Therapies in Canine Atopic Dermatitis: An Update

Domenico Santoro, DVM, MS, DrSc, PhD

KEYWORDS

• Atopic dermatitis • Dog • Therapy • Review

KEY POINTS

- Canine atopic dermatitis is a multifaceted chronic disease requiring a tailored therapeutic approach.
- New therapies have been designed for canine atopic dermatitis.
- Alternative and topical therapies are fundamental in the management of canine atopic dermatitis.
- Future therapies may include more biologics and more tailored treatments based on the individual clinical presentation.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common cutaneous inflammatory and pruritic diseases in dogs. AD is a genetically predisposed inflammatory and pruritic skin disease associated with well-defined clinical signs and immunoglobulin (Ig)E directed against environmental allergens.[1] Atopiclike dermatitis (ADL) is a disease characterized by the same clinical signs of AD in absence of demonstrable IgE.[1] The major difference between these 2 entities resides in the impossibility to demonstrate IgE in ADL, making it impossible to formulate an allergen-specific immunotherapy (ASIT).[1] The true incidence of ADL is unknown, and the therapeutic response to the common therapies for AD is also unknown. In one unpublished study performed in France by Prelaud and Cochet-Faivre,[2] 25.6% of dogs enrolled were diagnosed with ADL. A similar percentage (14.6%) was present in a more recent study in the United States.[3] A breed predisposition for English bulldogs was also suspected in one of these studies.[2] In addition, the efficacy of cyclosporine (CsA) for such patients is controversial. In the first study, a lower efficacy rate was seen in ADL compared with AD dogs (50% vs 92%)[2]; although in other studies, CsA has been shown to be effective in ADL dogs.[3,4] The effect of more recent drugs on ADL is unknown. The difficulty to treat AD/

Disclosure Statement: The author has nothing to disclose.
Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, 2015 Southwest 16th Avenue, Gainesville, FL 32610, USA
E-mail address: dsantoro@ufl.edu

Vet Clin Small Anim 49 (2019) 9–26
https://doi.org/10.1016/j.cvsm.2018.08.002
vetsmall.theclinics.com

ADL dogs resides also in the well-known diversity in clinical presentation and response to treatments within the 2 AD entities. Because of this enormous diversity, canine AD has been recently suggested to be classified as a syndrome more than a well-defined single cutaneous inflammatory entity, as proposed in human AD.[5]

CANINE ATOPIC DERMATITIS: CLINICAL AND PATHOGENETIC SYNOPSIS

AD is extremely common in dogs, affecting between 3% and 15% of the canine population or up to 58% of dogs affected by skin diseases.[6–8] The age of onset typically spans between 6 months and 6 years; however, more than 70% of AD dogs develop clinical signs between 1 and 3 years of age. Many breeds have been associated with AD, with terriers, retrievers, and brachycephalic dogs most commonly affected.[9–11]

Clinically, canine AD is characterized by chronic skin inflammation, pruritus, and recurrent skin infections. The most common clinical signs include generalized pruritus (seasonal, nonseasonal, or nonseasonal with seasonal worsening), erythema, papules, pustules, crusts, and excoriations.[12] Head (perioral, periocular, and ears), flexor aspect of elbows, carpal and tarsal joints, paws (digits, claws, and interdigital aspects), ventral abdomen, perineum, and ventral tail are most commonly affected.[12] However, few exceptions have been reported in West Highland white terriers, sharpeis, and German shepherds.[13] The diagnosis of canine AD is based on characteristic clinical signs and by excluding other pruritic diseases (eg, food allergy, demodicosis, scabies).[12]

The pathogenesis of AD is very complex and not completely elucidated. Both genetic and environmental factors are involved in the development of the clinical disease, with both types I and IV hypersensitivity reactions demonstrated. Classically, the first step involved in the development of AD is a sensitization to environmental allergens (eg, house dust mites) penetrating through the skin (mainly) able to lead to recruitment and activation of resident inflammatory cells and degranulation of mast cells via binding to IgE. On activation, multiple inflammatory mediators, including cytokines (specifically type 2 and proinflammatory) and chemokines are secreted, determining the course of the disease. With the chronicity of the lesions, a type 1 inflammatory response predominates. Last, a defect in the epidermal barrier is associated to a higher penetration of allergens through the skin and exacerbation of the inflammatory response. However, if such defect is primary or secondary is still controversial. Other major exacerbating factors include bacterial (*Staphylococcus pseudintermedius*) and fungal (*Malassezia pachydermatis*) infections along with psychogenic and environmental (eg, humidity) factors. Very recently, a series of review articles has been published. The series represents an extensive review on the current knowledge on the pathogenesis of canine AD.[14–20] Thus, for more in-depth information, the author refers the reader to such review articles.

Due to the diversity of the phenomena involved in the pathogenesis of canine AD and the variety of clinical presentations, a more rational and tailored therapeutic approach is required for each patient.[21,22] Such therapeutic options should be customized for each atopic dog, keeping in consideration the needs of each dog (eg, amount of drugs, side effects, severity of the clinical signs, easy administration of treatments) and the dog's owners (eg, financial circumstances, expectations, quality of life, time).

TREATMENT OVERVIEW

The treatment of canine AD is mainly centered on 4 factors: time (chronic vs acute lesions), presence of pruritus, inflammation, and infections. The chronicity of the lesions

and their severity will determine the choice of short-term (eg, flare) versus long-term medications, keeping in mind side effects, efficacy, and costs. Finally, cutaneous infections, bacterial and/or fungal, are major exacerbators, and as such need to be properly treated. Topical and systemic options are commercially available to treat AD. For the purpose of this review, only therapies that are available for dogs are discussed in depth. Finally, a discussion on ASIT, injectable or sublingual, is beyond the scope of this review.

TOPICAL THERAPIES

Recently, 2 documents highlighting the guidelines for the treatment of canine AD have shown that the improvement of the skin, and coat hygiene and care is fundamental in treating atopic dogs.[21,22] The skin care can be achieved in several ways by using different products with the goal of moisturizing the skin, reducing the inflammatory and/or pruritic response, and repairing the skin barrier.

MOISTURIZERS

Moisturizers (emollients and/or humectants) have multiple functions. The most important action is increasing the amount of water in the skin by reducing the transepidermal water loss (TEWL) via blocking agents (ie, oils) or using hygroscopic molecules. These latter act as occlusive agents and attract water from the environment and/or from the dermis/subcutaneous tissues (eg, oatmeal). The increase of hydration alone is able to significantly reduce the pruritus and the need of antipruritic drugs; weekly Allermyl shampoo (containing lipids, complex sugars, and antiseptics) for 3 to 4 weeks significantly decreases pruritus and lesional score in most dogs.[23,24]

ANTI-INFLAMMATORY/ANTIPRURITIC

The most important topical anti-inflammatory drugs include glucocorticoids (GCs) and calcineurin inhibitors (CIs); however, antihistamines and local anesthetics have been used in dogs with some success.

