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Alternative clinical approaches to the treatment of pruritus related with canine atopic dermatitis

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ABSTRACT

Canine atopic dermatitis (CAD) is a genetically inheritable, inflammatory and pruritic skin disease with characteristic clinical features, most commonly associated with immunoglobulin E (IgE) antibodies to environmental allergens. Itching is the most prominent clinical finding. Depending on the allergens involved, seasonal or non-seasonal pruritus may occur. In the first active phase of pruritus treatment, which consists of two stages, acute exacerbations should be controlled by drugs with active ingredients such as corticosteroids, oclacitinib, lokivetmab, etc. In the proactive pruritus treatment, it is aimed to prevent exacerbations and prolong the pruritus-free period with maintenance treatment. For this purpose, in addition to active phase of the therapy, different treatment options such as cyclosporine, tacrolimus, antihistamines, essential fatty acids, Palmitoylethanolamide (PEA), topical drugs and shampoos can be used to repair the skin barrier. Due to the side effects and costs of the drugs used in the treatment of pruritus in atopic dermatitis, researches on alternative treatment methods are still continuing. Applications such as mesenchymal stem cell therapy, recombinant canine gamma-interferon, luteolin, vitamin D, vitamin E, lactoferricin/verbascoside, mastinib, cannabidiol (CBD), probiotics and vaccination against interleukin-31 (IL-31) are the alternative treatment options for atopic dermatitis in dogs. However, more studies are needed before their inclusion in our routine clinical practices and added to the guidelines. In this review, it is aimed to provide information about new treatments used for pruritus in CAD and to encourage their use in routine veterinary clinical practice.

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Introduction

Canine atopic dermatitis (CAD) is a genetically inheritable, inflammatory and pruritic skin disease with characteristic clinical features, most commonly associated with IgE antibodies to environmental allergens (Noli et al., 2014). Itching is the most prominent clinical finding associated with this disease. Depending on the allergens involved, seasonal or non-seasonal pruritus may occur. The face, pinna, abdomen, inguinal region, perineal area and distal extremities are the most affected areas in CAD (Hensel et al., 2015). The treatment of atopic dermatitis in dogs varies depending on the clinical findings of the patient and should be planned individually. In general, treatment principles for CAD include: reduction of

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itching and inflammation with symptomatic treatments, allergen-specific immunotherapy, treatment and prevention of secondary bacterial and yeast infections, improvement of skin barrier function, and identification and prevention of exacerbation factors, including environmental allergens (Gortel, 2018). This review focuses on treatments aimed at reducing itching and inflammation with symptom-relieving treatments.

The main therapeutic goal when treating CAD is to stop itching quickly and safely to minimize skin damage and improve the patient's quality of life (Cosgrove et al., 2015). In the first active phase of pruritus treatment, which consists of two stages, acute exacerbations should be controlled by using drugs with active ingredients such as corticosteroids, oclacitinib, lokivetmab. In the proactive phase of pruritus treatment, it is aimed to prevent exacerbations and prolong the pruritus-free period with maintenance treatment (Olivry et al., 2015). In this review, routinely drugs used for the treatment of CAD and alternative treatment methods that can be applied in cases where there is no response to conventional treatment are included. In addition, it is aimed to provide information about new treatments used for pruritus in CAD and to encourage their use in routine veterinary clinical practice.

Drugs Routinely Used for The Treatment of Pruritus in CAD

Corticosteroids:

Systemic Corticosteroids: Systemic glucocorticoid therapy in CAD reduces the number of inflammatory cells. In addition, glucocorticoid therapy also reduces the production of inflammatory mediators that effectively control both acute and chronic cutaneous inflammation and itching (Saridomichelakis and Olivry, 2016). One of the main ways glucocorticoids affect inflammatory responses is through the effect on cytokine production. Generally, glucocorticoids suppress the production of cytokines, particularly interferon-gamma, IL-2, IL-3, IL-4, IL-5, IL-6 and IL-13 (Olivry et al., 2001).

