Atopic dermatitis in the dog: how to make a diagnosis and how to choose the best therapeutic options

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The International Task Force of Canine Atopic Dermatitis (ITFCAD) has defined canine atopic dermatitis (CAD) as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens. Canine atopic-like dermatitis (CA-LD) is defined as an inflammatory and pruritic skin disease with clinical features identical to those seen in canine atopic dermatitis in which an IgE response to environmental or other allergens cannot be documented. Based on these definitions the major diagnostic criteria are the characteristic clinical features. Pruritus is the essential clinical feature and will involve normal appearing skin or with erythema, small erythematous papular dermatitis, or erythematous macules. The location of the lesions and pruritus will include one or a combination of the following body areas: muzzle; perioral, periocular, pinnae, ear canals, paws, flexor surface of metacarpus, extensor surface of metatarsus, flexor surface of antebrachium, axilla, groin, and perineum. Seasonality of symptoms and concurrent rhinitis or conjunctivitis add to the probability a dog has atopic dermatitis. Gastrointestinal abnormalities are not associated with atopic dermatitis unless there is a concurrent disease such as an adverse food reaction. Secondary infections (bacteria or yeast) commonly occur and can alter the degree of pruritus and lesions seen. However since secondary infections may also mimic atopic dermatitis the diagnosis of CAD requires that the clinical features are present when there is no cutaneous infection present. Chronic pruritus and dermatitis often result in secondary changes such as alopecia, hyperpigmentation and lichenification. Since other diseases can have similar clinical features the diagnosis of atopic dermatitis is one of exclusion. The process of exclusion requires that the most notable differential diagnoses are ruled out by appropriate historical or clinical findings, diagnostic tests or trial therapies. Flea allergy, adverse food reactions and sarcoptic mange need to be ruled out. The diagnosis of CAD requires appropriate allergy testing that demonstrates allergen specific IgE to plausible causative allergens. The diagnosis of CA-LD requires negative tests for allergen specific IgE to a reasonable relevant selection of allergens.

Modified microemulsion cyclosporine (Atopica®, Novartis) at 5mg/kg q24h was shown effective for treating CAD. (Olivry, Rivierre et al. 2002; Olivry, Steffan et al. 2002) Those along with many other studies have extensively evaluated the drug. Once CAD has gone into remission it is often possible to lower the dose to q48h or less. Some dogs may also go off the drug and have prolonged remissions of several months. It is the first alternative therapy to glucocorticoids that has shown similar efficacy to prednisolone and methylprednisolone. Cyclosporin has multiple effects on the skin immune and inflammatory response. Originally the mode of action was felt to be relatively specific for effects on T helper lymphocytes. Cyclosporin complexes bind calcineurin and inhibit the signal transduction to the nucleus resulting in blocked or impaired synthesis of multiple cytokines, most notably interleukin-2 (IL-2) and inhibits T-cell proliferation and the formation of cytotoxic lymphocytes. Cyclosporine is also thought to inhibit, via suppression of calcium-mediated signal transduction, mast cells and IgE-mediated immediate and LPR reactions. A recent study in dogs showed that suppression of mRNA for IL-2, IL-4 and gamma interferon but not TNF alpha as described in humans.(Kobayashi, Momoi et al. 2006) In additions dogs do not have an up regulation of TGF beta as in man. These results suggest species differences may occur. Multiple studies have demonstrated influences on mast cells, Langerhans cells, keratinocytes, eosinophils and lymphocytes.

Adverse reactions have been reported in a study of up to 268 atopic dogs(Steffan, Parks et al. 2005). The most commonly encountered side effects are vomiting and diarrhea. Vomiting is often short term or administration with food may alleviate it. In other cases temporary concurrent use of metoclopromide 0.2 to 1mg/kg q24h may allow continued use. For diarrhea temporarily stopping the drug then treating again with the addition of metronidazole or fiber to the diet may alleviate the diarrhea. However this has been the most common medical reason the drug has to be discontinued. Hirsutism and gingival hyperplasia have also been seen at the doses used for atopic disease. Hirsutism is often a generalized thickened more dense hair coat often associated with increased shedding. In other cases there are patterns where the hair growth is exceptionally long. This seems to most often affect the paws and head or face region. Papillomatous hyperplasia may also be seen and infrequently is viral and more often bacterial. Bacterial infections may appear as atypical lesions. Nephrotoxicity and hepatic toxicity has not been observed in dogs, as a significant problem. This is more of a concern when ketoconazole is used for concurrently either for Malassezia or as dose sparing agent. Elevated blood pressure is concern in humans and though rare in dogs should be monitored for. In humans there is an increased risk for malignancy especially skin neoplasia with cyclosporine use.
Topical Immunomodulators (TIMs) are a new class of drugs that have been approved in humans for the treatment of atopic dermatitis. The initial approved formulation, Tacrolimus, has also been shown effective in dogs with atopic dermatitis, especially localized disease. (Marsella, Nicklin et al. 2004; Bensignor and Olivry 2005) Tacrolimus is a 23-member macrolide produced by Streptomyces tsukabaensis and the topical formulation is called Protopic® an ointment available as a 0.1% or 0.03%. The other approved drug in this category is Pimecrolimus (Elidel®) which is an ascomycin macrolactam derivative that acts similar to Tacrolimus. It is used similar to Protopic though studies documenting its efficacy have not been done. No comparisons have been done in dogs but anecdotal reports suggest that in some dogs it is less irritating and the cream base is preferred by some clients.

The TIMs have topical anti-inflammatory effects without the atrophogenic effects and metabolic effects of topical glucocorticoids. The mechanism of action is similar to cyclosporine by inhibition of calcineurin, but 10 to 100 times more potent. Large multicenter human studies indicate it is a very safe drug with minimal systemic absorption. However animal studies have shown an increase risk for skin cancers and there is a concern that humans with long term use may also be predisposed to skin cancers including melanoma and possible lymphoma. This led the Food and Drug Administration to include this warning on the label and now recommend these drugs in more limited settings when other forms of therapy have been ineffective.

These drugs are used for localized atopic dermatitis that is not effective to topical glucocorticoids. Initial treatment is a light application of the ointment or cream until it is completely rubbed in twice daily for two weeks. If a response is seen the frequency may be lowered to once daily or less. To date problems other than irritancy have not been noted in dogs.

Interferons (INF) are a group of glycoprotein cytokines produced by a variety of inflammatory cells and fibroblasts that have numerous immunologic effects. There are several recognized interferons and they do vary in their immunologic effects. The initial commercial form of interferon is the recombinant human INF alpha-2b (Roferon-A®) and more recently a veterinary product became available. Carlotti used recombinant feline INF-omega (Virbagen®, Omega) has been shown helpful in an open trial of atopic dogs. A small open pilot trial with canine interferon gamma also suggests efficacy at high doses. (Iwasaki, Park et al. 2005) Interferon alpha (Roferon®) comes as a 3 million IU/ml solution and is diluted in 999 ml lactated ringers and then divided into 30 ml ampoules that anecdotally will remain stable if frozen. Once thawed it is kept refrigerated for thirty days. The refrigerated ampoule is then used at 0.33 ml, 1,000 IU given orally daily. The oral administration is done by injecting the solution in the buccal cavity as it is believed the absorption is from the upper oral mucosa. Anecdotally they are cases convinced that this low dose regimen if effective and also have used it concurrently with allergen specific immunotherapy. Controlled studies are needed to see if it improves the efficacy of ASIT.