TREATING CANINE ATOPIC DERMATITIS

The atopic dog is an all-too-often presentation in first opinion clinics; this paper reviews the options for treatment and emphasizes the need for a multi-modal approach.

KEY POINTS

1. Canine atopic dermatitis is a common, chronic disease which affects the quality of life for many dogs and their owners.
2. The various factors that influence the pruritus threshold should be addressed simultaneously in order to achieve successful treatment, especially when flares are present.
3. Symptomatic immunosuppressive treatment and allergen-specific immunotherapy both play an important role in controlling canine atopic dermatitis, and may be used simultaneously.
4. Treatment should always be individualized and adjusted for flares, seasonality and the general health of the patient.

Introduction

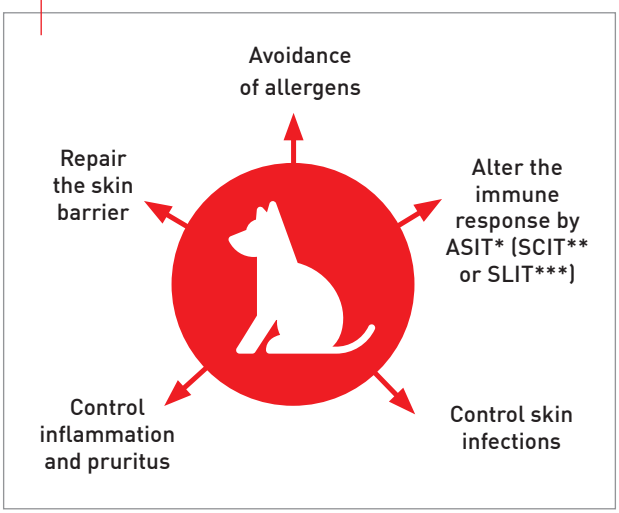
Canine atopic dermatitis (CAD) is a common allergic skin disorder that develops from predominantly environmental allergens, such as house dust mites and pollens of grasses, trees and weeds. The etiology is considered multifactorial, whereby an epidermal barrier dysfunction, combined with dysregulation of the immune system, leads to the development of clinical disease in dogs with a suggested genetic background of CAD. In most cases the problem starts at a young age, but causes discomfort by dermatitis and pruritus throughout life.

Several therapies have been developed for CAD, but each has its pros and cons regarding effectiveness and health interference. This article offers a logical approach to the daunting question "where do we start?" The challenge is not only to treat the patient successfully, but also to avoid severe flares. For this reason, the treatment of CAD requires multifaceted management **(Figure 1)**. Successful remission can only be achieved with a combination of approaches in order to control the clinical signs and prevent flares, and the options will depend on a patient's individual needs and the severity of disease over time.

Avoidance of allergens

Since the most common causal allergens are house dust mite glycoproteins and aeroallergens, such as pollens, prevention of allergen contact is difficult or impossible to achieve. An uncontrolled study that used an environmental benzyl benzoate acaricide spray in an attempt to reduce the amount of dust mite allergens reported some clinical improvement in atopic dogs (1). Other environmental sprays currently also marketed for the human field contain probiotics which produce enzymes for isolating house dust mites' fecal proteins. Further controlled studies are needed to clarify the correlation

Figure 1. The multimodal treatment and management of canine atopic dermatitis.



* Allergen-specific immunotherapy ** Subcutaneous immunotherapy
*** Sublingual immunotherapy

Annette van der Lee,

DVM, PhD, Dip. ECVD, IVC Evidensia Dierenziekenhuis, Arnhem, The Netherlands

After graduating in 2004 Dr. van der Lee followed a clinical rotation and dermatology residency at Utrecht University, achieving her ECVD Diploma in 2009. She has worked in various referral hospitals within the Netherlands since then, but alongside her clinical work she also participates in clinical dermatological research programs and she completed her Doctorate with a thesis on "T cells and immunomodulation in canine atopic dermatitis" in 2014. She joined the IVC Evidensia group in 2017, where she is currently Head of Dermatology for the Netherlands.

of clinical improvement in atopic dogs and the reduction in dust mites allergens with these sprays. Likewise, the use of dust mite-free mattresses, regular vacuuming, and washing blankets at 60°C is also likely reduce the canine skin's exposure to house dust mites allergens.

