IT IS NOT ALLERGIES- IT IS CANINE ATOPIC DERMATITIS- THE NEW PARADIGM

Paul B. Bloom, DVM, DACVD, DABVP (Canine and Feline Specialty)
Allergy, Skin and Ear Clinic for Pets, Livonia, MI. 48154
Michigan State University, East Lansing, MI 48823
734-422-8070

The understanding of canine atopic dermatitis (cAD) has changed dramatically over the last several years. This has lead to a change in our therapies. It is now accepted that the pathogenesis of cAD involves not only an immunologic component but also a barrier dysfunction. This disruption of normal barrier function leads to increased allergen penetration and sensitization. Thus, the therapeutic approach has changed from addressing only the immunologic abnormality (hypersensitivity) to one that also includes managing the barrier dysfunction. It is essential that before treatment for cAD is begun that the proper diagnosis has been established. It is recognized that the diagnosis of cAD is a clinical diagnosis made by ruling out other pruritic diseases.

Criteria that can help establish a diagnosis of cAD are:
1. Onset of signs under 3 years of age
2. Dog living mostly indoors
3. Glucocorticoid-responsive pruritus
4. Pruritus sine materia at onset (i.e. alesional pruritus)
5. Affected front feet
6. Affected ear pinnae
7. Nonaffected ear margins
8. Nonaffected dorso-lumbar area

If the dog meets 5 criteria- there is a specificity of 79% (21% false positives) and a sensitivity of 85% (15% false negative)
If the dog meets 6 criteria- there is a specificity of 89% (11% false positives) but the sensitivity decreases (more false negative) to 58% (42% false negative)

In the author’s experience an easier and very accurate modification can be used as follows. It is called the “One minute atopic dermatitis test”. If you have a pruritic dog- you can be fairly certain that he/she has cAD ectoparasites and infection (bacterial, yeast/fungal) have been ruled out. There are exceptions to the rule but they are very uncommon and suspicion for these diseases would be raised based on signalment, history and physical findings. Note that serum testing/intradermal testing and/or food trials may be needed to ID flare factors of cAD but are not used to diagnose cAD. Whether these additional tests are necessary depends on the severity of the cAD

TREATMENT OF THE PRURITIC DOG

There are a variety of therapies for the symptomatic relief of pruritus in dogs with atopic dermatitis which will help the disease at that moment. These treatments will do nothing to prevent recurrence, this can only happen if the underlying cause is identified and treated. You will be more effective long term in treating the pruritic patient if you find the “due to” rather than just treat the symptom (pruritus). This lecture is focused on new therapies for the treatment of cAD.

If a specific diagnosis for the pruritus has not been established after the initial diagnostic tests have been performed and infection is present it is best to treat the infection for 14-21 days and then re-evaluate how much pruritus remains. DON’T use GC during this time since it would make interpretation of response to therapy impossible (was it the steroid or the antibiotic/antifungal therapy that resolved the pruritus?).

If the pruritus has resolved after only treating the secondary infections and/or ectoparasites it means that the ectoparasites or the secondary pyoderma/Malassezia dermatitis was the major trigger of the pruritus at this time. This secondary infection was due to one (or more) of the following:
1. Ectoparasites
2. Seasonally triggered environmental allergen induced atopic dermatitis and the season has changed
3. Nonseasonally triggered environmental allergen induced atopic dermatitis that is not symptomatic when the infection is absent (threshold theory)
4. Environmental allergen induced atopic dermatitis that is triggered by a cutaneous food reaction that is not symptomatic when infection is absent (threshold theory)
5. An endocrinopathy (hypothyroidism, hyperadrenocorticism)- remember these are only pruritic when there is a secondary bacterial infection or Malassezia overgrowth.
If pruritus continues after treating the secondary infections and a specific primary disease has not been established through physical examination and laboratory testing, or there was not a secondary infection to begin with the next step is a therapeutic ectoparasiticidal treatment (if it has not been previously performed). Glucocorticoids or oclacitinib may be used during the first week or 2 of the ectoparasiticidal treatment but they need to be stopped a couple weeks before rechecking so that it can be determined whether it was the medication or the ectoparasiticidal treatment that resolved the pruritus. If the pruritus has continued in spite of treating for infection and ectoparasites a food trial should be instituted. A home cooked diet is the gold standard and owners should be encouraged to use this diet rather than commercial diets. It is beyond the scope of this lecture to discuss the many reasons that this is true but to summarize the high point- commercial foods contain ingredients that are not labeled. In addition commercial diets have only been shown to have a 50% negative predictive value (poor at ruling out the disease).