GCs are extremely potent and versatile compounds that can be used either systemically or topically. They are generally associated to a significant reduction in both inflammation and pruritus. Their mechanism of action is very broad, complex, and not completely understood. In allergic diseases, they seem to interfere with proinflammatory and pruritogenic mediators, inflammatory cell migration and function, and with inflammation-associated nerve hypersensitivity.[25]

Topical GCs have been largely used during the past decades for the reduced presence of systemic side effects (eg, polyuria, polydipsia, polyphagia, urinary tract infections, and muscle wasting) compared with oral GCs; however, cutaneous atrophy, comedones, and calcinosis cutis are potential side effects for some topical GCs. Based on their chemical structure, topical GCs can be divided into “old” and “new” generation. To the former belong compounds like hydrocortisone, prednisolone, triamcinolone acetonide, betamethasone, and dexamethasone. The new generation includes diester topical GCs, like mometasone furoate, hydrocortisone aceponate, and prednicarbate. These latter are metabolized in situ into inactive molecules, dramatically reducing the presence of systemic side effects.

Triamcinolone acetonide (0.015%, Genesis; Virbac, Fort Worth, TX) spray is the only “old” GC that has been shown to be highly efficacious in the treatment of canine AD. In a multicenter, randomized, double-blinded, placebo/vehicle-controlled clinical trial (RDBPCT),[26] triamcinolone acetonide spray was applied to allergic dogs for 4 weeks

at tapered frequency. At the end of the study, a significant improvement in pruritus, clinical signs, and overall assessment was present when compared with vehicle in absence of clinical and minor hematological adverse effects (slightly lower total leukocyte, lymphocyte, and eosinophil counts after treatment).

Similar response has been documented for hydrocortisone aceponate (0.0584%, Cortavance; Virbac), a "new" GC, through few RDBPCTs trials in Europe and Korea.[27–30] In the first clinical trial,[27] Cortavance was administered to dogs with mild AD for 70 days at tapered frequency. After 28 days of treatment, 73.0% and 46.6% of dogs achieved a reduction of $\geq$50% in clinical score and pruritus, respectively. These results were confirmed by a second study[28] comparing the efficacy of daily Cortavance with cyclosporine over 84 days.[27] This study showed the clinical equivalence between Cortavance and CsA in absence of clinical, hematological, or hormonal abnormalities.[26,27] Similarly, a third study[29] using Cortavance for 14 days showed a significant decrease in clinical signs, pruritus, and TEWL in absence of side effects, suggesting a positive effect of hydrocortisone aceponate on skin barrier function. Another RDBPCT[30] showed promising effects of Cortavance as prophylactic treatment (twice weekly), able to prolong the remission time in atopic dogs. Finally, more recently, the immunologic effects of Cortavance have also been assessed in 2 other studies performed in the United States[31] and Japan.[32] In the first study,[31] the investigators showed that once-daily Cortavance spray for 14 days is able to interfere with intradermal testing (IDT) in dogs, and a minimum of 2 weeks is necessary to avoid such effect on IDT. In addition, this was the first study showing that Cortavance may be able to induce, histologically, a significant decrease in dermal thickness that may be present. In addition, Cortavance may also induce, when used daily for 3 weeks, a significant reduction (36.0% decrease) in the post–adrenocorticotropic hormone cortisol level.[32] However, Cortavance did not have any effect on peripheral $CCR4^{+}CD4^{+}$ T-lymphocytes.[32] Altogether, these studies showed a significant beneficial clinical effect of Cortavance in the treatment of mild canine AD as preventive or as management therapy. In addition, they show a large margin of safety of Cortavance in both short-term and long-term treatment of canine AD.

An alternative to topical GCs is CIs (tacrolimus and cyclosporine). Only 3 RDBPCTs[33–35] have been published on the use of tacrolimus for localized lesions of AD in dogs, 2 of which[33,34] investigated the use of the 0.1% and 1[35] the 0.3% formulation. In all 3 studies, the use of tacrolimus, although expensive, was very promising in treating localized atopic lesions with minimal side effects. In all studies, most dogs enrolled were able to achieve a treatment success (defined as $\geq$50% reduction in clinical signs from baseline) after 4 or 12 weeks of treatment. Mild irritation was noticed in a minority of cases after application and a lack of hematological and biochemical changes was reported. Detectable levels of tacrolimus were present in the blood at the end of the study; however, tacrolimus concentration was below toxicity limits. When 0.3% tacrolimus ointment was used,[35] a fourfold increase in tacrolimus concentrations was observed in the blood of dogs using 0.3% ointment. Due to equal efficacy and lower blood levels of tacrolimus, the 0.1% ointment is recommended as a safer choice. Cyclosporine, another calcineurin inhibitor, has been recently investigated as a topical treatment option for canine AD.[36] In a placebo-controlled clinical study, the investigators showed a significant clinical efficacy (localized lesions of moderate-severe AD) and moderate speed of action (21 days) of a nanotechnology pharmaceutical formulation of cyclosporine able to penetrate the epidermis, guaranteeing good absorption and dermal action. On days 21 and 45 after treatment, a significant reduction in clinical and pruritus score was seen in the treatment group compared with placebo, showing a rapid and effective action of the

nano-compound in absence of side effects. However, more studies are needed to confirm the beneficial effect of this formulation in affected dogs.

Without a doubt, new-generation GCs and CIs are the most effective topical anti-inflammatory drugs used in canine AD. They are not only able to interfere with the inflammatory cascade, but also decrease pruritus. However, due to cost or potential side effects, their use may be limited. Good alternative medications that can be used as glucocorticoid-sparing drugs include topical antihistamines, local anesthetics, and skin barrier–repairing agents.

Antihistamines (H1 receptor antagonists) acts on histamine receptors, competitively blocking the formation of histamine-receptor complex.[25] Thus, they inhibit the histaminic cascade after histamine is released, with some antihistamines able to inhibit mast cell degranulation as well.[37] Common antihistamines used in veterinary dermatology include diphenhydramine, hydroxyzine, and cetirizine. Although inexpensive and extremely safe, their efficacy has been historically low in treating allergic conditions in dogs; however, the lack of efficacy of antihistamine in canine AD may be because histamine is not the major player in cutaneous inflammation in atopic dogs and also because antihistamines are not able to dislodge histamine from its receptors once they are bound.[21,22,37] Unfortunately, the efficacy of topical H1 (diphenhydramine) and H4 (JNJ7777120 and JNJ28307474) antagonists has been shown to be low in recent studies.[38,39] Topical diphenhydramine was able to reduce clinical signs of AD only approximately 20% to 38% after 28 and 56 days of use, respectively.[38] Similarly, H4 antagonists, were not able to prevent skin lesions in a canine model of AD.[39] These 2 studies indicate a potential use of topical antihistamines in canine AD, although more studies are needed to fully evaluate the usefulness of such mediations in canine AD.

Local anesthetics have been used in clinical practice to alleviate the clinical signs of allergic dermatoses in dogs. In particular, the use of pramoxine as shampoo or cream rinse is of common use, although not many clinical trials have been published on its efficacy in dogs.[40] Only 1 crossover open clinical trial has evaluated the efficacy of 2 topical formulations of pramoxine cream rinse (Relief, Bayer, Shawnee, KS, USA; Derma-Soote, Vetoquinol, Fort Worth, Tx, USA) in atopic dogs for a total of 4 weeks. At the end of the study, pramoxine was judged effective (51%–75% reduction in pruritus) by 41% of the owners. The pos-treatment antipruritic effects lasted for 48 hours.