Rarely, an atopic dog may be responsive to epithelia of other pets in the household (*e.g.*, parrot or guinea pig). In this situation it is advisable to relocate either the causal pet or the patient to another household.

When food-induced atopic dermatitis is present, both food allergens and environmental allergens play a causal role (2). Food allergens may especially be significant when flares occur, and determining the role of food with an elimination diet trial and provocation is always essential for the atopic dog; if proven, prevention of exposure to causal food allergens is often relatively easy to establish.

Repairing the skin barrier

It is well known that atopic dogs suffer from an impaired epidermal barrier, which results in an increased transepidermal water loss (TEWL). Dry and scaly skin (xerosis) may be seen in some breeds. Supporting the epidermal barrier with topical moisturizers such as glycerol, glycerin, propylene glycol, panthenol and urea will increase the water-binding capacity of the epidermis, especially when used after bathing. This has been recently demonstrated in a chronically disrupted canine epidermal barrier model (3). Products containing phytosphingosine and ophytrium, a natural ingredient extracted from the root of the Japanese mondo grass plant, may also help improve the skin barrier and reduce pruritus and colonization of microbes at the epidermis (4).

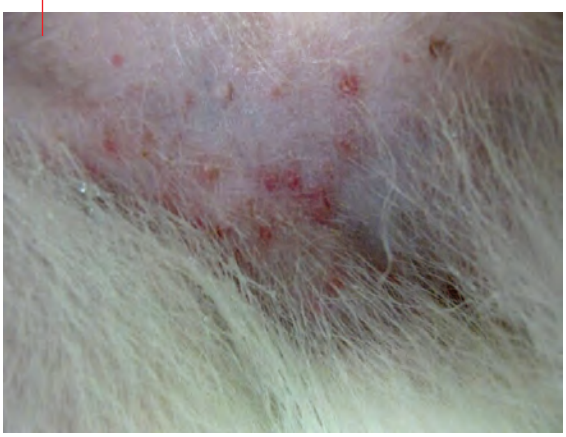
Atopic dogs also have disrupted intercellular lipid lamellae of their stratum corneum. To restore this, oral essential fatty acids (EFAs), either as supplements or incorporated in the diet, have been deployed with varying results. Of interest is one good quality study which showed a significant reduction in the required prednisolone dosage in atopic dogs when oral EFAs were administered for 12 weeks (5). Alternatively, it is possible to use a complete diet containing compounds that offer skin barrier support. Topical EFAs in a spot-on formulation have also been proven to be effective (6), although this option may be less cost-effective if long-term application is required. Other topical formulations including shampoo, sprays, and lotions containing fatty acids and ceramides have been introduced for CAD. Unfortunately, there is still some inconsistency in the effectiveness of these products, but the clinician should bear in mind that by restoring the epidermal barrier, skin penetration by environmental allergens is probably reduced.

