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CANINE ATOPIC DERMATITIS: OLD AND NEW THERAPIES

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INTRODUCTION

The pathophysiology and clinical signs of canine atopic dermatitis were discussed in another manuscript. In addition, the principles of diagnosing canine atopy were covered. There are numerous therapies for canine atopy. Some of these are non-specific, symptomatic treatments, such as antihistamines and corticosteroids. Allergen-specific immunotherapy is a long term therapy that directly addresses the patient's hypersensitivities. In this manuscript, we will not only discuss older therapies, we'll discuss the latest developments in the treatment of canine atopy.

SECONDARY INFECTIONS

Managing secondary infections is a critical part of treating any atopic dog. For dogs with superficial pyoderma, 3 weeks of an appropriate antibiotic is recommended. If deep pyoderma is present 4-8 weeks or longer may be necessary. A good antibacterial shampoo should also be recommended to assist in resolution of the infection. If *Malassezia* dermatitis is present, topical therapy alone, or in conjunction with systemic antifungal therapy should be utilized.

A significant reduction in pruritus will usually be seen when secondary infections are resolved. In addition, both steroidal and nonsteroidal antipruritic therapies will be more effective if the patient is free of secondary infections.

TOPICAL ANTIPRURITIC THERAPY

Don't forget the beneficial effects of water. Cool water baths decrease pruritus by soothing the skin and washing away inflammatory mediators and potential allergens.

Colloidal oatmeal is a safe and relatively effective antipruritic, although the exact mechanism of this effect is poorly understood. Veterinary oatmeal-based products are available as shampoos, conditioners, and bath treatments. These products are extremely safe, but tend to provide short-term relief (24-48 hours) of mild pruritus. Oatmeal has no antibacterial or antifungal properties.

Many oatmeal-based products are available with additional ingredients in attempts to potentiate the antipruritic effect. Some veterinary products have combined colloidal oatmeal with diphenhydramine, and one product is formulated as a "leave-on" conditioner to provide a residual effect. It is unclear whether topical antihistamines work directly on the skin, or via absorption into the systemic circulation.

Topical anesthetics are also available, and may have temporary antipruritic effects. Pramoxine has been the topical anesthetic of choice in veterinary medicine. Other products, such as lidocaine and benzocaine may cause cutaneous sensitivity or toxic effects (methemoglobinemia). Pramoxine is usually combined in shampoo or rinses with colloidal oatmeal. It is also available as a spray and a leave-on conditioner.

Colloidal-oatmeal products, with or without additional ingredients, are most useful for mild pruritus. They are safe for chronic use in most patients. When secondary infections are present, they should be resolved with systemic or topical antimicrobial therapy. Patients that are free of these infections will be most responsive to the colloidal-oatmeal topicals.

Lime sulfur (LymDyp®, DVM Pharmaceuticals) is a very effective, nonsteroidal antipruritic. Because it is applied as a rinse and allowed to dry on the animal, it provides residual effect. Lime sulfur is safe for use in both dogs and cats. However, I recommend that cats have an E-collar applied until dry, as there are anecdotal reports of GI upset and pharyngitis following ingestion of the dip. I often recommend the use of lime sulfur dips while animals are being withdrawn from antihistamines and corticosteroids for allergy testing.

In addition to its antipruritic effects, lime sulfur is antiparasitic and antifungal.

A recently introduced product may be an effective antipruritic by combining novel ingredients**. Allermyl® (Virbac)** contains linoleic acid and a monosaccharide,

L-rhamnose in a microemulsion. Topical application of linoleic acid has previously been shown to improve cutaneous barrier function in the dog. Barrier function is a protective mechanism of the skin, and may be defective in dogs with atopic dermatitis. *In vitro*, L-rhamnose has been shown to decrease inflammatory mediators that may be involved in the pathogenesis of atopic dermatitis. In addition to the shampoo, Allermyl lotion has recently been introduced. This product can be sprayed onto localized areas of pruritus between baths.

Topical corticosteroids are very effective antipruritic drugs, and are commonly used in treatment of pruritus in humans. Until recently, most veterinary topical steroid products came as ointments, creams, or powders for localized use. Generalized use of these products in our veterinary patients has been limited by the hair coat and concern over ingestion of the product. In recent years, products that lend themselves to generalized use have become available.

Two corticosteroid-containing shampoo products are available. CortiSoothe® (Virbac) is a 1-% hydrocortisone containing shampoo with a colloidal oatmeal base. Capex® shampoo (formerly known as F/S Shampoo) contains 0.01% fluocinolone acetonide, a fluorinated corticosteroid. While topical application of fluorinated corticosteroids can be associated with systemic absorption, use of this product twice weekly did not result in systemic evidence of absorption or adrenal suppression. There is minimal residual activity noted with use of corticosteroid shampoos.