SKIN BARRIER–REPAIRING AGENTS

The use of anti-inflammatory/antipruritic topical mediations is essential in the treatment of allergic conditions in dogs. However, recent studies have shown that a skin barrier alteration, primary and/or secondary in nature, is present in both human and canine atopic skin. These results have led researchers and clinicians to look into therapies focused on ameliorating the skin barrier defect in allergic patients. In particular, topical fatty acids[41–43] and (pro)ceramides[44–50] have been largely used as adjuvant therapies for the treatment of canine AD. A few studies have been published on the effects of topical skin barrier–repairing agents showing a normalization of the epidermal lipid lamellae and skin lipids. However, the clinical effects of such products have been demonstrated in only a few clinical trials, showing an overall mild to moderate efficacy.

The use of essential fatty acids (EFAs), as adjuvant therapy for allergic skin conditions and dry skin, has been adapted in the clinical practice for decades. Essential fatty acids, in form of ω-3 and/or ω-6, have been administered as oral supplementation or through commercially available EFA-enriched diets. Only recently, the use of

essential oil topical products has been considered as a potential alternative for delivering unsaturated EFA to affected skin. In 2011, an 8-week RDBPCT[41] was performed in Germany comparing the clinical effects of a spot-on formulation containing essential oils and unsaturated fatty acids (Dermoscent Essential 6 spot-on, Adventix, Burlington, ON, Canada) with a spray containing similar, although different, oils and fatty acids (Dermoscent Atop 7 spray). The outcomes measured included a clinical assessment, pruritus score, and skin barrier assessment (TEWL) at the beginning and at the end of the study. At the end of the study, there was a significant reduction in clinical signs (40% and 79% for spot-on and spray, respectively), pruritus score (32% and 43%), and TEWL (spray formulation). Finally, no side effects were reported for any of the treatments. The same research group performed another RDBPCT[42] analyzing the effects of the spot-on formulation against placebo over an 8-week period. The dogs were divided in mildly or moderately/severely affected atopic dogs. At the end of the study, a significant improvement of clinical signs and pruritus was seen in the treatment group. More recently, another RDBPCT43 evaluating the use of a topical lipid emulsion containing ceramides, fatty acids, and 18-β-glycyrrhetinic acid over a 3-month period was published. After the first month, a reduction of $\geq$50% in pruritus score was achieved in 50% of dogs; however, this beneficial effect was lost at the 3-month mark.

An alternative to essential oils and fatty acid topical formulations is the use of topical products containing a combination of ceramides, cholesterols, and fatty acids. In fact, early studies in people showed that products containing a specific molar ratio of ceramide, cholesterol, and fatty acids (3:1:1) to mimic the ratio naturally present in the skin were highly beneficial to improve skin lesions in atopic patients. In veterinary medicine, the first study[44] showing a beneficial effect of a spot-on product containing such molar ratio was published in 2008. In that study,[44] the investigators used a spot-on formulation (Allerderm spot-on by Virbac) every 3 days for 6 consecutive times. After 6 treatments, a significant reorganization of the intracorneal lipids, due to a possible increase in production and secretion of endogenous stratum corneum lipids, was seen. Another proof-of-concept study[49] was performed a few years later analyzing the expression of ceramides, cholesterol, and fatty acids in the stratum corneum of atopic dogs before and after 6 applications of Allerderm spot-on. At the end of the study, the investigators reported a significant increase in ceramide content and a more homogeneous distribution of protein-bound lipid content in the stratum corneum compared with before treatment. These studies were followed by 2 clinical trials evaluating the clinical benefits of Allerderm spot-on on atopic dogs[45,46]; both studies gave similar results. The use of Allerderm spot-on, applied twice weekly for 4 to 12 weeks, was associated with a significant decrease in clinical signs compared with baseline scores; however, no benefits were seen for pruritus and barrier function (TEWL). These studies demonstrated that the application of such products might improve the lipid biosynthesis and distribution in the stratum corneum ameliorating the skin barrier, however, its usefulness in clinical practice still needs additional studies.

The results obtained by Allerderm spot-on were confirmed by a more recent study[47] assessing the clinical and ultrastructural changes in atopic dogs before and after application of ceramide-based moisturizers for 28 days. The treatment involved the daily use of a moisturizing cream containing ceramide, cholesterol, and fatty acids (ration 3:1:1) (Atobarrier Cream, Aestura, Hangang-daero, Yongsan-gu, Seoul, Seoul, Korea) associated with a weekly moisturizing shampoo (Dermally shampoo, Dechra, Laewood, KS, USA). At the end of the study, a significant decrease in clinical signs, pruritus, and TEWL associated with an increase in skin hydration was reported. As

far as the ultrastructural study, it showed a significant increase in thickness and continuity of the lipid bilayer.

Other skin barrier–repairing products that have increased in popularity in the past few years are topicals containing plant-derived sphingosines (phytosphingosines). Sphingosines are natural derivates of ceramides that have been associated with significant anti-inflammatory, antimicrobial, and barrier-repairing activity. A recent study in France[48] evaluated the barrier-repairing activity of a mousse containing phytosphingosines, raspberry oil, and lipids (Douxo Calm mousse, Ceva, Paris, France) in an experimental canine model. At the end of the study, there were no significant changes in TEWL or pH; however, a significant reduction of proliferation markers (ki-67) and B-lymphocytes and dendritic cells (BLA36) was seen in the treated compared with the untreated skin, suggesting a significant effect of phytosphingosines on inflammation and proliferation.

Altogether, these studies have shown that topical skin barrier–repairing agents have a significant benefit in treating canine AD. In particular, they are able to reduce cutaneous inflammation and restore intracorneal lipids normalizing the skin barrier of atopic dogs.

SYSTEMIC THERAPIES

Many systemic therapies have been investigated and routinely used in dogs affected by AD. As for the topical medications, it is important to recognize pros and cons of systemic therapies. The most important limitations of these drugs are cost, side effects, and lag phase. Because of their diversity in lag phases, some therapeutic options are more suitable for treating acute flares (eg, GC, oclacitinib), whereas others are more indicated for maintenance and/or prevention of flares (eg, allergen-specific immunotherapy, cyclosporine, antihistamines). This section is more focused on novel therapies (oclacitinib and lokivetmab) with a brief update on older therapies (cyclosporine).