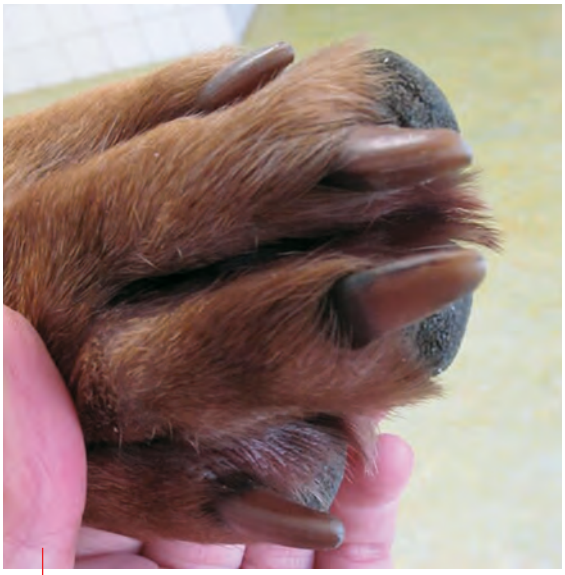
Controlling secondary skin infections

Most atopic dogs are prone to recurrent superficial pyoderma, and papules, pustules, collarettes, squames, and seborrhea are commonly seen **(Figure 2)**. Colonization of the atopic skin by pathogenic *Staphylococci* spp. (usually *S. pseudintermedius*) is increased compared to healthy skin, which may be partly explained by lower antimicrobial activity of the cutaneous antimicrobial peptides of the innate immune system. During flares, dysbiosis of the atopic skin microbiota develops, with a relative increase in *Staphylococci* levels. This dysbiosis is restored with antimicrobial therapy and the remission of lesions (7).

About 40% of atopic dogs have recurrent skin infections with the yeast *Malassezia pachydermatis,* with a strong odor, greasiness, honeycomb crusts, squames, and paronychia with brown staining of the nails often noticed **(Figure 3)**. A type I hypersensitivity reaction to *Malassezia* can also

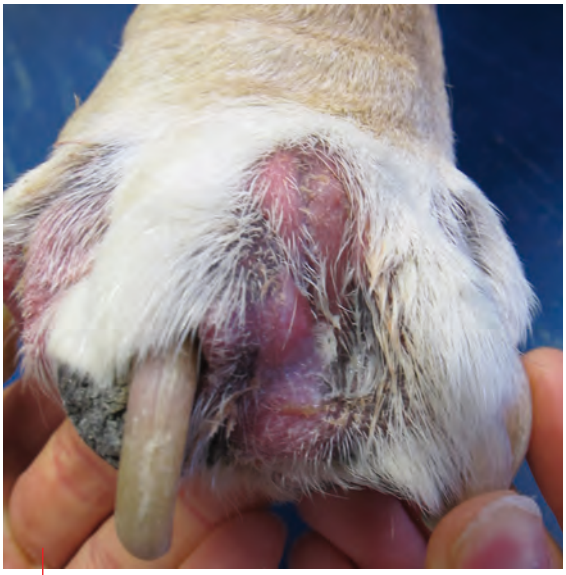
Figure 2. Atopic skin with classic lesions – papules, pustules and collarettes due to secondary superficial pyoderma.





© Annette van der Lee

Figure 3. Paronychia in an atopic dog with brown staining of the nails due to *Malassezia* dermatitis.



© Annette van der Lee

Figure 4. Interdigital pyogranuloma with secondary deep pyoderma in an atopic dog.

occur, leading to severe pruritus (8). Secondary skin infections by bacteria and yeasts must therefore always be controlled, and is achieved by regular use of topical antimicrobial therapy (shampoos, mousses, sprays, wipes and gels). Shampooing with 3% chlorhexidine has been shown to be clinically as effective against bacteria and yeasts as a 2% chlorhexidine solution and miconazole combination (9). Twice weekly washes are generally efficacious, but (depending on the severity of the infection) topical therapy should be administered more frequently initially. The author then uses daily washings for a week, followed by a week of every other day, and then twice a week. Protocols that include twice weekly application of a mousse, gel, or spray on the lesions, in addition to weekly shampooing, seem to work equally well.

Systemic antibiotics should only be used initially when the pyoderma is deep (*e.g.*, with furunculosis **(Figure 4)**, very generalized, or when the owner cannot treat the dog topically. When selecting an appropriate drug, this may either be done after culture and susceptibility testing, or following the basic principles of antibiotic therapy; options include clindamycin (10 mg/kg q12H), cephalosporins (cephalexin 10-30 mg/kg q8-12H), or clavulanic acid-potentiated amoxicillin (12.5 mg/kg q12H). Always treat until both clinical signs and cytological findings of pyoderma have resolved. Recurrent use of antibiotics should be avoided because of the risk of inducing bacterial resistance. Likewise, oral treatment with ketoconazole (10 mg/kg q24H or 5 mg/kg q12H) or itraconazole (5 mg/kg q24H) for yeasts should only be used in very severe cases, as yeasts can (rarely) become resistant to azole derivatives (10). However, remember that (especially with ketoconazole) various undesirable drug interactions are possible.

