CANINE ATOPY : A THERAPEUTIC UPDATE

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Contemporary therapies for canine atopy address our ever expanding knowledge regarding the pathogenesis of this disease : transcutaneous absorption of allergen being the major route of allergen exposure; the common presence of barrier defects in the lipid lamellae of the stratum corneum which alter cutaneous hydration and may potentiate allergen absorption; inappropriate T cell responses to allergen exposure; the importance of interleukin 31 as a mediator of pruritus and the interactions between the host and secondary bacterial and Malassezia colonization/infection. The successful management of the canine atopy has always emphasized a multi-modal approach: controlling secondary infections (bacterial and Malassezia); frequent bathing (to remove allergen from the surface of the skin), immunotherapy and a number of drug related options including fatty acids (for their anti-pruritic effects and capabilities to normalize barrier defects), glucocorticoids, antihistamines, oclacitinib, cyclosporine and others (pentoxifylline, misoprostol, maropitant, gabapentin, clomipramine). Where are we now with respect to some of these alternatives?

SECONDARY BACTERIAL PYODERMA

Secondary bacterial pyoderma and bacterial overgrowth are very commonly encountered in atopic individuals. Predispositions to infection may be related to the observations that atopic dogs are more heavily colonized with staphylococci and bacteria more readily adhere to atopic skin, compared to normal skin. Cutaneous antimicrobial peptides may also be abnormal in atopic skin. These secondary bacterial problems may contribute significantly to pruritus and inflammation in a number of ways, including the production of pruritogenic proteases. They may produce ceramidases that compromise the lipid lamellae and barrier function, possibly increasing the transcutaneous absorption of allergens. Individuals may develop hypersensitivities to staphylococci. Staphylococci may also function as a source of superantigens which directly stimulate Th2 responses, resulting in the production of pro-inflammatory, pruritogenic cytokines. The most effective method of controlling the tendency towards recurrent infections in affected individuals is to control the underlying allergy!

SECONDARY MALLASSEIZA

Malassezia overgrowth is also noted to contribute significantly to the inflammation and pruritus of atopic individuals. Malassezia may also produce pruritogenic proteases. Individuals may also develop Malassezia hypersensitivity. This may be assessed for by both intradermal and in vitro serologic testing. Successful hyposensitization has been reported. However, as for recurrent bacterial pyoderma, the most effective method of Malassezia control is to control the underlying allergy!

TOPICAL ANTI-PRURITIC THERAPY:

Topical Fatty Acids: These products are intended to normalize cutaneous barrier structure and function and studies support their ability to do so. They do appear to improve coat quality and skin condition. Most importantly, what affects to they have on pruritus control?

1. Dermoscent Essential 6 "Spot On" - (unsaturated fatty acids and essential oils); in one study, using the "Spot on" once weekly for 8 weeks resulted in a significant decrease in lesions and pruritus in approximately 35 – 40% of individuals (significantly higher than placebo).
2. AllerDerm Spot On (Virbac; no longer available in the United States) – ceramides, free fatty acids and cholesterol (Virbac). With 3 weeks of topical therapy, has been shown to improve the ultrastructure of the stratum corneum and increase the number of lipid lamellae in atopic skin. It has also been shown to increase the ceramide content of skin and normalizes the protein bound lipid content of skin. However, over this period of time, it produced limited clinical benefit. In one study, clinical improvement was shown with twice weekly application for 12 weeks (with significant improvement in erythema after 6 weeks). In another study, the product was used 3 times weekly for 4 weeks and it was associated with a significant decrease in clinical allergic signs (pruritus and lesions).
3. DouxoCalm "Spot On" and spray (Sogeval) – in one study, this phytosphingosine containing shampoo plus spray were noted to reduce clinical signs in atopic dogs, but it was unclear as to whether this was due to the phytosphingosines vs the bathing/emollient effects.

In the authors hands, these products do provide anti-pruritic effects but emphasis must be placed on more frequent, consistent use to achieve this end. Benefits appear to be more readily observed with milder allergic manifestations.