Oral prednisolone, prednisone or methylprednisolone at 0.5-1.0 mg/kg/day divided into one or two dosages provides improvement of clinical manifestations in dogs with severe or diffuse atopic dermatitis (AD) (Olivry et al., 2015). Systemic glucocorticoid therapy is known to have side effects such as susceptibility to infection, immunosuppression, decreased urinary osmolality and increased risk of urinary tract infection. These side effects are directly proportional to the dosage and duration of administration of the drug (Olivry et al., 2015; Elkholly et al., 2020).

Long-acting injectable glucocorticoids (dexamethasone and methylprednisolone acetate) are not recommended in dogs with atopic dermatitis due to risks such as hepatopathy and hyperadrenocorticism (Olivry et al., 2001; Elkholly et al., 2020).

Topical corticosteroids: Topical glucocorticoids are useful for short-term use, particularly in localized skin lesions. However, the long-term application of these products can cause steroid-induced skin atrophy (Olivry et al., 2015). Hydrocortisone aceponate (HCA) spray, which is a topical corticosteroid, contributes to the repair of the skin barrier by showing antipruritic and anti-inflammatory properties, and has fewer side effects when compared to other topical corticosteroids (Nam et al., 2012). In a randomized, double-blind, placebo-controlled study evaluating the efficacy of 0.0584% HCA, it was administered to dogs with atopic dermatitis once daily for 28 days, as two sprays from 10 cm distance to treat an area of 100 cm. According to the improvement, two applications per week were continued for 42 days. As a result of this study, a significant decrease in canine atopic dermatitis extent and severity index (CADESI) and pruritus visual analog scale (PVAS) scores in the HCA group were compared to placebo (Nuttall et al., 2009). As a result of a study comparing the efficacy of 0.0584% HCA spray and oral cyclosporine (5 mg/kg), no significant difference was found in the efficacy, tolerance, and ease of administration scores of the drugs (Nuttall et al., 2012). As a result of a study about CAD, dogs were administered HCA spray for 260 days, no side effects were seen. Therefore, it has been shown to be effective and well tolerated in the proactive treatment of CAD (Lourenço et al., 2016).

Another topical glucocorticoid, 0.015% triamcinolone spray, is also known to be well tolerated and effective in the treatment of atopic dermatitis in dogs for 28 days (Olivry et al., 2001; DeBoer et al., 2002). In addition, it has been shown that the application of another topical glucocorticoid, 0.025% budesonide cream, once a week for 3 times at 1 g/kg, is an effective treatment for the control of clinical manifestations of AD in dogs (Ahlstrom et al., 2010).

Oclacitinib: Oclacitinib is a janus kinase inhibitor that inhibits the cytokine IL-31, which causes pruritus in dogs (Denti et al., 2022). In addition to its antipruritic effect, it also shows an anti-inflammatory effect by inhibiting pro-inflammatory and pro-allergic cytokines such as IL-2, IL-4, IL-6 and IL-13 (Cosgrove et al., 2013). In active treatment, 0.4-0.6 mg/kg orally twice a day is prescribed for 14 days to reduce skin lesions and itching (De Caro Martins et al., 2022; Denti et al., 2022). In proactive treatment, it has been found that it can be used for up to 630 days with once a day

application following active treatment is safe and improves the quality of life of dogs (Cosgrove et al., 2015). The efficacy of oclacitinib treatment is limited when severe inflammation, lichenification, otitis, and pododermatitis are present. In addition, oclacitinib is contraindicated in the presence of neoplasia or severe infection and in dogs younger than 1 years old (Gortel, 2018).

Although it has not been licensed in cats yet, it has been found to be effective and safe in cats with feline atopy syndrome, using a dosage of approximately 1 mg/kg q12h. However, more studies are needed whether oclacitinib is a suitable alternative for the treatment of pruritus in feline atopy syndrome (Lopes et al., 2019; Noli et al., 2019; Mueller et al., 2021).