"The challenge is not only to treat the canine atopic patient successfully but also to avoid severe flares, and for this reason the treatment of CAD requires multifaceted management."

Annette van der Lee

Controlling skin inflammation and pruritus

Symptomatic therapy that has good evidence for reducing pruritus and dermatitis in CAD includes glucocorticosteroids, cyclosporine, oclacitinib, and lokivetmab, and these will be discussed in turn. Note that preventive flea treatment is always essential to reduce the itch threshold. There is no conclusive evidence that oral type-1 antihistamines effectively treat either active or chronic CAD lesions (11), but if required the best options are cetirizine (0.5-1.0 mg/kg q24H) or hydroxyzine (2 mg/kg q12H) (12).

Glucocorticosteroids

Glucocorticosteroids (GC) are effective through interference with multiple ubiquitous transcription factors leading to repression of genes coding for cytokines, cytokine receptors, adhesion molecules, pro-inflammatory enzymes, and chemotactic proteins. They therefore deactivate many inflammatory cells and reduce the itch, and as they are fast-acting in nature they can be used both

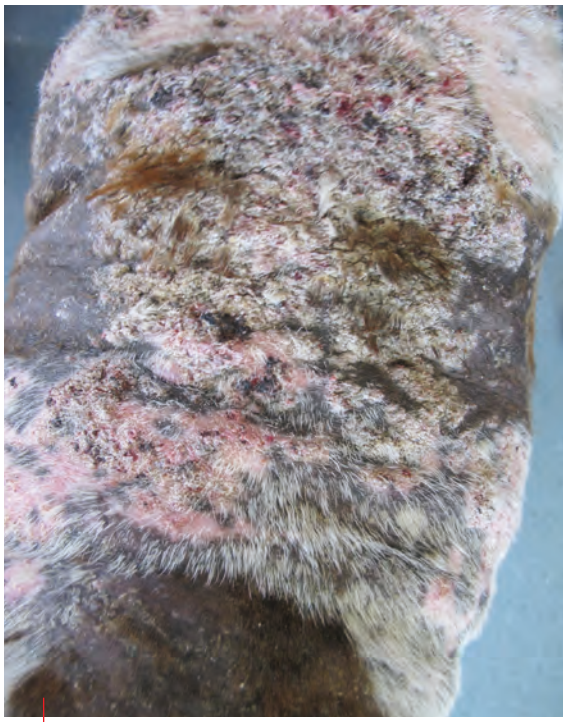
to induce remission of acute signs and maintain long-term control in CAD. However, because they impact on many different cellular mechanisms side effects are common with prolonged systemic administration; these include polyuria, polydipsia, polyphagia, muscle and skin atrophy, susceptibility for bacterial and fungal infections, demodicosis, and iatrogenic hyperadrenocorticism **(Figure 5)**. Parenteral formulations should therefore not be administered repeatedly, but short-acting glucocorticoids are recommended when clinical signs are severe. Oral prednisolone (0.5-1 mg/kg q24H) or methylprednisolone (0.4-0.8 mg/kg q24H) should be administered for 5 to 14 days, based on the patient's response to treatment. Dividing the dose twice daily may reduce polydipsia and polyuria in some individuals. The dose may then slowly be tapered and administered every other day as the clinical signs reduce.

The preferential GC formulation is a topical ointment, spray or lotion. Both triamcinolone acetonide and hydrocortisone aceponate sprays show high efficacy in bringing localized lesions under control (13); these should be used every day for about two weeks to induce remission and then continued on individual lesions as often as twice weekly. Hydrocortisone aceponate could potentially induce mild dermal degradation through inhibition of collagen I and III pro-peptides, but one study showed no visible skin atrophy during long-term intermittent (twice weekly) topical application in CAD cases (14). Human preparations such as betamethasone or mometasone furoate creams have also shown to be effective in veterinary practice. The ultimate goal of maintenance treatment with a topical GC is to actively reduce the risk for flares and extend the remission time, instead of only treating when lesions become clinically visible (14).

