieve these goals remain unclear. However, as essential fatty acid supplementation is generally considered to be safe, it can be recommended as an add-on therapy for long-term management of AD (31).

### Substitution of epidermal lipids

A relatively new approach to the therapy of AD is to substitute the lipids present in the stratum corneum of skin-healthy patients in a lamellar structure as this structure is disorganized in atopic patients (26). This leads to a reorganization of the skin lipids in the stratum corneum of atopic dogs and could thus contribute to an increased barrier function. This approach is supported by several published studies in which it was shown that even in non-lesional skin of dogs with AD, the lipid pattern is disturbed (33). As mentioned in the introduction, the ceramide pattern is altered in AD dogs, which leads to a disorganization of the lamellar structure. This modified ceramide content is therefore held responsible for a disturbed barrier function (8, 27). Nevertheless, the efficacy of local substitution with regard to the reduction of pruritus and reduction of skin lesions is not very impressive overall (31).

*Janus kinase inhibitor (oclacitinib):* The Janus kinase (JAK) inhibitor has been approved for several years as an interesting new treatment strategy ("first in class") for the treatment of canine AD. In contrast to ciclosporin A and glucocorticoids, which mainly inhibit the synthesis of inflammatory and itching mediators, JAK inhibitors inhibit the signal transduction of cytokines. Since some cytokines, e.g. interleukin (IL-) 31, also induce itching, the rapid onset of action (especially reduction of itch within hours) was explained by the inhibition of IL-31-induced neuronal activation. However, it is now known that oclacitinib also inhibits IL-31 independent itching (e.g. via histamine or serotonin) probably by inhibiting the calcium channel TRPV1 (13). Controlled studies have shown that oclacitinib is comparably effective to prednisolone or ciclosporine A (9, 10). The initial dosage of 0.4–0.6 mg/kg orally twice daily is recommended to be reduced to once daily after the first 2 weeks (9, 10, 14). Adverse effects seem to be uncommon, but include anorexia, vomiting and diarrhea. However, only long-term experiences will determine the safety of this quite new class of immune modulators.

*Anti-canine IL-31-antibody (Lokivetmab):* Based on the findings related to oclacitinib, a specific caninized antibody against the Th-2 and pruritus inducing cytokine IL-31 (Lokivetmab) was recently launched. In a comparative study with cyclosporine A, lokivetmab was not inferior in reducing itching and lesions (20). However, some dogs were "nonresponders" with regard to the

lesions. This indicates that this very narrowly focused therapy does not lead to the desired success in all dogs, as the pathogenesis of canine AD is probably too multifactorial. Lokivetmab (administered at 1 mg/kg s.c.) seems to be well tolerated, only some local reactions at the injection site or general hypersensitivity reactions are reported as adverse effects.

### New therapeutic approaches

Although most dogs suffering from atopic dermatitis can be treated successfully with the above-mentioned drugs, there are still dogs that do not respond sufficiently to current therapeutics. Thus, there is still a need for new therapeutics with novel mechanism of action. Two newer treatment strategies will be briefly discussed here as examples:

*Phosphodiesterase-4 inhibitors (PDE4 inhibitors):* Phosphodiesterase 4 (PDE4) is a central cAMP-inactivating enzyme in almost all inflammatory and immune cells. Inhibition of PDE4 leads to immunosuppressive signals in these cells (e.g. inhibition of pro-inflammatory cytokines, reactive oxygen species and inhibition of chemotaxis of immune cells). PDE4 inhibitors therefore show a distinct anti-inflammatory and immunomodulatory potential in several animal models and some clinical studies, which also makes this group of drugs interesting for the pharmacotherapy of canine atopic dermatitis. There is one clinical study in atopic dogs with the rather non-selective PDE4 inhibitor arofylline. Arofylline has an antipruritic and anti-inflammatory effect comparable to prednisone. However, the strong emetic effect of systemically administered arofylline requires to limit the dose (12). At this point in time, a comprehensive benefit-risk assessment cannot yet be provided. After systemic administration of PDE4 inhibitors, the undesired effects like nausea, vomiting and increased gastric juice production can be dose limiting. Therefore, topical application of PDE4 inhibitors with a higher therapeutic window can be a reasonable approach (1). Recently, the first topically active PDE4 inhibitor has been approved for human AD. Since 2016, crisaborol cream is on the market for the topical treatment of mild to moderate atopic dermatitis in humans (7). However, the clinical outcome is modest and thus only studies performed in dogs can tell us the therapeutic value of topically (or systemically) administered PDE4 inhibitors.