Lokivetmab: Lokivetmab is a canine-specific monoclonal antibody (mAb) that selectively binds to and neutralizes IL-31 (Souza et al., 2018). Since it binds only to IL-31 and does not affect other cytokines, its spectrum of action is more limited than oclacitinib (Gortel, 2018). Lokivetmab is administered at a dosage of 2.0 mg/kg by subcutaneous injection to dogs with atopic dermatitis and its efficacy is expected to last at least one month. The advantages of this drug compared to other antipruritic agents are its rapid onset of action, less frequent dosing, no age restriction, and compatibility with other drugs (Souza et al., 2018). Its spectrum of action is limited which could be a disadvantage (Gortel, 2018).

In a placebo-controlled study in which the safety of lokivetmab was investigated, side effects such as vomiting, diarrhea and anorexia were observed in both groups, but these effects were reported as temporary and disappeared with supportive treatment (Michels et al., 2016).

In another study evaluating its safety, no abnormal health findings associated with lokivetmab were observed as a result of its use for 6 months (Moyaert et al., 2017). In a study comparing lokivetmab and oclacitinib, no significant difference was found between their antipruritic effects (Lee et al., 2021).

Essential Fatty Acids

It is known that essential fatty acids, especially omega-6 (gammalinolenic acid, GLA) and omega-3 (eicosapentaenoic acid, EPA-docosahexaenoic acid, DHA) have anti-inflammatory effects and immunomodulatory properties on the skin (Abba et al., 2005).

Oral administration of essential fatty acids as supplements or enriched diets has been found to be beneficial in reducing the clinical manifestations of CAD. In addition, essential fatty acids are known to affect superficial skin lipids, improving coat shine and quality (Marchegiani et al., 2020). However, they are not effective for acute flares as they must be used for at least two months to be effective. Topical lipid formulations act by helping to heal stratum corneum lipid barrier damage in dogs with AD (Olivry et al., 2015).

Palmitoylethanolamide (PEA): PEA is a naturally occurring bioactive lipid compound which is produced on demand in response to stress and tissue damage. It has also an important role in the regulation of cutaneous inflammation and immunity (Noli et al., 2015). It is thought that PEA may be a promising treatment in dogs with atopic dermatitis, as it improves their quality of life by reducing skin lesions and itching scores (Marchegiani et al., 2020; Noli et al., 2015).

In an 8-week, open-label, multicenter study evaluating the efficacy and safety of PEA, oral administration of PEA at a dosage of 10 mg/kg in CAD was shown to significantly reduce itching and skin lesions in approximately 80% of dogs (Noli et al., 2015).

Shampoos: In dogs with atopic dermatitis, non-irritating shampoos containing agents such as chlorhexidine, lactoferrin, piroctone olamine, chitosan and essential fatty acids can be a part of the treatment (Schilling et al., 2012; Olivry et al., 2015). Their advantages are soothing effects on the skin, increasing skin moisture, and physically removing surface allergens and microorganisms (Olivry et al., 2015). A study was conducted to evaluate the effectiveness of a shampoo containing piroctone olamine and lipid complexes. In this study, dogs were bathed with this shampoo once in 3 days for 3 weeks, and as a result of the study, a decrease in pruritus and lesion indexes was detected in almost half of the dogs (Reme et al., 2004).

The type of shampoo should be tailored to each situation: emollient shampoos are the ones with the highest soothing effect, but anti-seborrheic and antiseptic shampoos are preferred in case of oiliness, crusting and infection on the skin (Olivry et al.,2010).

Antihistamines: Antihistamines act as reverse agonists on histamine receptors, stabilizing the negative structure of the receptor and exerting an effect by stopping signal transduction (Eichenseer et al., 2013). Although type I antihistamines have relatively good safety, their effectiveness in canine AD is limited. Due to its mechanism of action, it should be given before an acute exacerbation to block the effects of histamine (Saridomichelakis and Olivry, 2016). Cetirizine, dimetinden, fexofenadine, hydroxyzine, clemastine, oxatomid, trimeprazine, diphenhydramine, chlorpheniramine and hydroxyzine-chlorpheniramine maleate combinations are the antihistamines that can

be prescribed to dogs with AD (Olivry and Mueller, 2003). Instead of injections; syrup and tablet forms are usually used in CAD.