Oclacitinib

Oclacitinib is a Janus kinase (JAK) inhibitor. JAKs are nonreceptor tyrosine kinases that are activated by various cytokine receptors. In mammals, four JAK families (JAK1, JAK2, JAK3, and tyrosine kinase 2) exist, regulating the expression of multiple inflammatory genes. By selectively inhibiting JAK1- (and to a minimal extent JAK2-) dependent cytokines, oclacitinib can reduce the effects of pro-inflammatory and pro-allergic cytokines and is therefore considered as having a semi-broad working mechanism in CAD.

Because it has a fast onset of action for pruritus, oclacitinib is very useful for treating acute flares of itch. It is administered twice daily for 14 days and then continued with once-daily dosing (0.4-0.6 mg/kg). The twice-daily dosing is especially necessary when chronic dermatitis is present. It is considered safe for the long-term treatment of CAD in animals aged 12 months or more (15). Theoretically, oclacitinib may have immunosuppressive properties when used at dosages above recommendations (16), whilst its use in susceptible dogs may lead to opportunistic infections, viral papillomas, or demodicosis. In these cases the therapy should be discontinued, but in general routine hematologic evaluation, serum chemistry, and urine culture are not indicated for dogs receiving oclacitinib (17).

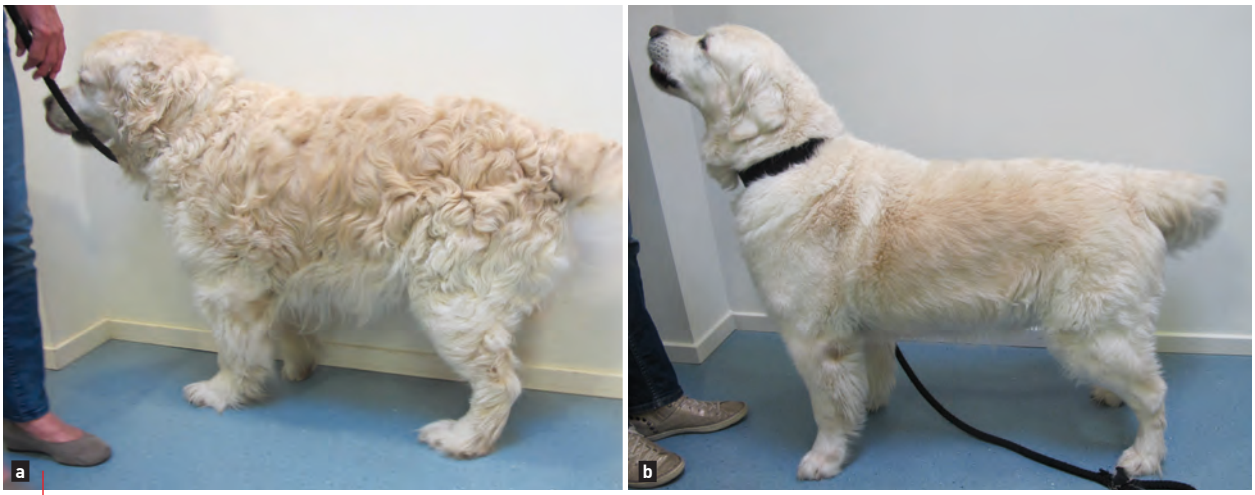


© Annette van der Lee

Figure 5. An atopic dog with iatrogenic Cushing's syndrome due to prednisolone treatment. Widespread firm calcinosis cutis lesions can be seen on the dorsum.