Both the diet trial and a therapeutic ectoparasiticidal treatment can be done simultaneously. If they are done simultaneously and there is a positive response you can do a food “challenge” to determine which therapy was effective. By going back and feeding the original diet and seeing if the pruritus resumes you will be able to determine the underlying cause. A short course of GC or oclacitinib at the beginning of the therapeutic trial may be done as long as you have eliminated the presence pyoderma, Malassezia, demodex and dermatophytes.

At the end of these steps, if the pruritus has resolved w/o the concurrent administration of GC or oclacitinib, you have identified your primary cause and can treat accordingly. If the dog has residual pruritus then the dog has environmental triggered atopic dermatitis.

Treatment of canine atopic dermatitis - overview

As previously mentioned it is now recognized that canine atopic dermatitis has both an allergic component and a barrier dysfunction component both of these should be addressed in your treatment.

Treatment options for dogs with atopic dermatitis include - (please note that these therapies are used as a preventative so they should be instituted before clinical signs recur):

1. Good skin care
   a. Restore barrier function
   b. Protecting the skin
      i. Wiping the dog off after coming in from outdoors
      ii. Clipping the hair coat to a short length (10 or 15 blade) which helps to decrease exposure to and contact with environmental triggers (allergic and irritant).
      iii. Clothing all the time and boots outdoors
   c. Bathing with a hypoallergenic veterinary shampoo that contain moisturizers or barrier repair ingredients (eg shampoo that contain phytosphingosine) weekly
   d. Follow the bath w/a humectants or barrier repair product
      i. In humans moisturizers are best applied w/in 2 minutes after finishing the bath for maximum effect
   e. Fatty acid supplementation- try an omega 3 product for 3 months and if there is no improvement, try a product with a combination of an omega 3 and 6
      i. Omega 3
         1. 18 mg/kg of EPA daily
      ii. Omega 6/3- double the bottle dose OR
      iii. High fatty acid diets
   f. Bathing is helpful to decrease antigen load and bacterial colonization

2. Identify and prevent/manage the triggers (ectoparasites, food, infection (bacterial/Malassezia))
   a. If the dog has environmental triggered atopic dermatitis, allergen specific immunotherapy (ASIT) is appropriate if the symptoms are present for more than 2 or 3 months/year and is severe enough to need corticosteroids or cyclosporine for symptomatic control. ASIT may be administered either subcutaneously or sublingually. See comments at the end of this article
   b. If the dog has a food trigger- avoid those foods
   c. Good flea control especially if the dog has flea bite hypersensitivity
3. During acute flares- treating infection and inflammation is necessary. Therapy would include antibiotics, antifungals and glucocorticoids along with the above recommendations.

4. Treatment options for symptomatic relief of dogs with atopic dermatitis w/o secondary infection are:

a. Glucocorticoids

   i. The author uses this drug in dogs with uncomplicated atopic dermatitis if the dog is moderately to severely pruritic and I want to avoid steroids (due to side effects or owner preference) and has failed to respond to Oclacitinib.

   ii. There may be a 4-6 week delay before seeing full effectiveness so you can give glucocorticoids during the first 3 weeks to help keep the dog comfortable during this lag time.

   iii. Side effects in dogs are very limited and are primarily GI. Other side effects reported include cutaneous papillomatosis and hyperplastic gingivitis. In order to minimize the most limiting factor of CSA (vomiting) I use Cerenia® or zofran (0.5-0.75 mg/kg) 30 minutes before administering mCSA. I do this for the first 4-7 days and administer Atopica® with a meal.