A 1-% hydrocortisone, **leave-on conditioner** is also available (ResiCort®, Virbac). This product may be applied to the entire body and allowed to dry. The base of the product is non-irritating, and is not intended to be rinsed off. When this product was applied to normal and allergic dogs twice weekly for 6 weeks, mean values for hematological, biochemical and adrenal response to exogenous ACTH remained within normal limits. In one dog with inflamed skin, a lack of response to exogenous ACTH was detected at the end of the study, suggesting that absorption of the product was increased through inflamed skin. For that reason, even use of 1%-hydrocortisone should be done cautiously in small dogs with generalized erythema and pruritus.

Fluorinated corticosteroid products are also available as ointments, creams, and sprays. While these products are effective antipruritics, they are only intended for short-term, localized use. Numerous studies have demonstrated that application of fluorinated corticosteroids to the skin, ears, and

eyes can result in systemic absorption and suppression of the adrenal axis. In addition to systemic effects, localized cutaneous atrophy, alopecia, comedone formation, and pyoderma may occur. Subepidermal bullous dermatosis has also been associated with topical application of some fluorinated corticosteroids.

Genesis Topical Spray® (Virbac) has recently been introduced to veterinary medicine. This is a 0.015% triamcinolone spray, approved by the FDA for generalized use in the pruritic dog. In a blinded, placebo-controlled study of 103 dogs with pruritus of various causes, 67% showed significant reductions in erythema, pruritus, and eruption over 28 days. In that study, hematological and biochemical results of treated dogs did not change significantly over the course of treatment. In a separate study, the product was demonstrated to be effective for symptomatic treatment of flea allergy dermatitis in the dog. This product is intended for generalized use over short periods of time (28 days or less) as an alternative to oral or injectable corticosteroids.

ANTIHISTAMINES AND TRICYCLIC ANTIDEPRESSANTS

Histamine is a potent inflammatory mediator, and may be a major mediator of pruritus in the dog. For that reason, antihistamines have been advocated for antipruritic therapy. The first generation antihistamines are H1 receptor blockers. In this manner, they antagonize the physiologic effects of histamine following its release. Some, such as hydroxyzine, also inhibit mast cell degranulation. Because the first generation antihistamines readily cross the blood-brain barrier (BBB), they may lead to increased sedation. The second-generation antihistamines are also H1 receptor antagonists. They are less lipid soluble, and therefore do not readily cross the BBB.

Several studies have evaluated the efficacy of systemic antihistamines in the dog. Significant improvement has been seen in 0% to 30% of patients in these studies. The first-generation antihistamines diphenhydramine, hydroxyzine, chlorpheniramine, and clemastine have been shown to be relatively effective in non-blinded, uncontrolled studies. Second-generation antihistamines, such as loratidine are less sedating, but also appear to be minimally effective in the dog. In addition, the second-generation antihistamines are very expensive. Trimeprazine was shown to be ineffective alone, but has been demonstrated to significantly decrease the dose of prednisone (by about 30%) necessary to control pruritus.

Because antihistamines are metabolized by the liver, they should be used with caution in the presence of hepatic disease. Due to their anticholinergic properties, they should be used cautiously in patients with glaucoma, gastrointestinal atony or urinary retention problems.

The tricyclic antidepressant (TCA) drugs, amitriptyline, and doxepin have also been recommended in the dog for control of pruritus. Both these drugs have potent antihistamine effects. In one study, doxepin did not provide relief for any of 30 dogs. Amitriptyline has been shown to be effective in approximately 30% of dogs. In my practice, sedation is the most commonly reported side effect. I usually start patients on half of the therapeutic dose for the first 1-2 weeks in order to acclimate to the drug. After 1-2 weeks, most dogs will tolerate the full dose without significant sedation. Other, rarely reported side effects of TCA's include dry mouth, hypersalivation, vomiting, cardiac arrhythmias, sedation, and urinary retention. Use of TCA's is contraindicated in dogs with cardiac problems or hepatic disease. Use is also contraindicated with other monoamine oxidase inhibitors like amitraz.

From an efficacy standpoint, it is important to note that there is tremendous variation in individual response to antihistamines. Therefore, it is often necessary to try several different products before finding the one that works best in each patient. In order to appropriately evaluate the efficacy of antihistamines, secondary infections should be resolved. In addition, the combination of antihistamines with essential fatty acid supplements (Table 1) may be synergistic.

ESSENTIAL FATTY ACIDS

Fatty acid supplements have been reported to be beneficial in management of pruritus in dogs and cats. There are numerous veterinary and over-the-counter products available. Very few products have been critically evaluated in good, scientific studies.

The way in which EFA's work is complicated, and a lecture unto itself. Simply put, however, the EFA's are incorporated into the epithelial cell membrane, and compete with arachidonic acid for utilization of lipoxygenase and cyclo-oxygenase pathways. This results in the production of less inflammatory mediators within the skin.