Cyclosporine and tacrolimus

Cyclosporine A is a calcineurin inhibitor with a specific immunosuppressive mode of action. It binds to the intracellular immunophilins, resulting in inhibition of the cytokine interleukin-2 (IL-2), leading to a reduction in T cell proliferation and antibody production by B cells dependent on T-helper cells. Cyclosporine also has a broad-spectrum working mechanism and should be dosed at 5 mg/kg q24H. However, efficacy onset is slow; it can take between 4-8 weeks before clinical signs of pruritus and dermatitis are in remission, so it can only be used for maintenance therapy in CAD. Concurrent treatment with other fast-acting drugs in the startup phase is found to be efficient and safe. Prednisolone given at 1 mg/kg q24H for a week, then continued by every other day dosing for two weeks, can be administered in the first three weeks of treatment with cyclosporine (18). Likewise, concomitant administration of oclacitinib (0.4-0.6 mg/kg q12H) for 14 days, then once daily for seven days, is well tolerated (17). Once an atopic dog is in remission with cyclosporine the dose should gradually be reduced (stepping down at around 1 mg/kg every two weeks) or given every other day to find the lowest possible dosing regime. Self-limiting side effects (*e.g.*, vomiting and diarrhea) occur in 30% of patients, predominantly within the first week of administration, so the author often uses a lower dose at startup (*e.g.*, 1.5 mg/kg q24H for 3 days, then 3 mg/kg q24H for another 3 days), especially in dogs with a sensitive digestive tract. Administration with food may also help to decrease gastrointestinal upset. Less frequent side effects, which may be dose-dependent, include gingival hyperplasia, excessive hair growth **(Figure 6)**, susceptibility for



© Annette van der Lee

Figure 6. An atopic dog with excessive hair growth; the dog had received maintenance therapy with cyclosporine for a year **(a)**. The same dog as in **(a)** six months after switching to maintenance treatment with oclacitinib **(b)**.

opportunistic (fungal) infections, hyperplastic verrucous lesions, and psoriasiform-lichenoid-like dermatitis. However, these side effects usually regress if the drug is discontinued.

The calcineurin inhibitor tacrolimus has been found to reduce lesional scores when used topically for several weeks (19). Although tacrolimus can irritate the skin in the first days of treatment, a twice-daily application using a 0.1% preparation seems to be well tolerated in dogs.

Lokivetmab

The anti-canine interleukin-31 monoclonal antibody lokivetmab has a narrow mode of action and is the most specific symptomatic atopic therapy with the least side effects. It is capable of neutralizing canine IL-31, a cytokine involved in itching. Its mechanism of action differs from that of oclacitinib; IL-31 is bound by lokivetmab before it even can bind to its receptor, thereby preventing the main pruritogenic effects of the molecule. Monthly subcutaneous injections of lokivetmab can be used at 1-2 mg/kg (depending on national licensing data), with some dogs responding well to the higher dose, and remission of 4-8 weeks is commonly achieved. The drug has a very long half-life and can be safely used with other drugs for symptomatic CAD therapy. Its efficacy in reducing both pruritus and skin lesion scores (using the Pruritus Visual Analog Score (PVAS) and Canine Atopic Dermatitis Extent and Severity Index (CADESI) respectively) is shown to be non-inferior after 28 days of treatment to the broad-spectrum cyclosporine. While the initial response to lokivetmab is shown to be fast (reducing the PVAS by over 50% in 77% of atopic dogs), its overall efficacy after nine months of treatment was found to be 59% (20). The author's experience is that the drug has few or no side effects, and is excellent to treat dogs with mild to moderate pruritus, and notably some cases with insufficient response to oclacitinib may respond well to lokivetmab. However, it is less efficient for treating atopic dogs with severe (chronic) lesions, and although it is considered to be a fast-acting and safe product for CAD, the high cost may limit its use as maintenance therapy for many owners.

Allergen-specific immunotherapy

Altering the immune response by allergen-specific immunotherapy (ASIT), also known as desensitization or hyposensitization, is the only disease-modifying therapy that neutralizes a hyper-responsive immune system to environmental allergens by inducing tolerance. ASIT can be defined as the practice of "gradually administering increasing quantities of an allergen extract to an allergic subject to ameliorate the signs associated with subsequent exposure to the causative allergen." Its mode of action includes the induction of allergen-specific regulatory T cells and their cytokine IL-10, induction of allergen-specific IgG4 levels, and reduction of both the ratio of Th2/Th1 cytokines and allergen-specific IgE levels (21).