ANTIHISTAMINES AND DRUGS WITH ANTIHISTAMINE-LIKE ACTIVITY

In one recent survey of Veterinary Dermatologists who were asked about the efficacy of antihistamines used in their practices(78 respondents), 45% suggested < 10% response; 51% 10 – 20 %, 4% - 30 – 40% (7th World Congress of Veterinary Dermatology, 2012). One cannot generally predict which antihistamine, if any, will be of help to a given individual. We will generally have the owner try several different antihistamines, each for 2 – 3 weeks. Our trial period for fexofenadine is one month. The following are the antihistamines used most frequently in our practice: Hydroxyzine HCl (2.2 mg/kg BID), Chlorpheniramine (.4 - .8 mg/kg BID to TID), cetirizine (0.25 mg/kg BID or 10 mg/day/animal < 25 kg and 10 mg BID > 25 kg), Diphenhydramine (2.2 mg/kg BID or TID), Clemastine (1.34 mg tabs, .05 mg/kg BID or for dogs under 10 kg 1/2 tab BID; 10 - 25 kg, 1 tab BID, bigger, 1 1/2 tab BID), Amitryptyline (2.2 mg/kg BID), Loratidine (0.5 mg/kg up to 10 mg given BID), Fexofenadine (Allegra; 18 mg/kg given once daily); other antihistamines that have been used in the dog, with low incidence of success include Cyproheptadine (.25 - .5 mg/kg TID) and Doxepin HCl (.5- 1.0 mg/kg BID). Combinations of antihistamines may produce a somewhat

enhanced benefit. The author has had most success using the combination of hydroxyzine or cetirizine and chlorpheniramine, although any can be used in combination. The antihistamines are used at full dosages and recommended frequencies.

PENTOXIFYLLINE

Pentoxifylline (a phosphodiesterase inhibitor; Trental or generic) has been noted to reduce the pruritus and erythema associated with atopy at a dosage of 10 - 15 mg/kg BID, although TID administration at dosages as high as 20 – 25 mg/kg may be more beneficial. The drug is noted to benefit about 30% of dogs. It may help to reduce steroid dosages in patients on glucocorticoids, and may work synergistically with antihistamines. It is usually used as part of a combination therapy (e.g. antihistamine and pentoxifylline or a steroid and pentoxifylline.)

ALLERGEN SPECIFIC IMMUNOTHERAPY

What is the most accurate test to define offending allergens? There is really no "gold standard". The agreement between intradermal testing and in vitro serologic testing tends to be poor. This may be a reflection of varying allergen specific IgE concentrations in the skin vs the blood. Intradermal testing appears to provide somewhat more specific data than serologic testing. In vitro serologic testing is considered a reasonable alternative. However, for either testing technique, significant short comings may exist. In a very recent study, the agreement of allergen-specific IgE assays and ensuing immunotherapy recommendations from four commercial laboratories were evaluated. Replicate serum samples from ten atopic dogs were submitted to each of four laboratories (Bio-medical Services, VARL Liquid gold, Heska and Greer). The overall diagnostic agreement between laboratories was only slightly better than expected by random guessing. No two laboratories displayed even moderate chance-correlated agreement with each other. The overall agreement of the treatment recommendations was also poor. 85% of the allergen treatment recommendations were unique to one laboratory or another. In spite of these apparent shortcomings associated with testing, there are several reports supporting the fact that the success of hyposensitization, based on in vitro serologic testing data and intradermal testing, are very similar (about 60%).

Subcutaneous Immunotherapy: This treatment modality is noted to benefit 60 – 70 % of patients. Approximately 30% - 40% of these will be controlled with just the "shots" themselves; the remaining will require adjunctive therapies (e.g. antihistamines, glucocorticoids etc) to maximize benefit. The average time to onset of benefit is 3-6 months, with the range being 2-12 months. Antihistamines, low dose steroids, cyclosporine or oclacitinib do not appear to affect the onset of benefit from immunotherapy and can be used for pruritus management while awaiting the onset of benefit of immunotherapy. There is some data to suggest that excessive allergen dilution (i.e. too many allergens in a mix) will compromise hyposensitization. Many allergists limit the number of allergens to about

12 in a given mix. However, it has also been suggested that this maximum number may be expanded to as many as 20 allergens, without compromising efficacy. For individuals with larger numbers of allergens deemed necessary to put in the solution, a "2 vial" system is strongly recommended (doubling the volume of hyposensitization solution for each "shot"). Subcutaneous immunotherapy protocols do vary. Our protocol involves giving gradually increasing concentrations and volumes of hyposensitization solutions over the first month (to a total of 1 ml of 20,000 PNU/ml), then once weekly until the maximal benefit of the shots is noted. The frequency of the shots is then gradually reduced. The majority of our patients get "maintenance" shots once every 1-2 weeks, life long. For patients who derive only transient benefits from a given shot (2-3 days), we divide our solutions and give .5 cc twice weekly. Reactions to hyposensitization shots tend to be uncommon. In one recent retrospective study, 27/1,730 dogs started on immunotherapy had reactions. Reactions included 12 that were urticarial, 10 with pruritus and 7 with angioedema. Boxers and English Bulldogs were over represented (Griffin C, NAVDF 2014). Those patients who develop more severe pruritus within 1-2 hours after a given shot, or whose pruritus is escalating after the first few months of the shots (e.g. 6 months) have their volume of hyposensitization solution reduced by 1/2 to .5 cc. Interestingly, others have shown that patients with reactions to immunotherapy may be overall more likely to respond to immunotherapy. For patients not responding after 12 months of hyposensitization, dosages are gradually decreased by 0.2 ml increments every 2 weeks. This may ultimately produce a benefit for those patients whose allergies are actually being perpetuated by reactions to the shots.

