

Veterinary Lecture II - Atopy therapy

Therapeutic options for atopic dermatitis includes; supportive care, corticosteroids, cyclosporin, and allergen specific immunotherapy. Oftentimes these therapies can be used in combination to obtain a synergistic effect regarding control of clinical signs with the least amount of drug therapy.

Atopy is rarely limited to a dog being allergic to one individual allergen. Most atopics are allergic to a number of different environmental allergens, and atopic patients will be more prone to developing a concurrent food, flea or *Malassezia* hypersensitivity. Secondary Staphylococcal pyoderma or *Malassezia* dermatitis is common and will significantly exacerbate the pruritus of an allergic dog. Staphylococcal bacteria can act as a super antigen which may further exaggerate the pruritus of an allergic patient.

Supportive Care

Supportive care of atopy includes physical removal of allergens, antihistamines, omega three fatty acids and topical non-steroidal anti-inflammatory products. These options are considered to be a good “first line” of therapy for an allergic dog, and will also potentially enhance the other systemic therapies.

Bathing

Many owners have a misconception that they are over bathing their allergic dog. In fact most allergic dogs should be bathed frequently, at least once weekly, and usually more often. All baths will have the value of removal of allergens off the skin and coat and thereby reduce percutaneous absorption of allergens. In addition Virbac produces an excellent line of antipruritic shampoos and leave on conditioners. Oatmeal has been used to treat pruritus for centuries and is found in Epi-Soothe and ResiSOOTHE. Hydrocortisone is the active ingredient of CortiSoothe shampoo and ResiCORT conditioner. ResiCORT is one of the more popular and widely used products in our dermatology referral practice. Allermyl shampoo contains L-rhamnose with chlorhexidine and acts by inhibiting pro-inflammatory cytokines, restoring cutaneous integrity, killing *Staphylococcus*, and removal of allergens from the skin. Pramoxine (ResiPROX) and diphenhydramine (ResiHIST) are two other antipruritic products available in both shampoo and leave-on conditioner form. Pramoxine can have a topical anesthetic affect and is often combined with oatmeal. In humans it has a very low tendency to cause contact allergy, and would be a good choice for patients with a history of developing irritation or allergic reactions from bathing. In our practice we have found ResiPROX to be useful prior to an intradermal allergy test when corticosteroids are contraindicated. Because so many of our allergic patients will have a secondary Staphylococcal or *Malassezia* infection, we will frequently use an antimicrobial shampoo followed with an antipruritic leave on conditioner such as ResiCORT. If the patient has a “greasy” skin with bacteria, then Pyoben would be chosen. For “dry” infected skin we would use Hexadene, and if the infection is *Malassezia* or mixed with both yeast and bacteria then KetoChlor shampoo would be appropriate. Additional strategies aimed at reducing allergen exposure include the wearing of clothes (T-shirts or baby sleepers) adapted to fit our

patient. Wipe downs of the hair coat and skin on at least a daily basis with a damp wash cloth can also help reduce the amount of allergens the patient is absorbing.

Antihistamines

Antihistamines are widely recommended and used for therapy of atopic animals. In our practice we recommend several different antihistamines usually for one week each at a time. Most block the H1 receptors. When pruritus is moderate or severe, owners are advised that it is unlikely an antihistamine will completely control the pruritus but hopefully the pruritus will at least be moderated. First generation antihistamines such as diphenhydramine and chlorpheniramine will cross the blood-brain barrier and potentially cause sedation. Second generation antihistamines such as loratadine, and astemizole will not cross this barrier and are therefore not sedating. Tricyclic antidepressants such as amitriptyline, doxepin and clomipramine can have both behavior-modifying effects along with potent H1 blocking properties. Antihistamines such as hydroxyzine, astemizole and cetirizine have mast cell and eosinophil stabilizing effects. Potential side effects of antihistamines include sedation, anticholinergic effects, paradoxical excitement, cardiovascular effects, lowering of the seizure threshold and the potentiation of monoamine oxidase inhibitors such as amitraz. They should be used with caution and can be contraindicated in patients with liver disease, glaucoma, seizure disorders, cardiovascular disease and hypertension. Published reports have reported variable efficacy from 0-37%, and as in humans, individual results can vary, thus the recommendation to try several different antihistamines for 1-2 weeks each. Their efficacy can be increased with concurrent bathing and fatty acid therapy. They are more likely to help control and prevent pruritus after the short term use of corticosteroids has suppressed the pruritus.

