Atopy represents the inherited tendency to mount an abnormal immunological reaction to environmental antigens such as pollens, molds, danders, mites, and sometimes foods. One of the key features is the development of reaginic antibody, which in mammals is represented by the immunoglobulin IgE. The pathogenesis of the IgE-mediated immunologic response involves both early and late phase reactions. The allergen binds to IgE on the surface of mast cells to trigger degranulation of preformed mediators, as well as the activation of inflammatory pathways. It is the later phases that result in the sustained inflammatory response we see in our patients, and pruritus is the major complaint!

While IgE plays a role, it is only the tip of the iceberg. Much more is going on with cellular infiltrates, and the cytokines known to accompany atopic states. Furthermore, the interaction of cytokines with the nervous system promotes the intractable itch that patients with atopic dermatitis often experience. Repressing these cytokines is the goal of therapy, and this is done using allergen specific immunotherapy, along with medications such as steroids, cyclosporine, or oclacitinib to reduce itch and inflammation. Oclacitinib (Apoquel) is a Janus kinase inhibitor that blocks the ability of cytokines to stimulate a response. It is more focused than cyclosporine, and appears to have fewer side effects. Currently it appears to be the safest and most effective medication we have to control itch in dogs.

There has also been great interest in the contribution of the skin barrier to atopic dermatitis. It is clear that in humans there are genetic mutations associated with various structural proteins in the stratum corneum and other proteins as well. One of these proteins, filaggrin, seems to have some abnormalities in distribution in canine atopics, although the presence of mutations is not well explored yet. Lipids in the stratum corneum have been shown to be abnormal in humans as well as dogs, and emphasis is being placed on trying to repair the barrier with topical lipid preparations as well as oral fatty acids. The dysfunctional barrier in the stratum corneum allows for penetration of allergens, as well as toxins from microbes such as Staphylococcus spp and Malassezia. Certainly infections exacerbates the skin barrier defect.

**CLINICAL PRESENTATION:** Classical clinical signs of atopic dermatitis in the dog include face rubbing, foot chewing, and axilla and belly scratching, lending support to the idea that most atopic dogs experience their allergenic exposure through their skin, rather than through the mucus membranes of the nasal passages. Atopic patients often are afflicted with secondary infections, which increase their discomfort and contribute significantly to the difficulties in managing their disease.

**DIAGNOSIS:** The diagnosis of atopy and/or atopic dermatitis is based on appropriate history and clinical signs, and ruling out other causes of itch, including occult scabies, flea allergy dermatitis, and in some cases, food allergy. Intradermal skin testing and/or blood allergy testing are used to select allergens for immunotherapy. Conceptually, skin testing is appealing, as we examine the organ directly affected in most of our veterinary patients. However, blood testing remains a valid choice for those animals who cannot be skin tested or whose skin test cannot be interpreted. The choice of the diagnostic lab should be based on the judicious balancing of sensitivity with specificity. Several companies offer serum allergy testing including Veterinary Allergy Reference Laboratory (VARL), Heska, Greer (now via IDEXX), Biomedical Services, Spectrum, and Nelco. It is important to keep in mind that neither skin testing nor serum testing
are perfect tests. Clinical knowledge must always be correlated to the results in order to make an effective allergy vaccine.

**TREATMENT:** Treatment of atopic dermatitis can be a complicated affair! One must take into account not only the animal’s threshold of tolerance for itch but the owner’s! One must also take into account how much work the owner is willing to do to get the disease process under control and their acceptance of the notions that the disease is not curable and that there is no quick fix! Success increases exponentially if we can combine multiple therapeutic approaches, including topical. This multimodal approach requires a dedicated owner, and I am always impressed with the devotion of most of our clients toward their animal companions. Basically we avoid allergens if we can (usually foods, fleas), use immunotherapy to modify the immune response, control infections with bathing and the use of antimicrobial medications when indicated, repair the skin barrier, and control itch.

**Avoidance:** Whenever possible we want to avoid the allergens or infections that are typical flare factors for pets with atopic dermatitis. Practically speaking, foods and ectoparasites such as fleas are the only allergens we can practically avoid in allergy management. Food allergy or adverse reactions to foods can be part of the atopic problem so it is always worth considering what role diet plays in an atopic patient. We can help reduce exposure to environmental allergens as well. For dogs with pollen allergens, reducing their time outside during the high pollen counts, along with wiping their faces and feet when they come inside, reduces the ability of the pollen proteins to absorb through the skin. For dogs allergic to house dust mites, frequent vacuuming of the carpets (or even removal of the carpets) will help. For dogs that sleep in the bed with their owners, we can recommend the hypoallergenic bedding that is recommended for people with similar allergies.