"Rush" Immunotherapy involves giving all the induction dosages in the hyposensitizing protocol in one day (shots given SubQ, once every ½ hour; monitoring closely for any signs of reactions). If a reaction is noted, the protocol is stopped. The highest volume/concentration attained in the "Rush" is then sent home as the weekly maintenance dose. Rush immunotherapy has been shown to produce a slightly (5 – 10%) more rapid onset of benefit and higher percent success rate, compared to conventional immunotherapy. Following the "Rush" induction, the patient remains on the weekly maintenance dose (usually 1 ml) until the maximal benefit of the shots has been noted. Rush immunotherapy is primarily recommended for those patients who are more severely affected (desiring a more rapid onset of benefit) or for owners who are not able or willing to give the more frequent shots (once every other day) during the induction period.

"Non specific" or "Shotgun" hyposensitization is available through RESPIT ™ . Allergens for inclusion (20) are chosen based on what are thought to be the major allergens in the patient's geographic area. It has been suggested that 75% of patients experience > 50% reduction in pruritus. There is no independently generated data to verify these observations. This may be an option for those atopic patients that consistently test negative (by either intradermal testing or in vitro serologic testing; estimated to be about 10%? of the atopic population).

Sublingual Immunotherapy (SLIT) is now made commercially available by several sources, including HESKA (ALLERCEPT Therapy Drops; given twice daily), IDEXX/Greer (Allerg-g-Complete Drops, given once daily), Respit (Oralmucosal spray), Nelco (Allerpaws), BioMedical Servies (ACTT Allergy Drops). Many Dermatologists formulate their own products. Allergens are in a glycerinated base (not the same aqueous solution used in conventional, subQ immunotherapy protocols). In a Heska study of 217 treated dogs, after 6 months, 68/124 (55%) showed a good to excellent response. In 47 dogs who failed injection immunotherapy (failure; adverse reactions; compliance difficulties), 23/47 (49%) were noted to respond. The trial period recommended is 10 months. It is suggested that SLIT may be used safely in patients with histories of reactions to immunotherapy. In such cases, it is started at a weaker dilution. Reactions are uncommon and include rubbing/scratching at the mouth, vomiting or worsening of allergy signs. If noted, the dosage is decreased. Our success rates with this treatment modality mirror those reported.

CYCLOSPORINE

Cyclosporine (Atopica, Novartis; 5 mg/kg/day; range of 5 – 10 mg/kg/day) is noted to produce good to excellent results in 70 – 80% of cases. Onset of benefit is 2-4 weeks. It may take up to 2-3 months to see the maximal degree of benefit. If a partial response to the 5 mg/kg/day dose is noted, the dosage can be increased and will often improve response (e.g increase to 7.5 – 8 mg/kg). Trial therapy should be 45 - 60 days. Once the maximal beneficial effect has been noted, the frequency of administration is reduced to every other day (40 – 50 % will be controlled at this frequency), then every 3rd day (about 20% may be controlled at this frequency). When the frequency of administration cannot be reduced, it may be possible to reduce the daily dose. Giving ketoconazole (2.5 mg/kg, 2 hrs. prior to cyclosporine) and 2.5 mg/kg/day of cyclosporine is noted to achieve the same cutaneous concentrations of cyclosporine as 5mg/kg/day cyclosporine when given alone. Higher circulating concentrations can be achieved by increasing the dose of ketoconazole. Fluconazole (2.5 – 5.0 mg/kg/day) has also been noted to "spare" the dose of cyclosporine, but only by about 30%. Cyclosporine should ideally be given on an empty stomach (i.e. at least 2 hours before or after feeding) to enhance absorption. However, in order to reduce the incidence of gastrointestinal side effects at the initiation of cyclosporine therapy, it is often given with a small amount of food. After 1 – 2 weeks, assuming the drug is well tolerated, it can then be given without food, to enhance absorption. Some individuals simply will not tolerate the drug well unless it is given with food. If such is the case, food is given with cyclosporine (long term). In many individuals, this will not affect the clinical response to the cyclosporine. Nausea and vomition can often be circumvented by freezing capsules prior to administration. We have data to support the fact that freezing for up to a month does not affect bioavailability. Gingival overgrowth is noted in 4.5% of treated dogs. The incidence increases with dose and duration. There is a higher incidence on concurrent ketoconazole (12%).