Fatty Acids

Another popular and widely used therapy for atopic animals are essential fatty acids. Omega-3 fatty acids include oils from fish, black currant, borage and evening primrose. Omega-6 fatty acids are from vegetable oils such as safflower oil. The Omega-3 fatty acids have been shown to modulate arachidonic acid metabolism, shifting production to less inflammatory prostaglandins and leukotrienes. This will result in decreased pruritus. Efficacy varies from 11-27% of patients having a good response. A trial therapy of 2-3 months is required to assess the response and they are potentially contraindicated in patients with pancreatitis. Unless otherwise contraindicated, all allergic patients should be on supplementation with fatty acids such as EfaCaps or Omegaderm.

When a combination of baths, fatty acids and antihistamines are controlling the pruritus these are excellent and safe products to continue long-term. An additional benefit is that specific testing (allergy testing) is not necessary to utilize these options. When effective, most patients will show improvement within a few days to weeks. Unfortunately some allergic patients will not be adequately controlled with supportive care and it becomes necessary to utilize some of the stronger options. Supportive care is also somewhat labor intensive for the owner and can have moderate maintenance cost. Even when these options are insufficient at controlling the pruritus, they still have value at enhancing the stronger therapies, which may lead to a steroid or cyclosporin “sparing” effect.

Corticosteroids

Corticosteroids are one of the most potent and fastest acting group of drugs for atopy. They are useful for acute flare-ups or in a crisis and are usually well tolerated over short-term use. They provide the fastest relief of all available options. The only injectable formulation used for dogs in our practice is dexamethasone which is given at a dose of 0.1 mg/kg IM or possibly SQ. In our practice we use the long acting “depo” formulations only in cats and these would include both methylprednisolone acetate (Depo-Medrol) and triamcinolone diacetate (Vetalog). Since allergic disease tends to be a chronic disorder, if corticosteroids are to be used, then oral, every other day administration is more appropriate. Prednisone and methylprednisolone have a shorter half-life in the dog making them preferable corticosteroids over dexamethasone, or triamcinolone. The maximum starting dose of prednisone or prednisolone for control of pruritus is 0.5 mg/kg orally for 5-7 days, and then we taper to the lowest every other day dose possible. Some cats will clearly respond better to prednisolone over prednisone for control of pruritus or other inflammatory conditions. The long-term administration of corticosteroids have numerous well known side effects including weight gain with muscle loss, diabetes, hepatopathy, bacterial, demodex, and dermatophyte infections of the skin, and recurring urinary tract infections. Dogs requiring prednisone over 2-3 months per year are better off with an allergy work-up to determine the specific allergy so that specific therapy can be provided.

Topical steroids have definite value in the treatment of atopy. Steroid sprays, lotion, cream and ointment preparations of drugs such as hydrocortisone, triamcinolone, and betamethasone should be used selectively. They may worsen bacterial infections and depending on the strength may cause local or systemic side effects with long-term use. Genesis spray (Virbac) contains 0.015% triamcinolone acetonide and is in a water/denatured alcohol base. The efficacy is good with 67% of patients responding in a published study involving 103 pruritic dogs treated for four weeks. There were minimal side effects reported, but again caution should be used with chronic usage of all corticosteroids, especially anything stronger than hydrocortisone. The inguinal and axillary areas are especially sensitive to chronic application of corticosteroids. Localized hyperglucocorticoidism effects include epidermal atrophy, comedone and milium formation, cutaneous calcification, and exacerbation and spread of any superficial pyoderma. These changes, once present, heal very slowly, and may never totally resolve. The strongest topical corticosteroids include products such as betamethasone and fluocinolone. Areas such as the feet and ears are more tolerant of the use of more potent topical steroids.