Oclacitinib is a Janus kinase (JAK) inhibitor recently approved for treatment of allergic pruritus in dogs. There are 4 main types of JAK[51] present in mammalian cells (JAK1, JAK2, JAK3, and TYK2). Of those, JAK1 is the JAK mainly involved in the inflammatory response, whereas JAK2 and 3 and TYK2 are mainly involved in cell differentiation, hematopoiesis, and homeostasis.[51] Mechanistically, once a cytokine binds to the specific receptor, this dimerizes, allowing the autophosphorylation of JAK leading to the activation of the signal intermediate signal transducer and activator of transcription (STAT) proteins.[51] Once activated, STAT proteins (7 STATs have been identified in mammalian cells) will migrate to the nucleus, leading to DNA transcription and regulation of gene expression.[52,53] JAK/STAT signaling is critical for cytokine signaling and signal transduction of many proinflammatory, pro-allergic, and pruritogenic cytokines (eg, interleukin [IL]-2, IL-4, IL-6, IL-13, and IL-31).[54] Oclacitinib had increased popularity almost immediately after its lunch on the US market due to its rapid action associated with few side effects. Oclacitinib is mainly a JAK1 and 2 inhibitor; however, a slight affinity for TYR2 and JAK3 has been reported as well.[55] Its affinity profile explains the significant inhibition of inflammatory cytokines (IL-2, IL-4, IL-6, IL-13, and IL-31) and a minimal effect on hematopoietic cytokines (erythropoietin, granulocyte/macrophage colony-stimulating factor, IL-12, and IL-23).[55] Pharmacologically,[54] oclacitinib maleate is rapidly (plasmatic peak <1 hour) and almost completely (bioavailability of 89%) absorbed orally, independently from the prandial state, with a half-life of 4 to 6 hours, and a lack of cumulative effect over 168 days. Because of its speed of action, oclacitinib has been compared wwith prednisolone and dexamethasone in an experimental canine model of pruritus in which IL-31 was injected after the

administration of each drug.[56] Prednisolone was able to inhibit the induced pruritus when administered 10 hours before the administration of IL-31, dexamethasone was able to reduce the pruritus up to 10 hours before IL-31 administration, whereas oclacitinib inhibited IL-31-induced pruritus when given 1, 6, 11, and 16 hours before IL-31 administration, making these compounds very similar from the clinical point of view. As far as efficacy, few studies[57–62] have assessed the clinical benefits and side effects of oclacitinib in treating allergic skin diseases in dogs. The first 2 studies[57,58] were very similar and showed that oclacitinib is a powerful drug, mainly active against pruritus. Oclacitinib was able to significantly reduce the pruritus within 7 days, with some improvement evident within 24 hours from administration.[57] In the second study, oclacitinib was administered for 112 days.[58] Over 28 days of treatment, a reduction in the pruritus score of 47.4% and 10.4% was detected in the oclacitinib and placebo groups, respectively; a reduction of 29.5% and 6.5% was seen within the first day of administration. From days 28 to 112, both the pruritus and clinical lesion scores remained unchanged. Minimal clinical and hematological abnormalities were reported in both studies. These studies were followed by a long-term compassionate use study[59] combining the information from dogs previously exposed to oclacitinib for a mean time of 401 days. The side effects reported in this study were also very similar to previous findings, highlighting the possibility of urinary tract infections, vomiting, otitis, pyoderma, and diarrhea. Four percent of dogs (mean age: 9.8 years) were euthanized because of confirmed or suspected malignancy. In addition, 19% of dogs developed new dermal, epidermal, or subcutaneous masses of unknown origin. There were no hematological abnormalities reported in the study.

Based on these exciting preliminary data, oclacitinib has significantly increased in popularity among clinicians, posing the question of whether oclacitinib would be more beneficial in treating AD than older systemic therapies such as GCs and cyclosporine. Thus, a first study[60] compared the use of oclacitinib with prednisolone over 28 days. Once again, pruritus and clinical signs were assessed, showing no difference between the 2 treatments after 4 hours, 6 days, and 18 days.[60] On the opposite hand, as expected, oclacitinib performed much better than cyclosporine in another prospective RDBPCT over 84 days of treatment at label doses.[61] In that study, a significantly higher reduction in pruritus score was seen in the oclacitinib group on days 1, 14, and 28, whereas a significant difference was seen only on day 14 for the clinical score. Because of the well-known long lag phase of cyclosporine, more recently, a study[62] evaluated the combined use of oclacitinib and cyclosporine, assessing the clinical safety of such combination over a 21-day trial. At the end of the study,[62] the investigators did not report any abnormalities except diarrhea in 2 dogs receiving both drugs.

Again, due to the numerous similarities between oclacitinib, GCs, and cyclosporine, potential complications (urinary tract infections),[63,64] reported in long-term use of these latter 2 medications, were evaluated for oclacitinib in a very recent study.[65] In that study, dogs receiving oclacitinib over 180 to 230 days did not show any signs (clinical or microbiological) of urinary tract infections. These studies indicate the usefulness of oclacitinib as good and safe alternative to other immunomodulatory drugs routinely used in veterinary dermatology to treat adult dogs affected by AD (eg, GC and cyclosporine).

Another treatment option that has acquired increasing popularity in treating canine AD is a caninized monoclonal anti-canine IL-31 antibody: lokivetmab. Lokivetmab was designed based on a recent study[66] showing a role of IL-31 in canine pruritus using a canine experimental model. However, whether IL-31 plays a significant role in canine AD is still controversial. In fact, in the original study,[66] only 57% of dogs with naturally occurring AD (detection limit 13 pg/mL) had a detectable serum level of IL-31. However, in a more recent study,[67] using a canine model of AD, the investigators were able to

detect IL-31 in all the samples analyzed (~40–50 pg/mL) and similar results were recently presented[68] at the European Veterinary Dermatology Meeting showing the presence of IL-31 in the serum of 243 privately owned atopic dogs and 55 normal dogs using a more advanced ultrasensitive enzyme-linked immunosorbent assay technology able to detect extremely low amounts of protein in serum (femtomolar level of 531 fg/mL and 13,541 fg/mL in healthy and atopic dogs, respectively).

Lokivetmab is the first biologic commercially available for the treatment of allergic conditions in dogs. Its mechanism of action is quite simple: once injected, lokivetmab recognizes and binds to naturally produced IL-31, making it unavailable to bind to its receptor and trigger the pruritic cascade. Because foreign antibodies are readily recognized by the host's immune system and destroyed, lokivetmab was made fully caninized (90% or more of the antibody structure is similar to antibody produced naturally in dogs) so as to avoid recognition and last longer. This type of technology has been largely used in human medicine to make humanized monoclonal antibodies to treat several immunologically driven diseases (eg, rheumatoid arthritis, psoriasis, AD). Since lokivetmab was initially commercialized, a few clinical studies[69–71] have been published assessing its efficacy and safety in atopic dogs.

The first study involved atopic dogs throughout the United States.[69] Dogs were assigned to receive a single subcutaneous injection of different dose of lokivetmab (0.125, 03.5, and 2 mg/kg) or placebo and monitored for clinical efficacy (pruritus and clinical signs) for 56 days. At full dose, a significant decrease in pruritus score was seen within 1 to 3 days, followed by a decrease in clinical signs after only 7 days. After 28 days, the success rate for the pruritus (decrease of $\geq$50% in score compared with baseline) was between 21% and 57%, depending on the dose used. Similarly, the success rate for the clinical score varied between 13% and 46% based on the dosage. Furthermore, pharmacokinetic data showed that, at full dose, the mean peak serum concentration of lokivetmab is 10 μg/mL observed after 9.8 days (2 mg/kg) with a mean half-life of 16 days.[69] Similar results were evident from a clinical field trial[70,71] evaluating the long-term efficacy and safety of lokivetmab for atopic dogs. In that study, lokivetmab was administered to atopic dogs for 9 consecutive months at monthly intervals. At the end of the trial, 76% of dogs were assessed as being "normal,"whereas 59% were assessed as clinically "in remission." Mild side effects were recorded and no immunogenicity (ie, anti-lokivetmab antibody development) was seen in any dog. Finally, a noninferiority study[71] compared the efficacy of lokivetmab with cyclosporine. In that study, atopic dogs were enrolled and assigned to receive monthly lokivetmab or daily oral cyclosporine for 3 months. Lokivetmab was not inferior to cyclosporine for either pruritus or clinical signs, with an overall response to treatment of 68.5% and 72.5% by the owner and 74.0% and 72.9% by the investigator for cyclosporine and lokivetmab, respectively.