Subcutaneous immunotherapy (SCIT) has been the mainstay of ASIT since the early 1980s. Two formulations are available for dogs, namely aqueous and alum-based solutions, and if the correct protocols are followed systemic side-effects are rarely seen. Adjustments to these protocols are often needed for the individual patient to improve efficacy or during certain periods (*e.g.*, seasonal variation). For example, when a patient has flares one week prior to redosing, the injection interval should be shortened, or if a patient responds with increased itch after each injection, a lower dose may be needed.

In previous studies with atopic dogs, the overall success rate of SCIT was estimated to be 50-70% after 9 to 12 months of treatment (22). Attempts have been made to increase the efficacy and decrease onset time to clinical effectiveness by using a "rush" protocol, and studies in atopic dogs show this to be a safe and efficacious method (23). However, this approach is not currently recommended by the author, unless undertaken by specialists at referral centers.

An alternative to SCIT is sublingual immunotherapy (SLIT), whereby a specific allergen dose is administered orally once or twice daily. Owner compliance is essential for this, as the dog should not eat or drink for 10 minutes before and after the application. In the few uncontrolled open studies performed, no consistent evidence supporting the increased effectiveness of SLIT above SCIT has been shown (24).

Of particular interest is the recent novel intralymphatic mode (ILIT) of application, with recent studies reporting a quicker onset of clinical improvement and possibly a more sustainable efficacy over time (25).

Regardless of which ASIT mode of application is used, symptomatic therapy to control skin inflammation and pruritus should be given temporarily to maintain a good quality of life until the immunotherapy is judged to be effective. Because ASIT is a tailor-made treatment, it requires adjustments of dose, intervals, and control of flares to achieve the best results.

CONCLUSION

The atopic dog needs long-term multimodal treatment management to secure a good quality of life, and there is a need for education, clear explanation, and coaching of owners to achieve the best treatment outcome. Exacerbations of pruritus and dermatitis by secondary skin infections should be controlled with topical treatment, taking into account the repair of the epidermal barrier. In general, the more broad-spectrum a drug, the more side-effects can develop, and combinations of drugs such as glucocorticosteroids, cyclosporine and oclacitinib should be used sparingly due to the risk of enhanced immunosuppression when used long term. Allergen-specific immunotherapy is the only disease-modifying therapy for canine atopic dermatitis and should be tailor-made for the patient.