Cyclosporin

Cyclosporin has been used for atopic dogs since the mid 1990s and has been used extensively since the year 2000. Cyclosporin decreases inflammatory cytokine production and inflammatory cell functions. There is significant suppression of the cell mediated immune system, and lesser suppression of the humoral immune system. The starting dose is usually 5 mg/kg once daily for four to six weeks, and then the drug is reduced to the lowest necessary dosage. Three proprietary formulations are available and include Atopica which is labeled for dogs, and Neoral and Gengraf which are labeled for human use. All three drugs are “modified” or micro emulsified to enhance absorption, which will result in higher

efficacy versus compounded products. This can be more noticeable when attempting to maintain control of pruritus at lower or less frequent dosing.

The two most significant draw backs to the use of cyclosporin for long-term control of atopy are the cost and the potential for gastrointestinal side effects. While vomiting or diarrhea are typically seen shortly after starting cyclosporin, there are some patients who do not start these side effects until after weeks or months of therapy. Other, less commonly reported side effects include gingival hyperplasia, hirsutism and papillomatosis (wart-like) growths on the skin. The development of other infections such as pyoderma, demodicosis, dermatophytosis and internal infections should be watched for as well. Most patients respond favorably to the drug within thirty days, and the drug is best absorbed and utilized if given on an empty stomach. Although usually beneficial, we have seen the drug fail, and have also seen cases where the pruritus was exacerbated from cyclosporin. If the patient does respond favorably we typically try and reduce the dose after 30 days, usually by administering less frequently. If the drug cannot be reduced to every other day dosing, then we try and reduce the frequency to five days a week. Because of the cost of the drug, cyclosporin is a more practical option in smaller dogs. We have found several other “niche” uses for the drug. Cyclosporin does not interfere with intradermal allergy testing and we will frequently use the drug to enable corticosteroid withdrawal so that intradermal allergy testing can be performed.

Cyclosporine interacts with many drugs that the practitioner needs to be aware of. Ketoconazole at a dose of 5 mg/kg daily has been shown to reduce the metabolism of cyclosporin by the liver which may allow a reduction of cyclosporin dosing by as much as 50%. This usually results in a cost savings for the owner as ketoconazole is less expensive than cyclosporin, but periodic blood work is then suggested to monitor for hepatopathy. A *partial* list of other drugs reported to increase cyclosporin concentration or potentiate renal dysfunction in humans includes fluconazole, itraconazole, trimethoprim/sulfa antibiotics, fluoroquinolones, cimetidine, verapamil, erythromycin and methylprednisolone. Phenobarbital has been shown to decrease blood levels of cyclosporin.

Recommendations for monitoring patients receiving cyclosporin starts with history and physical exam to screen for tumors, infections and concurrent medication administration. Bloodwork to monitor for kidney and liver function are suggested. If cardiac disease or hypertension is a risk, then monitoring of the blood pressure is also recommended. This is repeated 2-6 weeks after starting treatment and then every six months. If liver or kidney values exceed the baseline values by 30% or more, then the cyclosporin dose should be reduced, and discontinued if values exceed baseline by 50% or more. Examinations should include monitoring for any infection, neoplasia, and the oral cavity should receive close examination when patients are receiving cyclosporin. Blood levels of cyclosporin can be measured, but when the drug is used for dermatological reasons, there is a low predictive value for determining efficacy or side effects. It is more practical to monitor clinical efficacy. It may be prudent to measure blood levels if there is an insufficient response to treatment, or side effects are seen. If the trough levels are above 400-600 ng/ml then the dose should be reduced. If trough levels are below 50 ng/ml then the dose can be increased. Blood is drawn into an EDTA tube 12 hours post dose. It is preferable to use a monoclonal assay that measures only the parent compound.