These studies altogether show that lokivetmab is a safe and effective treatment alternative to systemic GC and cyclosporine.

Cyclosporine has been considered a good GC-sparing agent for the past 20 years. Many of the clinical studies, proving the efficacy and safety of cyclosporine in dogs affected by AD, have been published in the past 2 decades. Cyclosporine is widely recognized to be highly effective in the treatment of canine AD and associated with minimal side effects. The author refers the reader to previously published reviews on cyclosporine efficacy in atopic dogs.[72–77]

Recent studies have been mainly focused on the effects of cyclosporine on skin barrier function, skin microbiota, and effect on T-cell subtypes. In particular, one open study[78] analyzed the effects of cyclosporine on TEWL, as indirect measurement of skin barrier integrity, in severely affected atopic dogs. The investigators were able

to show that although a significant decrease in clinical signs was present after the second week on treatment, a significant decrease in TEWL, in selected areas, was detected from the first week on cyclosporine. Another single-blinded, randomized, placebo-controlled study[79] evaluated the effect of cyclosporine on skin barrier integrity on a colony of atopic beagles before and after chronic stimulation with house dust mites. In that study, the investigators showed that 28 days of cyclosporine did not have any significant effect on skin immunologic milieu (IL-2, IL-4, IL-10, IL-13, interferon-γ, tumor necrosis factor-α, and transforming growth factor-β) or skin barrier markers (canine antimicrobial peptides, filaggrin 2, and caspase 14) despite evident improvement of physical signs. Similarly, a lack of effect of cyclosporine on the skin microbiota was evident from another recent study[80] using Maltese-beagle atopic dogs. In particular, the investigators showed that both cyclosporine and prednisone administered for 1 month were not associated with any significant changes in the cutaneous microbiota (bacteria, fungi, and viruses). Finally, very recently, the effect of cyclosporine on lymphocyte subpopulations also has been investigated to better understand the specific immunomodulatory effect of this compound on the immune system. In that controlled study,[81] the investigators showed that 90 days of cyclosporine therapy, although significantly decreasing the clinical signs, did not modify the circulating T-cell ratio (CD4/CD8) and number of T-regulatory cells in atopic dogs. Thus, new studies have confirmed the beneficial clinical effect of cyclosporine for atopic dogs, but also showed that this compound has little effect on alteration of skin barrier, lymphocytic subpopulations, and cutaneous microbiota in atopic dogs.

ALTERNATIVE THERAPIES

The research of alternative therapies to treat canine AD has seen a tremendous increase in the past decade. In particular, researchers have invested in searching for more natural compounds with fewer side effects able to reduce or completely eliminate the needs of medications generally used for AD (eg, GC, cyclosporine, oclacitinib). The earliest and most repeated attempt was done looking into probiotics as a potential tool to reduce or prevent clinical signs of AD in dogs.[82–86] In particular, the use of *Lactobacillus rhamnosus* has been shown to be effective in preventing the development of AD in a canine model when given in utero (from the third week of gestation until lactation) and continued in the offspring from the third week to 6 months of age.[82] Immunologic and structural (skin barrier function) benefits were still evident after 3 years from the administration.[83,84] More recently, a study,[85] comparing cetirizine with *Lactobacillus paracasei K71*, showed a similar reduction in clinical signs (38.1% vs 45.8%) and pruritus (38.1% vs 26.8%) scores in mild cases of AD over 12 weeks of treatment. Similar results were confirmed by using *Lactobacillus sakei probio-65* after 8 weeks in dogs with severe AD.[86] Altogether, these studies suggest that the administration of probiotics could be beneficial in preventing or reducing the clinical signs (and drugs) of AD in dogs. However, it is essential to keep in mind that not all bacteria act as probiotics, and particular attention needs to be applied to the choice of probiotics to be administered to optimize their beneficial effects.

Other treatments reported to be useful in reducing the clinical signs or the need of drugs to treat atopic dogs have been studied. In particular, oral vitamin E, associated with fexofenadine, has been shown to be highly effective in reducing clinical signs in moderate cases of AD after 8 weeks of treatment when compared with placebo plus fexofenadine (96% vs 89%, respectively).[87] The investigators also reported an increase in circulating vitamin E and an increase in total antioxidant capacity. Similarly, the use of oral vitamin D has been shown to be promising when used in mild to

moderate cases of AD for 8 weeks.[88] As in the vitamin E study, an increase in circulating vitamin D was detected. In both studies, a lack of side effects was reported.

Other alternative therapies shown to be effective in the treatment of canine AD include the use of procaine (neural therapy), ultrapure water, pentoxifylline plus polyunsaturated fatty acids (PUFAs), and endocannabinoids, whereas other options have not been associated with a significant or questionable improvement of canine AD (eg, cold laser therapy, homeopathy, fluoxetine, CCR4 inhibitors, aminopterin) or associated with moderate to severe side effects (eg, masitinib).

Briefly, the use of procaine intravenously and intradermally (in affected areas), showed a significant reduction of 82.6% and 77.4% in clinical signs and pruritus score with 88% of dogs reaching a reduction of both scores of $\geq$50% after 13 weeks of treatment in absence of side effects.[89] Furthermore, a maintained improvement of the clinical signs was seen in 55% of the dogs enrolled after 19 weeks from last injection.

Recently, a placebo-controlled clinical trial[90] evaluated the efficacy of weekly Allermyl shampoo (ceramides and EFAs) using ultrapure soft water compared with Allermyl shampoo using tap water in moderate cases of canine AD over a 4-week period. Ultrapure soft water is characterized by low hardness, low calcium and magnesium, and high sodium compared with tap water. The study showed a significant decrease in clinical signs (21% vs −0.45%), pruritus (24.0% vs 3.6%), and TEWL (46.4% vs −6.0%) for the treatment group compared with the control.

Pentoxifylline is a nonselective phosphodiesterase enzyme inhibitor able to decrease fibronectin, production of proinflammatory cytokines, and leukocyte response to interleukins, and impairs T-lymphocyte binding to keratinocytes, decreases fibroblastic activity, and with long-term use, may decrease fibrosis. Although clinically used, only 1 placebo-controlled, randomized study[91] has been published assessing its efficacy in treating canine AD. Pentoxifylline was administered orally at the dosage of 20 mg/kg every 8 hours, alone (group I) or in combination with oral PUFAs (group II), for 60 days. On days 30 and 60, a significant reduction in both clinical signs and pruritus scores was seen in both treatment groups compared with placebo (group III) and with baseline. However, the combination of pentoxifylline and PUFAs was more efficacious than pentoxifylline alone.