b. mCSA

   i. An important drug interaction is ketoconazole (KCZ). KCZ inhibits the enzyme responsible for CSA metabolism (cP450 3A4) thereby increasing concentrations and prolonging elimination of CSA. Because of the cost of CSA, coadministration with ketoconazole has been used by some authors in DOGS. This combination with KCZ can lower the amount of CSA that needs to be administered. Doses suggested are 2.5 mg/kg of CSA and 7.5 mg/kg of KCZ sid. Please note failure to respond to this combination doesn't mean that a full dose of CSA will be ineffective. The author therefore rarely begins therapy w/this combination. Note recently the author has seen resistant cutaneous Malassezia infections. Is this due to the indiscriminate use of KCZ orally and topically?

   ii. Dosage is 5 mg/kg sid on an empty stomach. There may be a 4-6 week delay before seeing full effectiveness so you can give GC during the first 3 weeks to help keep the dog comfortable during this lag time.

   iii. Side effects in dogs are very limited and are primarily GI. Other side effects reported include cutaneous papillomatosis and hyperplastic gingivitis. In order to minimize the most limiting factor of CSA (vomiting) I use Cerenia® for the first 4 days and administer Atopica® with a meal.

   iv. Drug interactions – the most important is ketoconazole (KCZ). It inhibits the enzyme responsible for CSA metabolism (cP450 3A4) thereby increasing concentrations and prolonging elimination of CSA. You need to be aware of this when treating Malassezia with KCZ if the dog is also on CSA.

c. Oclacitinib

   i. During inflammation, a variety of mediators such as cytokines, chemokines, and neuropeptides are released into the microenvironment by Th2 lymphocytes. (note in dogs w/AD there is an increase in the number of Th2 lymphocytes) Cytokines convey their information by binding to specific receptors on the cell membrane to induce a biologic response. The cytokine receptors are transmembrane receptors composed of multiple subunits. On the intracellular portion of each receptor subunit are one of 4 JAKs – JAK1, JAK2, JAK3 and TYK2.

   ii. Afferent nerves, in close proximity to the inflammation that are responsible for pruritus are activated by these mediators. They transmit signals that travel along unmyelinated C nerve fibers and are received by the dorsal root ganglia (DRG) within the dorsal horn of the spinal cord. The signal finally reaches the brain and affects regions involved in pruritus. Adjacent afferent nerves are stimulated (axon reflex) when the peripheral nerve endings of the affected area release neuropeptides (e.g., substance P, calcitonin gene-related protein, CGRP) and neurotropins (e.g., NGF). These mediators can
also modulate inflammatory responses as well as directly triggering vascular responses in the skin. In the skin, cytokines regulate acute and chronic processes such as neuronal itch stimulation and inflammation.

iii. After a cytokine binds to its cell membrane receptor it triggers specific intracellular pathways. One such intracellular pathway is the Janus kinase (JAK) pathway. Cytokines implicated in allergic skin disease (such as Interleukin IL-31 and IL-4) bind to their receptor on the cell membrane and activate the JAK pathway. JAKs activate intracellular proteins called Signal Transducer and Activator of Transcription (STAT) to induce gene transcription and biological responses.

iv. What types of proteins or functional changes are produced by activation of the AK/STAT pathway? Some are 1) ↑ IgE production 2) lymphocyte proliferation 3) ↑ cytokine production 4) cytokine receptor expression 5) ↑ chemokine production 6) pruritus.

v. Oclacitinib is a JAK inhibitor with more selectivity to block JAK1 than JAK2, JAK3 or TYK2. It blocks the activation and function of cells that use the JAK1 enzyme as a part of the cytokine receptor. The result is a decrease in the activity of pro-inflammatory and pruritogenic cytokines that use JAK1 such as IL-2, -4, -6, -13, -31.