Although their efficacy is limited, type I antihistamines can be used in dogs with mild atopic dermatitis because of their sedative effects (Saridomichelakis and Olivry, 2016). It can be used as part of combined therapy in the long-term management of AD to reduce the dosage of other drugs such as corticosteroids (Olivry et al., 2010).

Cyclosporine: Cyclosporine is a calcineurin inhibitor that reduces cytokine synthesis by binding to cyclophilin in the cytoplasm of lymphocytes. Compared to glucocorticoids, cyclosporine is similarly effective and has fewer side effects. However, onset of action is slower (usually 2-3 weeks) and more expensive than glucocorticoids (Saridomichelakis and Olivry, 2016). Cyclosporine is used in atopic dermatitis, especially in cases of chronic otitis externa, severe inflammation and conditions such as lichenification. In addition, it is preferred as an alternative to the long-term use of corticosteroids (Gortel, 2018).

Cyclosporine should be administered to dogs with AD at 5 mg/kg once a day. This dosage should be continued until control of clinical signs is achieved, which will usually last 4 to 6 weeks. Afterwards, the dosage or frequency of treatment required to maintain remission should be reduced and the drug should be discontinued (Olivry et al., 2015).

In dogs with atopic dermatitis, ketoconazole inhibits cyclosporine metabolism and prolongs its half-life when administered orally at a dosage of 2.5 mg/kg once daily with cyclosporine. In this way, the dosage and cost of the treatment can be reduced by approximately 50%, but the possibility of increased side effects such as hepatotoxicity should also be considered (Saridomichelakis and Olivry, 2016).

Tacrolimus: Tacrolimus is a topical calcineurin inhibitor that can be used instead of systemic immunosuppressive therapy to treat localized inflammation and pruritus (Kaya et al., 2020; Santoro et al., 2019). It has been shown to be effective as an alternative to topical glucocorticoids, particularly in dogs with localized atopic dermatitis. Although it is not suitable for the treatment of acute AD exacerbations in dogs due to its slow onset of clinical benefit, it is used in proactive therapy (Olivry et al., 2010). It has been determined that the use of tacrolimus ointment (0.1-0.3%) twice a day for 4-6 weeks is safe and especially effective in proactive treatment (Bensignor and Olivry, 2005).

In cases where the itching cannot be stopped with conventional treatment methods in dogs with atopic dermatitis, alternative treatment methods can be used.

Alternative Treatment Methods for Pruritus in CAD

Recombinant Canine Gamma-Interferon: Interferons (IFNs) are cytokines that have important roles in the immune response of animals and humans (Mueller and Hartmann, 2021). In dogs, interferons are used in the treatment of viral diseases, neoplasms, and immune-mediated disorders due to their potent antiviral, antiproliferative and immunomodulatory properties (Klotz et al., 2017).

As a result of studies evaluating the efficacy of recombinant canine interferon-gamma in dogs with atopic dermatitis, subcutaneous administration of 5,000–10,000 IU/kg three times a week for 4 weeks and then once a week for 4 weeks was found to be effective for the treatment of CAD (Olivry et al., 2015; Yasukawa et al., 2010).

A study was conducted in Japan in which dogs with atopic dermatitis were administered recombinant canine interferon-gamma (KT-100) subcutaneously at a dosage of 10,000 IU/kg three times a week for 4 weeks or a topical antihistamine (diphenhydramine) twice daily topically. The efficacy of the two drugs was compared using pruritus, excoriation, erythema and alopecia as evaluation criteria. As a result of the study, the effectiveness rates of the KT-100 group; it was found 72.1% for pruritus, 73.8% for excoriation, 75.4% for erythema and 60.7% for alopecia (Iwasaki and Hasegawa, 2006).

Studies using subcutaneous injections of recombinant feline interferon omega (rFeIFN-ω) suggest that it may have clinical efficacy for treatment in dogs with AD. Dosages of 1-4 million units per injection for 6 months have been shown to be well tolerated (Carlotti et al., 2009).