Last, the oral use of naturally occurring bioactive lipid endocannabinoidlike compounds has been investigated in dogs affected by AD. In particular, an open-label clinical trial[92] using ultra-micronized palmitoylethanolamide at 10.9 mg/kg per day for 8 weeks showed a significant reduction in both clinical signs (day 28: 31.6%; day 56: 48.2%) and pruritus (day 28: 26%; day 56: 36.8%), and an increase in quality of life. This study, although it is the first one published in dogs, is very promising.

As far as homeopathic remedies for treating AD in dogs, only 1 small pilot study showed a potential benefit of individualized remedies in canine AD.[93] However, due to the very low number of dogs enrolled and the lack of a controlled, blinded, randomized clinical trial, the use of homeopathy is not justified at the moment. The use of cold laser therapy was investigated in a placebo-controlled, clinical trial.[94] However, after 5 weeks of treatment, no difference in clinical signs and pruritus was present between low-level laser therapy (cold laser) and placebo. Finally, a double-blinded, placebo-controlled crossover 2-month clinical trial[95] evaluated the efficacy of fluoxetine for severe AD, showing no efficacy after 2 months of fluoxetine.

FUTURE THERAPIES

Looking at the future, it is possible that safer and more targeted compounds will be available for canine AD. Specifically, biologics targeting molecules involved in the

treatment of specific clinical subtypes of AD are desirable.[96] On the other hand, the use of viral-particle-associated cytokines[97] or bacterins[98,99] have also been studied as potential treatments for allergies in animals. Their efficacy is variable but promising in the face of mild side effects. Among others, humanized anti-interleukin antibodies (targeting IL-4, IL-13, IL-17, and IL-22) have been studied, or are currently under evaluation, for the treatment of human AD. Along with anti-interleukin antibodies, the use of anti-human IgE and anti–IL-31 receptor antibodies have been highly promising as well. In veterinary medicine, the only biologic approved is lokivetmab. It is plausible to assume that more biologics will be readily available in the near future; however, based on the complexity of the atopic disease, instead of a single monoclonal antibody, maybe the use of cocktails of monoclonal antibodies may increase the efficacy of this therapeutic option.

SUMMARY

In conclusion, canine AD is an extremely complex clinical syndrome characterized by different clinical manifestations and therapeutic response. Because of its complexity, multiple therapies have been evaluated in different clinical subtypes, with sometimes contrasting results. At the moment, a pool of few compounds represent the "core" of treatment options for canine AD (eg, GC, cyclosporine, oclacitinib). However, alternative drugs and topical therapies have been looked at with increased interest due to their low toxicity and high efficacy, specifically if associated with "core" medications. Furthermore, it is fundamental to remember to strive for preventive medicine using compounds able to delay rather that treat flares and skin infections in atopic dogs. In addition, it is important to recognize the difference in drugs more suited for treating flares and drugs more effective in preventing the flares. Treatment options should be regularly reassessed and adjusted based on the specific needs of patients and their owners. The key of a successful treatment for canine AD often combines high efficacy with low cost and mild side effects.

REFERENCES

1. Halliwell R. Revised nomenclature for veterinary allergy. Vet Immunol Immunopathol 2006;114:207–8.
2. Prelaud P, Cochet-Faivre N. A retrospective study of 21 cases of canine atopic-like dermatitis. Vet Dermatol 2007;18:385.
3. Botoni LS, Torres SMF, Kock SN, et al. Comparison of clinical and epidemiological features of canine atopic dermatitis and atopic-like dermatitis: a retrospective study. Vet Dermatol 2018;29:8.
4. Fujimura M, Nakatsuji Y, Ishimaru H. Cyclosporin A treatment in intrinsic canine atopic dermatitis (atopic-like dermatitis): open trial study. Pol J Vet Sci 2016;19:567–72.
5. Marsella R, De Benedetto A. Atopic dermatitis in animals and people: an update and comparative review. Vet Sci 2017;4 [pii:E37].
6. Hillier A, Griffin CE. The ACVD task force on canine atopic dermatitis (I): incidence and prevalence. Vet Immunol Immunopathol 2001;81:147–51.
7. Hill PB, Lo A, Eden CA, et al. Survey of the prevalence, diagnosis and treatment of dermatological conditions in small animals in general practice. Vet Rec 2006;158:533–9.
8. Nodtvedt A, Egenvall A, Bergvall K, et al. Incidence of and risk factors for atopic dermatitis in a Swedish population of insured dogs. Vet Rec 2006;159:241–6.

9. Jaeger K, Linek M, Power HT, et al. Breed and site predispositions of dogs with atopic dermatitis: a comparison of five locations in three continents. Vet Dermatol 2009;21:119–23.
10. Santoro D, Marsella R, Hernandez J. Investigation on the association between atopic dermatitis and the development of mycosis fungoides in dogs: a retrospective case-control study. Vet Dermatol 2007;18:101–6.
11. Sousa CA, Marsella R. The ACVD task force on canine atopic dermatitis (II): genetic factors. Vet Immunol Immunopathol 2001;81:153–7.
12. Hensel P, Santoro D, Favrot C, et al. Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification. BMC Vet Res 2015;11:196.
13. Wilhem S, Kovalik M, Favrot C. Breed-associated phenotypes in canine atopic dermatitis. Vet Dermatol 2011;22:143–9.
14. Pucheu-Haston CM, Eisenschenk MN, Bizikova P, et al. Introduction to the review articles by ICADA on the pathogenesis of atopic dermatitis in dogs. Vet Dermatol 2015;26:77–8.
15. Bizikova P, Santoro D, Marsella R, et al. Review: clinical and histological manifestations of canine atopic dermatitis. Vet Dermatol 2015;26:79-e24.
16. Santoro D, Marsella R, Pucheu-Haston CM, et al. Review: pathogenesis of canine atopic dermatitis: skin barrier and host-micro-organism interaction. Vet Dermatol 2015;26:84-e25.
17. Bizikova P, Pucheu-Haston CM, Eisenschenk MN, et al. Review: role of genetics and the environment in the pathogenesis of canine atopic dermatitis. Vet Dermatol 2015;26:95-e26.
18. Pucheu-Haston CM, Santoro D, Bizikova P, et al. Review: innate immunity, lipid metabolism and nutrition in canine atopic dermatitis. Vet Dermatol 2015;26:104-e28.
19. Pucheu-Haston CM, Bizikova P, Eisenschenk MN, et al. Review: the role of antibodies, autoantigens and food allergens in canine atopic dermatitis. Vet Dermatol 2015;26:115-e30.
20. Pucheu-Haston CM, Bizikova P, Marsella R, et al. Review: lymphocytes, cytokines, chemokines and the T-helper 1-T-helper 2 balance in canine atopic dermatitis. Vet Dermatol 2015;26:124-e32.
21. 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;21:233–48.
22. 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.
23. Loeflath A, von Voigts-Rhetz A, Jaeger K, et al. The use of a whirlpool in topical antipruritic therapy–a double-blinded, randomized, cross-over study. Vet Dermatol 2007;18:427–31.
24. Reme CA, Mondon A, Calmon JP, et al. Efficacy of combined topical therapy with antiallergic shampoo and lotion for the control of signs associated with atopic dermatitis in dogs. Vet Dermatol 2004;15:S33.
25. Olivry T, Bäumer W. Atopic itch in dogs: pharmacology and modeling. Handb Exp Pharmacol 2015;226:357–69.
26. Deboer DJ, Schafer JH, Salsbury CS, et al. Multiple-center study of reduced-concentration triamcinolone topical solution for the treatment of dogs with known or suspected allergic pruritus. Am J Vet Res 2002;63:408–13.