Cyclosporin is not yet labeled for cats, but the drug is known to be helpful in the treatment of atopic cats. The necessary dose is potentially higher, ranging from 5-10 mg/kg daily. Cats also frequently require a higher maintenance dose compared to dogs. Fortunately cats will absorb the drug when given with food. In addition to the gastrointestinal side effects, higher rates of fatal toxoplasmosis and mycobacterium infections have been reported. Cats should be screened for toxoplasmosis prior to starting cyclosporin therapy, and should be used in caution in cats allowed to hunt outside which increases their exposure and risk of infection.

Allergen Specific Immunotherapy

Allergen specific immunotherapy (desensitization or “allergy shots”) has been one of the mainstays of care in specialized dermatology practice for years. In the mid 1980s serology (RAST) testing was marketed to veterinarians, and since then numerous companies have developed their own RAST or ELISA tests. The number, purity, and specificity of extracts available for skin testing have improved over the years. It should be emphasized that the only reason to perform any type of allergy testing (blood or skin testing) is to follow up with immunotherapy. The diagnosis of atopy should be made based on history, clinical presentation and ruling out other potential hypersensitivities such as parasite and food allergy.

Allergen specific immunotherapy is most definitely not a “once size fits all.” If a veterinarian wants to become proficient at administering immunotherapy, she or he should first become familiar with the regional pollen producing plants, when they bloom, how long they bloom, and how prevalent the plant is in the area. Understanding of the prevalence of indoor, potentially year round allergens such as house and storage mites, mold spores, animal and human dander and insect particles should be learned. This knowledge will enable the veterinarian to more effectively help decide what each individual patient should be desensitized to. The first critical step in achieving success with immunotherapy is determining *accurately and completely* what the patient is allergic to. This includes historical information regarding seasonality. If allergy testing reveals positive reactions to only seasonal pollens in a patient which is pruritic year-round, then something is being missed! In our practice we utilize intradermal skin testing almost exclusively as we feel we get the most specific and sensitive information from this test. Unfortunately this is mostly performed only in a specialty setting and may not be available to all practitioners or patients. If intradermal testing is not available, then serology testing must be utilized.

The only reason to perform any allergy testing is to follow up with immunotherapy. Once allergy test results are obtained, these results should *always* be critically analyzed to insure that the results are consistent with the patients’ pruritus history. Choosing the allergens to be included in the extract is something the veterinarian should direct based on the specifics of each individual patient. This is where a knowledge of the regional allergens is important and useful. For the outdoor working dog that is pruritic summer and fall, then grasses and weeds need to be emphasized when developing the extract. For the indoor Chihuahua which sleeps under the covers at night and who is pruritic year round, then indoor allergens such as dander, mold spores, house dust and house mites need to be strongly considered. Yet another factor to consider when developing the “correct mix or recipe” is how long a particular pollen is present. In our practice Bermuda grass is one of

the dominant pollens, and Bermuda will bloom for over six months in our area. Most tree pollens are present for 2-6 weeks. Does it make sense to put equal levels of a tree pollen and Bermuda grass? Or equal levels of house mites and Ash tree pollen? We currently skin test our patients with 70 allergens. A number of our patients will have significantly strong skin test reactions to over twenty different positive allergens and some will have over 50 significantly positive reactions. In such cases we will often utilize two different allergen vials to try and more fully incorporate all the positives into the extract. Another reason to utilize two different vials of allergens is when we find significant reactions to mold spores on our skin test. Some molds may have proteolytic enzymes which have the potential to degrade pollen proteins when mixed in the same vial.