Several studies have evaluated the efficacy of DVM DermCaps®. Depending on the study, significant improvement was seen in 11% to 27% of dogs. Additionally, a double-blinded, placebo-controlled study using high doses of marine fish oils (180 mg EPA and 120 mg DHA per 10 # body weight) has been published. In this study, treated dogs had significantly less pruritus and alopecia, and significantly better hair coat quality than placebo-treated dogs.

Some diets have been fortified with essential fatty acids. These include Eukanuba Response Formula (FP) and Science Diet Sensitive Skin. Since these diets have such high levels of fatty acids, additional supplementation is unnecessary. Essential fatty acids must be incorporated into the cell membrane before they can effect a change in the inflammatory cascade, so it may take up to eight weeks before improvement is noted.

Side effects due to fatty acid supplements are rare, but may include pancreatitis, weight gain, diarrhea, flatulence, and fish-breath. In addition, high doses of fatty acids may affect platelet aggregation, so use in dogs with known coagulation problems is contraindicated.

Table 1. Antihistamines in the dog

Drug	Dosage
Diphenhydramine (Benadryl)	2.2 mg/kg q 8 hrs.
Hydroxyzine HCl (Atarax) or pamoate	2.2 mg/kg q 8 hrs.
Chlorpheniramine (Chlor-Trimeton)	0.2-0.8 mg/kg q 8 hrs.
Clemastine fumarate (Tavist)	0.05-0.1 mg/kg q 12 hrs
Loratidine (Clariton)	10 mg/dog q 24 hrs
Cetirizine (Zyrtec)	5-10 mg / dog q 24 hrs
Amitriptyline (Elavil)	1-2 mg/kg q 12 hrs.
Doxepin (Sinequan)	1-2 mg/kg q 12 hrs.

MISOPROSTEL

Prostaglandin E_1 (PGE_1) has been shown to inhibit the late-phase reaction (LPR), but not the immediate reaction to intradermally injected allergens in atopic people. This inhibition is the result of decreased eosinophil chemotaxis and survival. In addition, histamine release from basophils and mast cells is also inhibited by misoprostel. In a blinded, placebo-controlled study of 20 atopic dogs, misoprostel resulted in a significant reduction in lesional and pruritus scores. Dogs were treated with 5 mgc/kg, orally, three times daily for three weeks. The median reduction in lesional and pruritus scores was about 30%. The drug was well tolerated by all patients, with only one owner reporting intermittant (but tolerable) diarrhea during the course of the study. This drug provides moderate relief of pruritus in some atopic dogs, but probably gets very little use due to its high cost.

PENTOXIFYLLINE

Pentoxifylline (PTX) is a phosphodiesterase inhibitor with multiple immune modulating effects. Its use in human medicine is primarily for circulatory problems. However, its effects on the immune system have resulted in its evaluation for treatment of contact allergy and atopic dermatitis in the dog. In a small, blinded, placebo controlled study, PTX was used in dogs with atopic dermatitis. Dogs were given 10 mg/kg twice daily during the study. A significant reduction in pruritus and erythema was seen in treated dogs. The half-life of this drug is extremely short in the dog, so the authors of the study have suggested more frequent administration (three times daily). In addition, PTX has been evaluated for treatment of canine familial dermatomyositis at higher doses (20-25 mg/kg twice daily). In my practice, I typically recommend trying PTX at 10-20 mg/kg twice daily for atopic dogs.

CORTICOSTEROIDS

Corticosteroids have long been a standard therapy for allergies in the dog. Corticosteroids work primarily by gene repression, which prevents the activation of many immune cells involved in the allergic response. These drugs also decrease the conversion of membrane phospholipids into arachidonic acid (AA). With decreased AA, there is a reduction in the secretion of inflammatory mediators of the cyclo-oxygenase and lipoxygenase pathways.

Despite common use, there are relatively few controlled studies evaluating the efficacy of corticosteroids in the treatment of canine allergies. In one study, atopic dogs treated with prednisolone at 0.5mg/kg/day had a median reduction in pruritus scores by 81%. In another study, 57% of dogs treated with prednisolone (0.4 mg/kg/day) had a "good to excellent" reduction in pruritus, while 77% of dogs treated with prednisolone plus antihistamine had a good to excellent response.

When using corticosteroids for treatment of AD, I generally recommend using prednisone at .5 mg/lb once daily for 7 days, then 0.25 mg/lb once daily for 7 days, then 0.25 mg/lb every other day.

The acute side effects of corticosteroids are well known, and include polyuria, polydipsia, polyphagia, and excessive panting. If these adverse effects are excessive, methy-prednisolone (starting at 0.4mg/lb daily) or another corticosteroid with fewer mineralocorticoid effects can be utilized.