1. The organ systems that are affected by the inhibition of JAK1 mainly are the epidermis, lymphocytes and the peripheral nervous system.
2. Inhibiting JAK 1 inhibits the production of IL 31. IL31, which is made principally by activated Th2-type T cells, induces production of several chemokine involved in inflammatory skin disease. These chemokines are not only involved with inflammation but also recruit to the skin IL 31 producing T cells thereby amplifying inflammation and pruritus.
3. IL 31 receptors are also present on nociceptive neurons in the dorsal root ganglion. Currently it is unclear whether IL 31 induces pruritus by directly modulating the function of sensory neurons or stimulating keratinocytes, which may induce a yet unknown keratinocyte-derived mediator that subsequently activates unmyelinated C fibers in the skin.

vi. The dosage is 0.4-0.6 mg/kg bid x 14 then sid. Some dogs will have their pruritus increase when the dose is changed from bid to sid. Before adjusting the medication be sure to collect your minimum data base to evaluate for bacterial pyoderma, Malassezia dermatitis and ectoparasites. If the dog has uncomplicated atopic dermatitis and sid oclacitinib is inadequately controlling the pruritus the author will do the following step wise adjustments.

vii. If the dog is not responding at all (or minimally) to sid then increase the dose if possible (the chart accompanying the drug has a some dogs receiving the low end of the dose while others are at the high end)

viii. In those cases that it is effective but it is not lasting all day, take the daily dose and divide it into 2 doses. The doses don't have to be the equal – if the dog is on 1 ½ pills daily you can do 1 in the am and ½ in the pm.

ix. If the above doesn't work and you have not used modified cyclosporine you should do so.

x. Regardless of the response to oclacitinib – identifying and treating the underlying cause is the best course of action rather than just masking the symptoms.

xi. Because this drug blocks the neurogenic component of pruritus other pruritic skin diseases (pyoderma, flea allergy, scabies) may also respond to this medication. This emphasizes the importance of a thorough dermatologic examination and a minimum data base of skin scrapings and cytologies. Pruritic dogs, whether or not they are given oclacitinib, should have flea control therapy instituted.
The author is concerned cases may not have a thorough evaluation before dispensing oclacitinib and that dogs may have these other pruritic diseases present but not addressed. The author will dispense oclacitinib in the same situations as mCSA except if the dog needs instant, predictable relief, mCSA would not be appropriate due to the lag effect, while oclacitinib would be effective. Before dispensing oclacitinib the author discusses the following with the owners:

1. Identifying and treating the underlying cause is the best long term therapy
2. The long term safety of the drug is unknown at this time

d. Canine Atopic Dermatitis Immunotherapeutic is an injectable formulation containing a caninized monoclonal antibody (mAb) against interleukin-31 (IL-31). These mAb remains in circulation for several weeks. It exerts a therapeutic effect by binding to and neutralizing soluble IL-31, thus inhibiting pruritus and reducing skin lesions. Like other naturally-occurring antibodies and antibody-antigen complexes, elimination is via normal protein degradation pathways.
   i. It is administered by a subcutaneous injection and is repeated monthly, as needed.
   ii. It is for DOGS only
   iii. This product license is conditional. Safety and efficacy studies are in progress.

e. Antihistamines/tricyclic antidepressants – there are a variety of antihistamines available that may help mildly pruritic dogs.

5. ASIT
   a. May be administered either subcutaneously (SCIT) or sublingually (SLIT)
   b. SCIT
      i. Has a long term track record of safety and efficacy
         1. Extremity rare for life threatening reactions
            a. Will see less serve reactions that need injection modification (localized swelling, increase in pruritus, etc)

6. SLIT
   Recently sublingual immunotherapy (SLIT) has become available to veterinarians for the treatment of canine atopic dermatitis (cAD). The author has some reservations about the use of this therapy for cAD. Recognizing that SLIT has been used for many years in Europe for the treatment of human asthma we can review the information that is available in that species. The vast majority of studies and protocols in humans are for rhinitis/asthma and NOT atopic dermatitis. A review in human medicine (2006) found the following –
   a. Dosing summary
      i. The studies included doses that varied by 30,000-fold
      ii. Frequency of dosing varying from daily to weekly
      iii. Duration of treatment varying from 2 months to 5 years

   Their conclusion was that SLIT is an effective treatment (for rhinitis or asthma) but it was unclear what the proper dose, treatment schedule and overall duration of treatment was to be effective.