Once noted, mild improvement may be seen with oral azithromycin (10 mg/kg SID for 4 - 6 weeks) or daily brushing with an 8.5 % azithromycin toothpaste (readily available as a formulated product). Capsules are associated with more GI upsets than with azithromycin toothpaste. Improvement in gingival overgrowth may be seen by reducing the daily dose of cyclosporine or going to less frequent administration. Improvement / resolution is usually seen with discontinuation of the cyclosporine. Once improvement is noted, reinstitution of cyclosporine is sometimes not associated with recurrence of the overgrowth. Refractory cases can be treated with gingival resection (e.g. surgery or laser). UTI's are noted to develop in about 15% of patients on chronic cyclosporine therapy, warranting the periodic performance of urinalyses and urine cultures in patients who are on long term, maintenance regimens (e.g. once or twice yearly). Other infrequently encountered side effects include deranged glucose metabolism (increased insulin; increased fructosamine), hypersensitivities (i.e. increased pruritus after administration), tremors, stumbling/ataxia, hyperactivity, anxiety, panting, seizures, bacterial pyoderma, nephropathies, bone marrow suppression, a lymphoplasmacytic dermatosis (Psoriaform-lichenoid dermatitis), neoplasia . In one paper, it was suggested that approximately 10 – 20% of individuals who have been well controlled on oral cyclosporine for many months to a couple of years may go in to spontaneous remission.

OCLACITINIB (APOQUEL®, ZOETIS)

Oclacitinib is a Janus kinase (JAK) inhibitor. Interleukin 31 (IL-31) is produced from T helper type 2 lymphocytes. IL 31 receptors are located on a variety of cells and nociceptive nerves. IL-31 interaction with these receptors activate signaling enzyme systems (Janus Kinases) that in turn results in the activation of nuclear transcription to produce pro-inflammatory and pruritogenic cytokines (inducing pruritus). Pruritic responses can also be mediated by interactions with these nerves. Oclacitinib inhibits the Janus Kinases and the signaling mechanism.

Published experiences:

IL-31 is noted to be elevated in 57% of atopic dogs; not elevated in normal dogs. Overall, oclacitinib is noted to benefit at least 70% of atopic dogs. In a study of 436 client owned dogs, oclacitinib (.04-.06 mg/kg BID) had pruritus score reductions of 30% within 24 hours; 65% reduction within 7 days (faster onset of benefit than prednisolone). In 5/436, GI side effects were noted: 5 diarrhea, 5 vomiting, 3 depression. In yet another study of 299 atopic dogs, (BID for 14 days, then q 24 hr for 112 days) there was a 66% reduction in pruritus and 50% reduction in dermatitis at day 28 and this held through day 112. With this protocol, a transient increase in pruritus was seen with transition to q24 hrs. In this group of dogs, 7 developed diarrhea, 6 vomiting and 4 anorexia. Oclacitinib did not benefit 18%. In 36 flea bite hypersensitivity dogs with repeated exposure to fleas over 29 days, 0.04mg/kg BID produced a > 56% reduction in pruritus within 24 hours; > 76% within 2 weeks. Oclacitinib has been shown to reduce pruritus in scabies infested dogs. Oclacitinib is labelled for us in dogs > 1 year of age. In younger dogs it may increase susceptibility to infection and demodicosis.

Because of its mode of action, oclacitinib may exacerbate neoplastic conditions. There is no data on concurrent glucocorticoids or cyclosporine (to date), and for this reason, concurrent use is not recommended.

Our experiences to date:

Significant benefit has been noted in 80 – 85% of patients. Responses do not appear to be dictated by the severity of disease manifestation. Although significant pruritus reductions are usually noted within 1-2 days, some individuals experience significant benefit within hours of first administration. Following reduction to once daily therapy (after the initial two weeks of BID therapy), there is often an increase in pruritus. This is usually transient, slowly returning to the degree of pruritus control associated with the BID administration. However, in some instances, once daily therapy will not sufficiently benefit the problem. For patients who consistently worsen on once daily therapy, consider increasing the dose to 0.6 mg/kg/day (recommended starting dosages are usually closer to 0.4 mg/kg). If this is not sufficiently effective, consider adding in other anti-pruritic medication (e.g. antihistamines). Although anthistamines in general have a relatively poor track record for pruritus control, as adjunctive therapies in this scenario, they actually appear to do quite well. The duration of anti-pruritic activity over a 24 hour period may vary from individual to individual. It is not uncommon for individuals to become somewhat more pruritic 16 – 24 hours after once daily dosing. Changing the time of administration , depending on when the individual is most pruritic, may be of some benefit (e.g. if most pruritic first thing in the morning, give later in the evening).