In a study comparing oral and subcutaneous use of recombinant rFeIFN-ω, oral IFN treatment was found to have higher efficacy than SC treatment. However, it is thought that the efficacy of oral IFNs as a treatment for CAD should be confirmed by larger, randomized, double-blind clinical trials (Litzlbauer et al., 2014).

Mesenchymal stem cell: Mesenchymal stem cells (MSCs) have tissue repair potential due to their self-renewal and differentiation abilities (Daltro et al., 2020). After the discovery of the immunosuppressive effect of MSCs on T cells, studies have been conducted on their use as a therapeutic agent for diseases such as CAD. In these studies, allogeneic MSC (cAd-MSC) produced from adipose tissue was administered intravenously and intramuscularly to dogs that did not

respond to conventional therapy. As a result of these studies, an improvement in the clinical signs of dogs with AD was observed, and no side effects were found in dogs (Oliveira Ramos et al., 2020; Reis et al., 2021).

In a study of 26 dogs who had suffered from CAD for at least 1 year and were not responding to conventional therapy, the dogs were administered a single dosage of 1.5×10^6 cAd-MSCs per kg intravenously (IV) and then followed for 6 months. From the 26 animals involved, 22 completed the study within six months of treatment without the need for a systemic immunosuppressant and showed a significant improvement in PVAS and CADESI-04 scoring. No systemic or local side effects were observed during this study (Villatoro et al., 2018).

In another study, 0.5×10^6 cAd-MSC per kg was administered intramuscularly (IM) in the pelvic femoral muscle region once a week for 6 weeks to 12 dogs previously diagnosed with CAD. As a result of the study, a significant reduction in pruritus scores was observed in patients, while no systemic or local adverse reactions developed (Enciso et al., 2019).

A double-blind, placebo-controlled evaluation of adipose-derived mesenchymal stem cells was conducted in the treatment of canine atopic dermatitis. In this study, dogs with atopic dermatitis were randomly assigned to placebo (PBS saline), low-dosage (5×10^5 cells/kg), and high-dosage (5×10^6 cells/kg) treatment groups. Each patient received three subcutaneous injections of MSC treatments or PBS saline at four-week intervals from five sites. At the end of the study, the PVAS and CADESI-4 scores of the high-dosage group were found to be significantly lower than the placebo group, and no serious side effects were observed in any patient. High-dosage MSC treatment has been found to be effective in alleviating clinical manifestations of CAD up to 30 days after the last subcutaneous administration of MSCs (Kaur, G., 2022). Although there is no standardization for the use of MSC in CAD yet, it can be used as an alternative treatment method in patients who do not respond to conventional treatment (Reis et al., 2021).

Mastinib: Masitinib mesylate is a potent and selective tyrosine kinase inhibitor of the cKIT receptor. It is approved for the treatment of mast cell tumors in dogs. Canine mast cells are known to produce a variety of inflammatory mediators that are partially responsible for the complex inflammatory processes associated with allergic disease and cause the development of clinical symptoms of CAD. Therefore, it is thought that molecules that can inhibit the survival or activation of mast cells can be used for the treatment of CAD (Daigle et al., 2010).

Stem cell factor, the ligand of the c-Kit receptor, is a critical growth factor for mast cells. Therefore, there is a strong link between c-Kit and the pathogenesis of CAD (Cadot et al., 2011). It was assumed that dermatological diseases such as CAD could be controlled by disrupting this link with the inhibitory effect of masitinib on c-KIT tyrosine kinase activity, and studies were conducted on this subject (Daigle et al., 2010; Cadot et al., 2011). In a pilot study with 11 dogs, mastinib was administered orally at a mean dosage of 11.0 ± 1.83 mg/kg/day for 28 days. As a result of the study, a decrease was observed in the pruritus scores and surface area of the lesions in dogs (Daigle et al., 2010).