27. 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;20:191–8.
28. Nuttall TJ, McEwan NA, Bensignor E, et al. Comparable efficacy of a topical 0.0584% hydrocortisone aceponate spray and oral ciclosporin in treating canine atopic dermatitis. Vet Dermatol 2012;23:4–10, e1–2.
29. Nam EH, Park SH, Jung JY, et al. Evaluation of the effect of a 0.0584% hydrocortisone aceponate spray on clinical signs and skin barrier function in dogs with atopic dermatitis. J Vet Sci 2012;13:187–91.
30. 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;27:88–92e25.
31. Bizikova P, Linder KE, Paps J, et al. Effect of a novel topical diester glucocorticoid spray on immediate- and late-phase cutaneous allergic reactions in Maltese-beagle atopic dogs: a placebo-controlled study. Vet Dermatol 2010;21:70–9.
32. Fujimura M, Ishimaru H. Influence of a diester glucocorticoid spray on the cortisol level and the CCR4(+) CD4(+) lymphocytes in dogs with atopic dermatitis: open study. J Vet Med 2014;2014:492735.
33. Marsella R, Nicklin CF, Saglio S, et al. Investigation on the clinical efficacy and safety of 0.1% tacrolimus ointment (Protopic) in canine atopic dermatitis: a randomized, double-blinded, placebo-controlled, cross-over study. Vet Dermatol 2004;15:294–303.
34. 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.
35. Marsella R, Nicklin CF. Investigation on the use of 0.3% tacrolimus lotion for canine atopic dermatitis: a pilot study. Vet Dermatol 2002;13:203–10.
36. Puigdemont A, Brazís P, Ordeix L, et al. Efficacy of a new topical cyclosporine A formulation in the treatment of atopic dermatitis in dogs. Vet J 2013;197:280–5.
37. DeBoer DJ, Griffin CE. The ACVD task force on canine atopic dermatitis (XXI): antihistamine pharmacotherapy. Vet Immunol Immunopathol 2001;81:323–9.
38. Iwasaki T, Hasegawa A. A randomized comparative clinical trial of recombinant canine interferon-gamma (KT-100) in atopic dogs using antihistamine as control. Vet Dermatol 2006;17:195–200.
39. Bäumer W, Stahl J, Sander K, et al. Lack of preventing effect of systemically and topically administered histamine H(1) or H(4) receptor antagonists in a dog model of acute atopic dermatitis. Exp Dermatol 2011;20:577–81.
40. Scott DW, Rothstein E, Miller WH. A clinical study on the efficacy of two commercial veterinary pramoxine cream rinses in the management of pruritus in atopic dogs. Canine Pract 2000;25:15–7.
41. Tretter S, Mueller RS. The influence of topical unsaturated fatty acids and essential oils on normal and atopic dogs. J Am Anim Hosp Assoc 2011;47:236–40.
42. Blaskovic M, Rosenkrantz W, Neuber A, et al. The effect of a spot-on formulation containing polyunsaturated fatty acids and essential oils on dogs with atopic dermatitis. Vet J 2014;199:39–43.
43. Marsella R, Cornegliani L, Ozmen I, et al. Randomized, double-blinded, placebo-controlled pilot study on the effects of topical black currant emulsion enriched in essential fatty acids, ceramides and 18-beta glycyrrhetinic acid on clinical signs

and skin barrier function in dogs with atopic dermatitis. Vet Dermatol 2017;28: 577-e140.
44. Piekutowska A, Pin D, Rème CA, et al. Effects of a topically applied preparation of epidermal lipids on the stratum corneum barrier of atopic dogs. J Comp Pathol 2008;138:197–203.
45. Fujimura M, Nakatsuji Y, Fujiwara S, et al. Spot-on skin lipid complex as an adjuvant therapy in dogs with atopic dermatitis: an open pilot study. Vet Med Int 2011; 2011:281846.
46. Marsella R, Genovese D, Gilmer L, et al. Investigations on the effects of a topical ceramides-containing emulsion (Allerderm® Spot on) on clinical signs and skin barrier function in dogs with atopic dermatitis: a double-blinded, randomized, controlled study. Intern J Appl Res Vet Med 2013;2:110–6.
47. Jung JY, Nam EH, Park SH, et al. Clinical use of a ceramide-based moisturizer for treating dogs with atopic dermatitis. J Vet Sci 2013;14:199–205.
48. Pin D, Bekrich M, Fantini O, et al. An emulsion restores the skin barrier by decreasing the skin pH and inflammation in a canine experimental model. J Comp Pathol 2014;151:244–54.
49. 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;37:665–71.
50. Cerrato S, Ramió-Lluch L, Brazís P, et al. Effects of sphingolipid extracts on the morphological structure and lipid profile in an in vitro model of canine skin. Vet J 2016;212:58–64.
51. Cinats A, Heck E, Robertson L. Janus kinase inhibitors: a review of their emerging applications in dermatology. Skin Therapy Lett 2018;23:5–9.
52. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med 2013;368:161–70.
53. Villarino AV, Kanno Y, Ferdinand JR, et al. Mechanisms of JAK/STAT signaling in immunity and disease. J Immunol 2015;194:21–7.
54. Collard WT, Hummel BD, Fielder AF, et al. The pharmacokinetics of oclacitinib maleate, a Janus Kinase inhibitor, in the dog. J Vet Pharmacol Ther 2014;37: 279–85.
55. Gonzales AJ, Bowman JW, Fici GJ, et al. Oclacitinib (APOQUEL®) is a novel Janus Kinase inhibitor with activity against cytokines involved in allergy. J Vet Pharmacol Ther 2014;37:317–24.
56. Gonzales AJ, Fleck TJ, Humphrey WR, et al. IL-31-induced pruritus in dogs: a novel experimental model to evaluate anti-pruritic effects of canine therapeutics. Vet Dermatol 2016;27:34-e10.
57. Cosgrove SB, Wren JA, Cleaver DM, et al. Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis. Vet Dermatol 2013;24:479-e114.
58. Cosgrove SB, Wren JA, Cleaver DM, et al. A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel®) in client-owned dogs with atopic dermatitis. Vet Dermatol 2013;24: 587-e142.
59. Cosgrove SB, Cleaver DM, King VL, et al. 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.
60. Gadeyne C, Little P, King VL, et al. Efficacy of oclacitinib (Apoquel®) compared with prednisolone for the control of pruritus and clinical signs associated with