**Immunotherapy:** Specific immunotherapy remains the treatment of choice for the atopic patient. It is a biologic long term plan for management. The notion that we can retrain the immune system to perceive the environment differently is a powerful one. The observation that this is a difficult process speaks to the fact that allergen specific immunotherapy has to be given frequently and for long periods of time. The success of this therapy will depend on the accuracy of the diagnostic testing, the formulation of the vaccine, and the realization that “one size fits all” will not work. Each program will need to be tailored to the specific needs of the patient with regard to frequency of injections and number of allergens used. In the old days, we generally used one vaccine containing 10-12 antigens and encouraged the owners to believe that eventually one injection every 3-4 weeks would be sufficient to control their allergens. Now we are finding that many patients can benefit from two vaccines. This enables us to hyposensitize against 20 or more allergens without diluting the vaccine. These can be given at the same time, although some dermatologists prefer to separate them. Many of us find that continuing injections weekly for the first 9-12 months is more effective than trying to decrease the frequency too early. This individualized approach requires a lot of communication back and forth between clinician and client. Sublingual immunotherapy offers an attractive alternative to injection therapy. Sublingual immunotherapy has been shown to be as effective in dogs as injection therapy. In some dogs, it seems to work faster, and it has been successful in a subset of dogs who have failed injection immunotherapy. The advantages are that no injections have to be given; a potential disadvantage is that the drops have to be given at least once or twice daily depending on the laboratory used. In humans, the goal is to use the allergy drops (or injections) for 3-5 years with a goal toward permanent tolerance and stopping the vaccine. We have some anecdotal evidence that some dogs can stop immunotherapy after a few years whether they use drops or injections, but this is not well documented in our literature.
If immunotherapy is the long term plan, it is clear that we need a short term plan to control the pruritus and clinical signs while we get immunotherapy underway. The short term plan will involve a detailed analysis of the individual's skin condition. These are the questions I like to ask myself.

Controlling ectoparasites and infections

**What role do insect hypersensitivities play in this patient's skin disorder?** In most of the United States, insects, particularly fleas, really complicates the response to immunotherapy. Fortunately, flea control these days is very effective, and we can meet the clients' preferences as well as the pets' medical needs with either oral or topical treatments. Whether we can successfully use immunotherapy in the management of insect hypersensitivities, particularly those to fleas, remains controversial. In general, our approach has been to put most of our atopic dogs with flea allergy on vigorous flea control throughout the year. For dogs being bathed frequently oral flea control may be preferred, as bathing more than once weekly reduces efficacy of topical flea control.

**What role do infections play in this patient's skin disorder?** Bacterial and yeast infections of the skin contribute significantly to the allergic animal's discomfort. Even if these organisms merely sit on the surface of the skin, they produce toxins and metabolites than are significantly irritating or in some cases, allergenic. In addition, some patients develop an allergic reaction to the staphylococci and/or yeast. Although not well documented in our canine patients, superantigen reactions contribute greatly to atopic dermatitis in humans, and I believe they do in dogs as well. Creative approaches to infection control really help our atopic patients. Look carefully for the presence of superficial and deep pyodermas, but also be aware that the mix of bacteria and yeast on the skin surfaces of the muzzle, feet, perianal and perioral areas, and ventrum may manifest as erythematous greasy patches. Cytologies are indicated in almost all atopic patients. A subset of dogs with recurrent pyodermas associated with their allergies will benefit from the use of Staphage Lysate in addition to their allergy vaccine. Bacterial skin infections should be managed with topical therapy and when indicated systemic antibiotics. Yeast infections can also be managed with topical therapy, but in many cases systemic antifungal agents may be needed as well. Because some patients are hypersensitive to yeast, immunotherapy is also an option.

Reparing the skin barrier.

There are two ways in which we can help repair the skin barrier. The first is by using optimal nutrition which includes essential fatty acids. There is good evidence that diets such as Iam’s Response FP and other fatty acid enriched diets improve the skin and coat quality of atopic dogs. The second way to improve the skin barrier is by using topical therapy. The choice of shampoos and rinses will be determined by the individual. For dogs with itch but no infection, we can use shampoos containing fatty acids, phytosphingosine, or ceramides. It is critical to remember that with shampoo therapy, formulation is a critical part of its efficacy. All of the above can be followed with a soothing crème rinses or leave-ons such as Resicort. Some newer approaches in addition to bathing include the use of topical lipids to stimulate repair of the skin barrier. There is some evidence to show that the topical application of ceramide, phytosphingosine, or fatty acids stimulates the keratinocytes to repair the barrier and to resume production of their own lipids. Phytosphingosine is contained in the DOUXO line of products by Sogeval (CEVA) as well as their conventional line. Dermoscent makes a line of products containing essential oils from herbs and grains which supply fatty acids to the skin. Many shampoos and sprays contain ceramides, including those by Dechra. Time will tell how useful
these products will be, but we have seen very encouraging results so far. Coat quality and skin quality are enhanced, with a reduction in the frequency of pyoderma recurrences. In mild atopics, we have noted that these products may even reduce itch.