A 12-week, prospective, multicenter, randomized, double-blind, placebo-controlled, pivotal phase 3 study was conducted to evaluate the efficacy and safety of 12.5 mg⁄kg per day macitinib in the treatment of CAD. In this study, 61% of dogs treated with masitinib and 35% of the control group ($P < 0.001$) 12. a decrease of ~50% was observed in the CADESI-02 score at week 12 ($P < 0.001$). However, serious side effects were detected in a total of 13.2% of dogs during the study. A risk of reversible protein loss from mastinib has been observed in dogs. As a result of this study, it was found that masitinib can be an effective and mostly well-tolerated treatment of CAD, including severe and resistant cases with medically manageable side effects (Cadot et al., 2011).

Luteolin: Luteolin is one of the most powerful and potent polyphenols found in vegetables, fruits and herbs. Luteolin is known to have various biological properties such as anticancer, antioxidant, neuroprotective and anti-inflammatory effects in both in vitro and in vivo models. Luteolin modulates many inflammatory processes in the skin by suppressing proinflammatory mediators and regulating various signaling pathways (Gendrisch et al., 2021). In a study investigating the effect of luteolin on IL-33, which causes itching in CAD, it was found that it significantly reduced the expression levels of IL-33, IL-1β, IL-6 and IL-8 (Gugliandolo et al., 2020).

Lactoferricin/Verbascoside: Lactoferricin is a natural antimicrobial peptide that shows a wide spectrum of activity against bacterial, fungal, viral and parasitic pathogens. Lactoferricin/Verbascoside is known to promote skin repair and improve skin inflammation due to its antioxidant, iron chelator, glutathione transferase activity inducer, antibacterial and anti-inflammatory effects (Sijbrandij et al., 2017; Belvedere et al., 2021).

In dogs, AD causes damage to the skin barrier, making the skin vulnerable to secondary infections. Therefore, local antibacterial agents are used to reduce the most relevant symptoms and limit skin infection. In a study of thirty-eight dogs with atopic dermatitis and secondary bacterial or yeast overgrowth, a lotion containing lactoferricin, verbascoside (a caffeoyl phenylethanoid glycoside) and glycerophosphoinositol lysine (derived from sunflower lecithin) was obtained and applied to lesions in dogs with atopic dermatitis. As a result of the study, clinical signs improved and no side effects were reported in any of the dogs (Biasibetti et al., 2018).

Vaccination against IL-31: In dogs, IL-31 is an important cytokine that triggers pruritus. A study showed that a virus-like particle-based developed vaccine against canine IL-31 induced a potent IgG response that essentially eliminated pruritus symptoms in dogs sensitized to house dust mites. In this study, dogs were vaccinated at a dosage of 100 µg followed by two dosages of 300 µg, and the vaccinated dogs were sensitized to house dust mites. As a result of the study, it was determined that a strong IgG response was formed in dogs, which eliminated the symptoms of itching. The vaccine is thought to be an alternative treatment option for CAD as it induces a longer-lasting antibody response compared to other treatments (Bachmann et al., 2018).

Cannabidiol : CBD is a non-psychoactive component in cannabis plants that has multiple beneficial effects on the body (Samara et al., 1988). CBD can be used in the management of pain, seizures and anxiety in dogs (Gamble et al., 2018; McGrath et al., 2019; Kogan et al., 2019).

Studies have shown that cannabinoid receptors (CB1 and CB2) are highly expressed in the skin of dogs with CAD compared to healthy dogs. It is involved in the regulation of the endogenous cannabinoid system of CBD. Therefore, CBD is expected to improve skin symptoms in dogs with atopic dermatitis. In a study of 8 dogs with atopic dermatitis, broad-spectrum cannabis oil containing 10% CBD and free of delta-9-tetrahydrocannabinol (THC) was administered orally every 12 hours at a dosage of 0.14 to 1.43 mg/kg/day for at least 8 weeks. As a result of this study, a decrease in the itching levels of the dogs has been observed (Mogi et al., 2022).