REFERENCES

1. Swinnen C, Vroom M. The clinical effect of environmental control of house dust mites in 60 house dust mite-sensitive dogs. *Vet Dermatol* 2004;15(1):31-36.
2. Picco F, Zini E, Nett C, *et al*. A prospective study on canine atopic dermatitis and food-induced allergic dermatitis in Switzerland. *Vet Dermatol* 2008;19(3):150-155.
3. Panzuti P, Vidémont E, Fantini O, *et al*. A moisturizer formulated with glycerol and propylene glycol accelerates the recovery of skin barrier function after experimental disruption in dogs. *Vet Dermatol* 2020;31:344-e89
4. Ollivier E, Zemirline C, Marchand L, *et al*. Effect of the ingredient A97614A1 on the adhesion and biofilm formation of *Staphylococcus pseudintermedius* in a model of reconstructed canine epidermis. In; *Proceedings,* 62nd BSAVA Congress, Birmingham, 2019.
5. Saevik BK, Bergvall K, Holm BR, *et al*. A randomized, controlled study to evaluate the steroid sparing effect of essential fatty acid supplementation in the treatment of canine atopic dermatitis. *Vet Dermatol* 2004;15:137-145.
6. Popa I, Remoue N, Osta B, *et al*. The lipid alterations in the stratum corneum of dogs with atopic dermatitis are alleviated by topical application of a sphingolipid-containing emulsion. *Clin Exp Dermatol* 2012;37(6):665-671.
7. Bradley CW, Morris DO, Rankin SC, *et al*. Longitudinal evaluation of the skin microbiome and association with microenvironment and treatment in canine atopic dermatitis. *J Invest Dermatol* 2016;136(6):1087-1089.
8. Morris DO, DeBoer DJ. Evaluation of serum obtained from atopic dogs with dermatitis attributable to *Malassezia pachydermatis* for passive transfer of immediate hypersensitivity to that organism. *Am J Vet Res* 2003;64(3):262-266.
9. Maynard L, Rème CA, Viaud S. Comparison of two shampoos for the treatment of canine *Malassezia* dermatitis: a randomised controlled trial. *J Small Anim Pract* 2011;52(11):566-572.
10. Kano R, Yokoi S, Kariya N, *et al*. Multi-azole-resistant strain of *Malassezia pachydermatis* isolated from a canine *Malassezia* dermatitis. *Med Mycol* 2019;57(3):346-350.
11. Olivry T, DeBoer DJ, Favrot C, *et al*. Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the International Task Force on Canine Atopic Dermatitis. *Vet Dermatol* 2010;21:233-248.
12. Olivry T, DeBoer DJ, Favrot C, *et al*. Treatment of canine atopic dermatitis: 2015 updated guidelines from the International Committee on Allergic Diseases of Animals (ICADA). *BMC Vet Res* 2015;11:210.
13. Nuttall T, Mueller R, Bensignor E, *et al*. Efficacy of a 0.0584% hydrocortisone aceponate spray in the management of canine atopic dermatitis: a randomised, double blind, placebo-controlled trial. *Vet Dermatol* 2009;20:191-198.
14. Lourenço AM, Schmidt V, São Braz B, *et al*. Efficacy of proactive long-term maintenance therapy of canine atopic dermatitis with 0.0584% hydrocortisone aceponate spray: a double-blind placebo-controlled pilot study. *Vet Dermatol* 2016;27:88-92.
15. Cosgrove SB, Cleaver DM, King VL. Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life. *Vet Dermatol* 2015;26:171-e35.
16. Banovic F, Gordon H, Tarigo J, *et al*. Modulatory effects of oclacitinib on *in vitro* canine T-cell proliferation and cytokine production. *Vet Dermatol* 2019;30(1):17-e6.
17. Panteri A, Strehlau G, Helbig R, *et al*. Repeated oral dose tolerance in dogs treated concomitantly with ciclosporin and oclacitinib for three weeks. *Vet Dermatol* 2016; 27:22-e7.
18. Dip R, Carmichael J, Letellier I, *et al*. Concurrent short-term use of prednisolone with cyclosporine A accelerates pruritus reduction and improvement in clinical scoring in dogs with atopic dermatitis. *BMC Vet Res* 2013;9:173.
19. Bensignor E, Olivry T. Treatment of localized lesions of canine atopic dermatitis with tacrolimus ointment: a blinded randomized controlled trial. *Vet Dermatol* 2005;16:52-60.
20. Moyaert H, Van Brussel L, Borowski S, *et al*. A blinded, randomized clinical trial evaluating the efficacy and safety of lokivetmab compared to ciclosporin in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2017;28(6):593-e145.
21. Keppel K, Campbell K, Zuckermann F, *et al*. Quantitation of canine regulatory T cell populations, serum interleukin-10 and allergen-specific IgE concentrations in healthy control dogs and canine atopic dermatitis patients receiving allergen-specific immunotherapy. *Vet Immunol Immunopathol* 2008;123:337-344.
22. Loewenstein C, Mueller RS. A review of allergen-specific immunotherapy in human and veterinary medicine. *Vet Dermatol* 2009;20(2):84-98.
23. Hobi S, Mueller RS. Efficacy and safety of rush immunotherapy with alum-precipitated allergens in canine atopic dermatitis. *Tierarztl Prax Ausg K Kleintiere Heimtiere* 2014;42(3):167-173.
24. DeBoer DJ, Verbrugge M, Morris M. Clinical and immunological responses of dust mite sensitive, atopic dogs to treatment with sublingual immunotherapy (SLIT). *Vet Dermatol* 2016;27(2):82-7e23.
25. Timm K, Mueller RS, Nett-Mettler CS. Long-term effects of intralymphatic immunotherapy (ILIT) on canine atopic dermatitis. *Vet Dermatol* 2018;29(2):123-e49