**Control of itch.** Itch is the most common sign that drives the owners of atopic dogs into our clinic. We must control itch to buy us the time we need to utilize immunotherapy effectively. Up until recently, the only good evidence we have is for steroids and cyclosporine; however, recently oclacitinib (Apoquel, Zoetis) has been approved, and it was released early in 2014.

**Steroids:** Glucocorticoids have profound effects on inflammatory pathways, and they are very effective in reducing itch. The potential side effects can be divided into two groups: short term and long term. The short term side effects include polyuria, polydipsia, polyphagia, and behavioral changes, which are offputting to many clients. The long term side effects include liver enzyme elevations, muscle loss, weakening of the ligaments, thinning of the skin, reduced coat quality, and increased susceptibility to infections. While these side effects do not occur in all dogs, they occur with enough frequency to make the routine use of glucocorticoids less desirable. For some dogs, however, glucocorticoids were the only medication that was effective. We try to avoid using glucocorticoids for long-term management of atopy if we can, but using prednisone, prednisolone in short bursts and getting dogs to low dose alternate day therapy is necessary for some dogs during the induction phase of immunotherapy. Recent evidence suggest that steroids may actually enhance the induction of T regulatory cells, one of the mechanisms by which immunotherapy is supposed to work. Therefore steroids are NOT contraindicated in dogs on immunotherapy. Some dogs may require low dose maintenance steroids with their immunotherapy to remain comfortable. I like to start with the veterinary drug Temaril-P, a tablet containing the antihistamine trimeprazine and 2 mg prednisolone. I find this drug to be very effective in most patients, allowing us to keep the steroid use down and achieve good control of itch. I think it is important to try to use this drug and steroids in general in bursts and to stop often to see how the animal will do without it.

Candace Sousa has published an easy calculation for long term steroid use that I have found very helpful. The body weight in lbs is multiplied by 15 (if kg, by 30); the resulting number is the mg of prednisone or prednisolone that the dog can take annually. This dose, based on her experiences, has been least likely to cause problems. If this dose is exceeded, the likelihood of problems may be increased.

**Cyclosporine** initially released as Atopica (Novartis) revolutionized the treatment of atopic dogs and cats, particularly those who had become refractory to steroids or could not tolerate them. Cyclosporine can also be used concurrently with immunotherapy and many dermatologists have said they believe this makes the immunotherapy work better. We use 5-7 mg/kg daily for 4-6 weeks, then we try to lower the frequency. When used concurrently with immunotherapy, the hope is that we will phase out the cyclosporine after several months. Many dogs can live on Atopica with good control of their allergies, but we still find they need bursts of steroid during bad times. It is not always possible to reduce the frequency, though, and some dogs and cats require daily therapy to remain comfortable. Side effects in the short term include nausea, vomiting, and diarrhea; these can often be ameliorated by using maropitant (Cerenia, Zoetis), for the first 4 days of cyclosporine therapy. Long term side effects include chronic soft stool, gingival hyperplasia, lichenoid psoriasiform dermatitis and unusual bacterial and fungal infections. In cats, fatal toxoplasmosis has been observed.

**Oclacitinib (Apoquel, Zoetis)** is a new medication to control allergic itch. It can be used for short term control of itch associated with several allergic skin diseases, and for long term use in chronic atopic dermatitis. It is a focused inhibitor of allergy cytokines that works by inhibiting
Janus kinases (selectively JAK1); these kinases helps transmit the signal of the cytokine to the inside of the cell, resulting in activation. The most common side effects include vomiting, diarrhea, and anorexia (in less than 5% patients). A few dermatologists have seen anemia, thrombocytopenia, or leukopenias with this medication. Aggression has been reported in a very low number of patients. The medication is available in 3 tablet sizes (3.6, 5.4, and 16 mg). Dosing is 0.4 to 0.6 mg/kg BID for 14 days, then once daily for chronic use. The drug has been shown to be safe and effective for long term use. For more information, see https://online.zoetis.com/US/EN/Products/Pages/Apoquel/index.aspx#sthash.4h58DeNi.dpbs and the articles by Cosgrove et al. below. Also visit ExcellenceInDermatology.com and ItchCycle.com for access to more information about canine atopic dermatitis and downloadable resources.

REFERENCES


   (this article is available for download at no charge at the following URL) http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3164.2010.00889.x/full it is also available at ExcellenceinDermatology.com


   These papers offer evidence that response to immunotherapy based on serum allergy testing is equivalent to that based on intradermal skin testing.


  *Recent review of the pathogenesis of atopic dermatitis*


  *Apoquel (oclacitinib)*