Cannabidiolic acid (CBDA) is the precursor carboxylic acid form of CBD. In a recent study, it was shown that CBDA in dogs is similar to CBD but has better absorption (Wakshlag et al., 2020). Immunomodulatory and anti-inflammatory effects of CBD/CBDA have been reported in mammals. To determine whether CBD/CBDA is an effective treatment for canine atopic dermatitis, in a study of 32 dogs, either 2 mg/kg of CBD/CBDA mixture was administered for 4 weeks. The results of the study showed that CBD/CBDA did not affect lesion severity, but had a positive effect on pruritus as adjunctive therapy in some dogs with CAD. Although side effects such as behavioral changes, loss of energy, and changes in appetite were observed in some of the dogs in the study, it was well tolerated (Loewinger et al., 2022).

Probiotics: In humans with atopic dermatitis, probiotics and prebiotics are known to modulate T helper cytokine activation, upregulate regulatory T cells and accelerate recovery of barrier function (Nole et al., 2014). Based on this, studies have been conducted in dogs with atopic dermatitis evaluating the role of probiotics for preventing the disease and their effectiveness in treatment (Marsella, 2009; Kim et al., 2015; Yamazaki et al., 2019). An experimental study of 2 adults and 16 puppies genetically predisposed to atopic dermatitis evaluated the efficacy of Lactobacillus rhamnosus GG strain for alleviating or preventing clinical manifestations. As a result of this study, it was determined that the administration of L. rhamnosus GG to puppies reduced the immunological indicators of AD but did not provide a significant reduction in clinical signs (Marsella, 2009). Another study with 42 experimental dogs with atopic dermatitis found that administration of the L.sakei probio-65 strain for 2 months significantly reduced the disease severity index compared to the placebo group (Kim et al., 2015). A study was conducted to evaluate the effect of Enterococcus faecium SF68 in reducing the dosage of oclacitinib as adjunctive therapy for dogs with atopic dermatitis responsive to oclacitinib. In this placebo-controlled study of 21 dogs, the SF68 group was administered at a dosage of 1× 108 colony forming units/g orally twice daily for 12 weeks. After 8 weeks of supplementation the dosage of oclacitinib was reduced by approximately 25%. As a result of the study, no significant difference was observed in dogs that received SF68 supplementation compared to placebo (Yamazaki et al., 2019). In a study conducted with dogs with mild or moderate atopic dermatitis, the efficacy of cetirizine and L. paracasei K71 in addition to AD treatment was compared. As a result of this 12-week study, CADES and pruritus scores in the K71 group were slightly lower than in the control group, and the reduction in drug scores in the K71 group was significantly lower ($P < 0.05$) compared to the control group (Ohshima Terada et al., 2015).

These studies suggest that the administration of probiotics may be beneficial in preventing or reducing the clinical manifestations of AD in dogs. However, larger studies are needed to standardize probiotic use in CAD.

Psychogenic therapy: Psychogenic factors may also contribute to the clinical manifestations of AD in some dogs. Anxiolytic agents such as tricyclic antidepressants and specific serotonin reuptake inhibitors and N-methyl-D-aspartate can be used in such patients (Saridomichelakis and Olivry, 2016). Tricyclic antidepressants act as both serotonin and norepinephrine inhibitors. They also have antihistamine and anticholinergic effects and are a1-adrenergic antagonists (Crowell Davis and Murray, 2006). Doxepin (1-2 mg/kg, orally twice a day) and amitriptyline (1-2 mg/kg, orally twice a day) can be used in dogs with atopic dermatitis (Saridomichelakis and Olivry, 2016). However, their efficacy is limited and variable (Olivry and Mueller, 2003).

In a randomized, double-blind, placebo-controlled study evaluating the efficacy of fluoxetine (1mg/kg), one of the selective serotonin reuptake inhibitors, no statistically significant difference in CADESI-03 and PVAS scores was observed between fluoxetine and placebo (Fujimura et al., 2014). Dextromethorphan is an N-methyl-D-aspartate receptor antagonist with some non-specific serotonin reuptake inhibition properties. In a study of 12 dogs with allergic dermatitis, 2 mg/kg orally administered twice daily resulted in a mild to moderate improvement in clinical signs (Dodman et al.,2004).