Chronic use of corticosteroids can lead to iatrogenic Cushing's disease, pancreatitis, gastrointestinal ulceration, opportunistic infections (especially UTI), obesity, and musculoskeletal problems (muscle wasting, CCR). Dogs should be treated with the lowest effective dose necessary to control symptoms. Concurrent use of antihistamines and topical therapy may have a "steroid-sparing" effect. When chronic use is necessary, owners should be advised that every other day dosing is always safer than daily dosing. There is no pharmacologic advantage to using injectable corticosteroids over oral preparations. Due to the increased likelihood of adverse effects, the use of injectable, long-acting corticosteroid formulations is not recommended for the treatment of canine AD.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy (ASIT) is a safe and effective nonsteroidal therapy for dogs with atopic dermatitis. Most studies indicate that 65-70% of patients will show significant (>50%) improvement with immunotherapy. When possible, intradermal testing should be utilized in order to formulate ASIT. It is important for owners to realize that ASIT is a chronic therapy for atopy, and it may take 3-6 months or longer to see a significant reduction in symptoms. In order for immunotherapy to be effective, control of secondary infections and concurrent allergies is critical. In addition, frequent follow-up (by phone or in person) is necessary. A recent study has shown that immunotherapy is most successful in those dogs whose owners have frequent contact with their dermatologist. In my practice, immunotherapy schedules are individualized to each patient depending on the response to therapy. A cookbook approach to immunotherapy is less likely to be effective.

CYCLOSPORINE FOR TREATMENT OF CANINE ATOPY

Cyclosporine (CsA) is an immunosuppressive drug originally developed to prevent human organ transplant rejection. Modified cyclosporine was developed to have more reliable absorption and greater bioavailability following oral dosing. CsA has been used in the management of human atopic dermatitis, and recent studies have demonstrated that CsA is an effective therapy for canine atopic dermatitis (AD), as well.

The recommended dose for treatment of canine AD is *5* mg/kg, once daily, using the modified formulation of CsA (Atopica®, Novartis). In some dogs, the dose can be reduced to every other day after 4-8 weeks. With chronic use, twice weekly dosing may be effective for some patients. The most common side effects include vomiting and diarrhea. These side effects are usually transient, and resolve spontaneously within a few days. Cutaneous flushing, excessive panting, hepatotoxicity, renal changes, gingival hyperplasia, muscle tremors, and secondary infections have been reported on rare occasions. People taking CsA for long periods of time have occasionally developed malignancies. While this has not been reported in the dog, CsA should not be used in dogs with a history of malignancy. I recommend doing a CBC and serum chemistry panel prior to, and 30 days after initiating therapy. If no abnormalities are seen, repeating these tests every 3-6 months may be prudent. Urinalysis and/or urine cultures should be done 1-2 times yearly to monitor for bacterial cystitis. While some have advocated measuring serum levels of CsA, I have not found this to be useful or necessary. Serum levels do not necessarily correspond to a clinical reduction in pruritus. I make adjustments in the dose regimen based on the patient's clinical signs, rather than

serum levels. Many drugs, including ketoconazole and cimetidine may interact with CsA, so caution is recommended when using CsA with other drugs. Modified CsA, as Atopica®, has recently been FDA-approved for the treatment of atopic dermatitis in the dog.

While CsA appears to be a promising new treatment, the principles of managing canine AD have not changed. Other pruritic diseases (sarcoptic mange, FAD, food hypersensitivity) must be effectively ruled out or managed.
In addition, secondary infections need to be controlled. Allergen-specific immunotherapy is still the only therapy that directly addresses the cause of canine AD.

CHRONIC MANAGEMENT OF THE ATOPIC DOG

Client education is one of the most important aspects of managing an atopic dog. Owners must understand that AD cannot be "cured." Long-term management with drugs that are safe for the patient is the goal of therapy.

For those patients with relatively short seasons, aggressive therapy is often unnecessary. As always, secondary infections should be managed. In addition, nonspecific therapies, such as antihistamines and corticosteroids should be utilized. I usually recommend a combination of topical therapy, antihistamines, and a short course of oral corticosteroids. Depending on the length of the patient's allergy season and/or adverse effects to corticosteroids, cyclosporine could be incorporated into therapy for distinctly seasonal patients.

In those patients with lengthy or nonseasonal symptoms, ASIT is indicated. ASIT is typically utilized in combination with other therapies. I commonly have owners bathing regularly, utilizing systemic medications, and using ASIT in order to manage their pruritic dogs. Both corticosteroids and cyclosporine can be used on conjunction with ASIT. Management of concurrent allergies (flea and food allergy) is also necessary.

Even the most successfully managed atopic dog will have occasional flares. When these flares occur, look first for the presence of secondary infection and flea exposure. If pruritus persists once these problems are addressed, then try adding in concurrent therapies in order to keep the patient comfortable.