allergic dermatitis in client-owned dogs in Australia. Vet Dermatol 2014;25:512-e86.
61. Little PR, King VL, Davis KR, et al. A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs. Vet Dermatol 2015;26:23-e8.
62. 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.
63. Peterson AL, Torres SM, Rendahl A, et al. Frequency of urinary tract infection in dogs with inflammatory skin disorders treated with ciclosporin alone or in combination with glucocorticoid therapy: a retrospective study. Vet Dermatol 2012;23:201-e43.
64. Torres SM, Diaz SF, Nogueira SA, et al. Frequency of urinary tract infection among dogs with pruritic disorders receiving long-term glucocorticoid treatment. J Am Vet Med Assoc 2005;227:239–43.
65. Simpson AC, Schissler JR, Rosychuk RAW, et al. The frequency of urinary tract infection and subclinical bacteriuria in dogs with allergic dermatitis treated with oclacitinib: a prospective study. Vet Dermatol 2017;28:485-e113.
66. Gonzales AJ, Humphrey WR, Messamore JE, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. Vet Dermatol 2013;24:48-e12.
67. Marsella R, Ahrens K, Sanford R. Investigation of the correlation of serum IL-31 with severity of dermatitis in an experimental model of canine atopic dermatitis using beagle dogs. Vet Dermatol 2018;29:69-e28.
68. Messamore JE. An ultrasensitive single molecule array (Simoa) for the detection of IL-31 in canine serum shows differential levels in dogs affected with atopic dermatitis compared to healthy animals. Vet Dermatol 2017;28:546.
69. Michels GM, Ramsey DS, Walsh KF, et al. A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client owned dogs with atopic dermatitis. Vet Dermatol 2016;27:478-e129.
70. Moyaert H, Van Brussel L, Borowski S, et al. A clinical field trial evaluating the long-term efficacy and safety of lokivetmab in client owned dogs with atopic dermatitis. Vet Dermatol 2017;28:547.
71. 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;28:593-e145.
72. Nuttall T, Reece D, Roberts E. Life-long diseases need life-long treatment: long-term safety of ciclosporin in canine atopic dermatitis. Vet Rec 2014;174(S2):3–12.
73. Forsythe P, Paterson S. Ciclosporin 10 years on: indications and efficacy. Vet Rec 2014;174(S2):13–21.
74. Archer TM, Boothe DM, Langston VC, et al. Oral cyclosporine treatment in dogs: a review of the literature. J Vet Intern Med 2014;28:1–20.
75. DeBoer DJ. Ciclosporin in canine dermatology: a decade of comfort. Vet Rec 2014;174(S2):1–2.
76. Palmeiro BS. Cyclosporine in veterinary dermatology. Vet Clin North Am Small Anim Pract 2013;43:153–71.
77. Kovalik M, Thoday KL, van den Broek AH. The use of ciclosporin A in veterinary dermatology. Vet J 2012;193:317–25.

78. Zając M, Szczepanik M, Wilkołek P, et al. The influence of non-specific anti-pruritus treatment with cyclosporine A on transepidermal water loss (TEWL) in natural atopic dermatitis in dogs. Pol J Vet Sci 2015;18:415–24.
79. White AG, Santoro D, Ahrens K, et al. Single blinded, randomized, placebo-controlled study on the effects of ciclosporin on cutaneous barrier function and immunological response in atopic beagles. Vet Immunol Immunopathol 2018; 197:93–101.
80. Widmer G, Ferrer L, Favrot C, et al. Glucocorticoids and cyclosporin do not significantly impact canine cutaneous microbiota. BMC Vet Res 2018;14:51.
81. Beccati M, Martini V, Comazzi S, et al. Lymphocyte subpopulations and Treg cells in dogs with atopic dermatitis receiving ciclosporin therapy: a prospective study. Vet Dermatol 2016;27:17-e5.
82. Marsella R. Evaluation of *Lactobacillus rhamnosus* strain GG for the prevention of atopic dermatitis in dogs. Am J Vet Res 2009;70:735–40.
83. Marsella R, Santoro D, Ahrens K. Early exposure to probiotics in a canine model of atopic dermatitis has long-term clinical and immunological effects. Vet Immunol Immunopathol 2012;146:185–9.
84. Marsella R, Santoro D, Ahrens K, et al. Investigation of the effect of probiotic exposure on filaggrin expression in an experimental model of canine atopic dermatitis. Vet Dermatol 2013;24:260-e57.
85. Ohshima-Terada Y, Higuchi Y, Kumagai T, et al. Complementary effect of oral administration of *Lactobacillus paracasei* K71 on canine atopic dermatitis. Vet Dermatol 2015;26:350-e75.
86. Kim H, Rather IA, Kim H, et al. A double-blind, placebo controlled-trial of a probiotic strain *Lactobacillus sakei* Probio-65 for the prevention of canine atopic dermatitis. J Microbiol Biotechnol 2015;25:1966–9.
87. Plevnik Kapun A, Salobir J, Levart A, et al. Vitamin E supplementation in canine atopic dermatitis: improvement of clinical signs and effects on oxidative stress markers. Vet Rec 2014;175:560.
88. Klinger CJ, Hobi S, Johansen C, et al. Vitamin D shows in vivo efficacy in a placebo-controlled, double-blinded, randomized clinical trial on canine atopic dermatitis. Vet Rec 2018;182:406.
89. Bravo-Monsalvo A, Vázquez-Chagoyán JC, Gutiérrez L, et al. Clinical efficacy of neural therapy for the treatment of atopic dermatitis in dogs. Acta Vet Hung 2008; 56:459–69.
90. Ohmori K, Tanaka A, Makita Y, et al. Pilot evaluation of the efficacy of shampoo treatment with ultrapure soft water for canine pruritus. Vet Dermatol 2010;21: 477–83.
91. Singh SK, Dimri U, Saxena SK, et al. Therapeutic management of canine atopic dermatitis by combination of pentoxifylline and PUFAs. J Vet Pharmacol Ther 2010;33:495–8.
92. Noli C, Della Valle MF, Miolo A, et al. Efficacy of ultra-micronized palmitoylethanolamide in canine atopic dermatitis: an open-label multi-centre study. Vet Dermatol 2015;26:432–40, e101.
93. Hill PB, Hoare J, Lau-Gillard P, et al. Pilot study of the effect of individualised homeopathy on the pruritus associated with atopic dermatitis in dogs. Vet Rec 2009;164:364–70.
94. Stich AN, Rosenkrantz WS, Griffin CE. Clinical efficacy of low-level laser therapy on localized canine atopic dermatitis severity score and localized pruritic visual analog score in pedal pruritus due to canine atopic dermatitis. Vet Dermatol 2014;25:464-e74.

95. Fujimura M, Ishimaru H, Nakatsuji Y. Fluoxetine (SSRI) treatment of canine atopic dermatitis: a randomized, double-blind, placebo-controlled, crossover trial. Pol J Vet Sci 2014;17:371–3.
96. Fabbrocini G, Napolitano M, Megna M, et al. Treatment of atopic dermatitis with biologic drugs. Dermatol Ther (Heidelb) 2018. [Epub ahead of print].
97. Fettelschoss-Gabriel A, Fettelschoss V, Thoms F, et al. Treating insect-bite hypersensitivity in horses with active vaccination against IL-5. J Allergy Clin Immunol 2018. [Epub ahead of print].
98. Ricklin Gutzwiller ME, Reist M, Peel JE, et al. Intradermal injection of heat-killed Mycobacterium vaccae in dogs with atopic dermatitis: a multicentre pilot study. Vet Dermatol 2007;18:87–93.
99. Marro A, Pirles M, Schiaffino L, et al. Successful immunotherapy of canine flea allergy with injected Actinomycetales preparations. Immunotherapy 2011;3:971–8.