Vitamins: The effect of vitamin D in canine atopic dermatitis was evaluated in a placebo-controlled, double-blind, randomized clinical trial. As a result of this study, oral vitamin D reduced both itching and acute and chronic skin lesions in dogs with AD. The reduction in pruritus scores was significantly associated with an increase in serum 25-hydroxycholecalciferol levels (Klinger et al., 2018; Kotnik, 2018).

As a result of a study investigating the effects of vitamin E supplementation on clinical manifestations improvement and oxidative stress markers in canine atopic dermatitis, it was shown that vitamin E supplementation was highly effective in reducing clinical manifestations in moderate AD cases after 8 weeks of treatment (Plevnik Kapun et al., 2014).

Additional treatments: Pentoxifylline is a phosphodiesterase inhibitor that down-regulates activation of inflammatory cells and TNF-α production (Saridomichelakis and Olivry, 2016). Its effectiveness is moderate, but it appears to be relatively safe. Although it has not yet been officially approved in dogs with atopic dermatitis, it is used at 10-20 mg/kg two or three times daily to reduce glucocorticoid use (Singh et al., 2010; Saridomichelakis and Olivry, 2016).

Misoprostol is a synthetic prostaglandin E1 analog that reduces the production of IL-1, tumor necrosis factor -a and leukotriene B4 (Saridomichelakis and Olivry, 2016). A randomized controlled trial of misoprostol monotherapy for canine atopic dermatitis found that the use of 3-6 µg/kg three times daily for 3 weeks resulted in a moderate reduction in pruritus scores (Olivry et al., 2003b). Some drugs such as leukotriene inhibitors, dextromethorphan, and capsaicin are not recommended for use in the treatment of CAD, as some evidence has been confirmed that they have no or very low efficacy (Olivry et al., 2010; Olivry et al., 2010b).

In a study to evaluate the clinical efficacy of neural therapy (NT), procaine was used intravenously and intradermally (in the affected areas). As a result of this study, a significant reduction in clinical signs and pruritus score was observed (Bravo-Monsalvo et al., 2008). The purpose of using topical neuromodulators in atopic dermatitis is to control the itch by overriding the itch sensation with another. Examples of these drugs include menthol, capsaicin, and pramoxine (Paterson, 2019). The mode of action of such treatments is not always clear, but it is thought that they can normalize the defective epidermal barrier, remove allergens and irritants from the skin surface, and reduce inflammation and itching (Saridomichelakis and Olivry, 2016).

A study was conducted to evaluate the effectiveness of shampoo treatment with ultrapure soft water. In this study, dogs with moderate atopic dermatitis were divided into two groups, and both groups were bathed with the same shampoo, while ultrapure soft water was used in one group and tap water in the other group. As a result of the study, a significant decrease was found in the clinical symptoms and itching scores in the pure water group compared to the control group (Ohmori et al., 2010).

A double-blind, randomized, controlled, cross-over evaluation of zinc methionine supplementation as an adjunctive treatment for canine atopic dermatitis found that zinc supplementation reduced clinical signs and pruritus scores, especially in dogs using glucocorticoids (McFadden et al., 2017).

Conclusion

Canine atopic dermatitis is a disease that reduces patients' quality of life and is difficult to control. Due to the side effects and costs of the drugs used in the treatment of pruritus in CAD, researches on alternative treatment methods are still continuing. Different treatment techniques such as mesenchymal stem cell therapy, recombinant canine gamma-interferon, luteolin, vitamin D, vitamin E, lactoferricin/ verbascoside, mastinib, CBD, probiotics and vaccination against IL-31 can be among alternative methods in the treatment of atopic dermatitis in dogs. More scientific studies are still needed for these protocols to be included in our routine practices and added to the definite guidelines. Treatment responses may vary due to individual differences. However, based on up-to-date information, we believe that these methods can be beneficial, especially in patients who do not respond to conventional treatment.

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