*The histamine-4 receptor as a target for the treatment of allergic skin diseases:* With the discovery of the histamine-4-receptor (H4R) in the year 2000, the involvement of histamine in (allergic) inflammation and itching has to be revisited (see only limited efficacy of H1 antihistamines). The H4R is mainly expressed by hematopoietic cells, such as mast cells, eosinophils, basophils, dendritic cells and T-cells. In addition, our

working group showed for the first time that the H4R is functionally expressed on sensory neurons in the skin (28). This expression profile indicates the central importance of H4R in the inflammatory process and in the course of the immune response. Due to the co-expression of H1R and H4R on many immune cells, a combination of H1R and H4R antagonism is suggested as a new strategy for the treatment of allergic inflammatory diseases (34). A highly selective H4R antagonist (JNJ7777120) was investigated in a murine models of allergic contact dermatitis (30). While it was possible to inhibit hapten-induced itching considerably, the effects on inflammation were only moderate (30). However, more recent studies of our own indicate that H4R antagonism has anti-inflammatory effects if the allergic eczema is chronic (29). Interestingly, our own studies also support the use of combined H1R and H4R antagonism in a mouse model of AD (17). In an acute dog model of AD in maltese-beagles, the H4R antagonists JNJ7777120 and JNJ 28307474 had no effect on lesions. However, at that time, itch reaction could not yet be determined (4).

Taken together, only long-term studies and combination studies (H1R and H4R antagonists) can provide us the therapeutic value of inhibiting the H4R. In human medicine, a very promising clinical study has been performed with the H4R antagonist ZPL-3893787. ZPL-3893787 could significantly reduce the lesions in AD patients compared to placebo group (35).

### Outlook

After years of very few innovative approaches, there has been an interesting and exciting development within the last 5 years. With oclacitinib, a first in class was introduced to veterinary medicine before a similar drug was approved for human medicine (actually, there are promising clinical phase III studies in human medicine, however, no licensed Janus kinase inhibitor for the treatment of human AD). The circumstances are similar in terms of the monoclonal antibody lokivetmab, where again, a similar approach is in clinical trials for human medicine, although it more precisely targets the IL-31 receptor (Nemolizumab), not the IL-31 itself (16). The clinical data concerning the efficacy of Janus kinase inhibitors and the anti-IL-31 approach are very comparable between human and canine AD, which is a further indication that dogs with naturally occurring AD can serve as a translational model for human AD (19). Apart from PDE4 inhibitors and H4R antagonists, further monoclonal antibodies might find their way into clinical trials, as e.g. an antibody against the interleukin-4 receptor alpha (dupilumab) shows fairly impressive efficacy in human patients suffering from moderate to severe AD (32).

As far as a treatment strategy is concerned, there is an interesting, recently published position paper Olivry

and Banovic (22) to suggest that it makes sense to start treatment with a broad-acting anti-inflammatory agent like a glucocorticoid to induce fast clinical remission. Once clinical remission is achieved, the authors suggest to switch to a JAK inhibitor like oclacitinib, or to administer it in combination. In the next step, when lesions are well controlled, a proactive treatment with e.g. a topical steroid is recommended (see description in glucocorticoid section above). It might make sense to add a targeted therapy like lokivetmab at this point of treatment. In case of flare-ups, again, systemic glucocorticoids (and a JAK inhibitor) should be started until the resolution of lesions (22).

In conclusion, there is an exciting development in new treatment options as well as treatment schedules for clinical management of canine AD and further candidates might find their way to clinical trials pretty soon.

### Conflict of Interest

The author declared that there is no conflict of interests.

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