The immunotherapy protocols that a veterinarian receives from the company which may have performed the serology testing should be considered a starting point and not set in stone. The efficacy of immunotherapy is dependant upon many factors including which allergens are included in the extract, the concentration of the extract, the quantity of protein injected and the frequency of the injections. The starting “goal” of immunotherapy is for the patient to receive 10,000-20,000 PNUs (protein nitrogen units) every 1-3 weeks as quickly as possible. There are many different protocols which have been published to achieve this goal. The most concentrated treatment vial should average 20,000 PNU/ml. Most protocols advocate diluting the concentrated vial 1:10 to achieve a vial with 2,000 PNU/ml and some advocate a third vial diluted 1:10 again which results in a vial of 200 PNU/ml. These dilutions are performed by the company preparing the allergen extract. Injections are then started with the most diluted vial, usually with an increasing volume injected every other day. Once 1.0 ml is given, injections are then moved on to the next most concentrated vial. This can require several weeks to months before 10,000 PNU of allergen is actually administered. In fact by the time 1.0 ml of a 2,000 PNU vial is administered, the patient is only receiving 20% of the “necessary” 10,000 PNU dose. To further illustrate how low this level actually is, when a patient is skin tested at our practice with 70 allergens, he or she is receiving over 5,000 PNU injected during the intradermal testing. At our practice we start with an allergen vial which averages 20,000 PNU/ml of each allergen included in the extract (Appendix A). We do not dilute this vial into weaker vials and start injections weekly in what some would call a “rush” protocol. In most cases the owners are injecting 0.5 ml (10,000 PNU) by week two. We have used this protocol almost exclusively in thousands of dogs and cats for 20 years. We feel we see a positive response more quickly than more “traditional” protocols, oftentimes by week four. This can be advantageous when dealing with a suffering patient and an understandably impatient owner. There are times when we will utilize two different *concentrated* vials of allergen (appendix B). We will use a two-vial protocol when the patient has more than twenty significant positive reactions, or when there are a number of positive mold reactions which should be included in the immunotherapy.

“Maintenance” injections are usually given at a dose of 1.0 ml every 2-4 weeks but this is variable based on the patients’ response. As part of our follow-up we find it helpful to reexamine the patient 4-6 weeks after starting immunotherapy to determine if any “trends” are emerging. Some patients, especially smaller dogs, do not tolerate the full 20,000 PNU injection. Other patients may respond well to an injection, but flare before the next injection is given. Immunotherapy can be like trying to “steer a parked car” and it is easier to steer once we are moving. Occasionally during the course of immunotherapy, owners will observe exposure to certain allergens such as a walk in the park, or a trip to the mountains.

Such observations by the owner can be helpful in “fine tuning” the extract contents. With many patients we will make slight or moderate changes in the contents of the extract to try and correlate any patterns the patient is showing. For example, when an owner reports the patient flares after going outside and walking on the lawn, increasing the grass content in the extract of that particular grass would be indicated.

Immunotherapy continues to improve partly due to advances in allergen purification as well as isolation of specific allergen isotypes. We also continue to have additional allergens available for testing and treatment. Significant additions in the last five years include *Malassezia* allergen, human dander and storage mites.

Keep in mind that immunotherapy will never be effective if the wrong diagnosis has been made, and potentially if additional concurrent allergies are present but not recognized or treated. We find many of our atopic patients to have a concurrent food allergy or parasite (flea) allergy. It is not uncommon to have to repeat food trials, or reinstitute parasite control if or when immunotherapy has failed to help after an “adequate” amount of time. Many of our patients will respond within the first 2-5 months of starting immunotherapy, yet we will recognize the occasional patient which requires over 18 months before improvement is seen. Obviously in such cases it is imperative that the diagnosis be completely accurate and complete.

For many atopic patients immunotherapy is one of the more safe, cost effective and medically effective options for managing their disease. In general it is easy for most owners to administer. It is an excellent choice in large and or young patients where the long term lower maintenance costs are best realized. It is also an excellent choice for the non-seasonal patient where treatment with corticosteroids or cyclosporin would have medical or financial concerns. Consequently it is not as good a choice for the geriatric patient, or patient with short-term seasonal disease. Immunotherapy does not lend itself to starting and stopping (using as needed) unlike the other medical options.

In conclusion atopy in the dog and cat is usually relatively easy to diagnose, with the challenge being the treatment. Multiple therapies are available and the “best” option depends on the client, patient, age, seasonality and severity of clinical signs.