   Other review articles found that the cumulative monthly dose varied between 0.017 and >500 times the customary subcutaneous maintenance dose. In addition that each manufacturer uses its own standardization, formulation, and administration schedules. In a review of SLIT for human atopic dermatitis the authors could only find 1 double blinded, placebo controlled randomized study (DBPCR). That study evaluated the efficacy and safety of SLIT using house dust mite containing drops. They concluded that for mild–moderate disease there was significant improvement but there was no improvement in cases of severe disease. But it went on to say that standardized treatment was essential to ensure therapeutic efficacy. They used 80 umg protein concentration/day once daily with instructions for the patients to keep the drops under the tongue for 1–3 minutes and then swallow. Note in this study the treatment group had a total efficacy rate of 77.78% (cured + marked improvement) vs. 53.85% in the control group. These were statistically significant but look at the placebo effect! The other important finding was that during the first year of immunotherapy there was no difference between placebo and
SLIT response and the difference was only noticeable at 2 years. In 2015 there was a systematic review to evaluate the evidence supporting the use of SLIT for hAD. They could only find 5 studies to fit their criteria. They found that in 4/5 studies there was an improvement in AD but in 2/4 there was a substantial placebo effect making the true effect of SLIT difficult to determine. They found serious shortcomings such as lack of control group, lack of randomization and data analysis was not by intention to treat. The group graded 1 of the studies to have moderate quality, 2 to have low quality and 2 to have very low quality.

As you review the studies in veterinary medicine concerning SLIT and eAD you will note that all studies except for 1 have the same very serious limitations- they are open studies, there are no placebo groups and the studies only applies to mite sensitive dogs. Also the studies state that there are statistically significant changes in CADESI and PVAS but doesn’t state if this translated into CLINICAL improvement- for example pruritus may go from +10/10 to a +7/10- which may be statistically different but not clinically different. In the 1 DBPCR study that has been done to date in veterinary medicine, they found that overall the percentage of dogs that improved >40% were 50% in the control and 66% in the active group. Once again look at that placebo response! Two problems with this study- 1 they don’t state if the response rate is statistically different and also the criteria that has been establish states there must be at least a 50% improvement in pruritus to be considered clinically significant- so why did that study use a 40% cutoff?

Lastly, things that give the author great pause about this whole subject is that there are some companies that refuse to tell the veterinarian what is in the SLIT formula that they expect us to give to our patients. In addition the different antigen companies are using different strengths in their SLIT (one company offers a dilution of 20,000 pnu or 40,000 pnu whichever you want – but doesn’t give guidelines how to chose), different volumes and different frequency (sid vs bid). So how can they all be effective? Discussion about dermatologist who formulate their own SLIT in their hospitals also reveals a lack of standard protocols. The author uses SLIT in very limited, specific situations such as when owners are absolutely adamant that they won’t give SCIT and won’t bring the pet in for you to give the injection, an animal that has had a severe reaction to SCIT or if the animal fails to respond to SCIT after 1 - 1 ½ years. I tell the owner that we really don’t know how successful this method is but that it is very safe to try.

Summary from the ACVD task force on AD

**Treatment of acute flares of canine atopic dermatitis**

1. Identification and avoidance of flare factors:
   a. Identification and elimination, whenever possible, of allergenic flare factors (fleas, food and environmental allergens)
   b. Evaluation of use of antimicrobial therapy if clinical signs of infection or colonization with bacteria or yeast are present on the skin or in the ears

2. Improvement in skin and coat hygiene and care:
   a. Bathing with a nonirritating shampoo

3. Reduction of pruritus and skin lesions with pharmacological agents:
   a. Treatment with topical glucocorticoids, especially for localized lesions, as needed to control signs
   b. Treatment with oral glucocorticoids, especially for widespread or severe lesions, as needed to control signs

**Treatment of chronic canine atopic dermatitis**

1. Identification and avoidance of flare factors:
   a) Dietary restriction-provocation trials in dogs with nonseasonal signs
   b) Implementation of an effective flea control regimen in areas where fleas are present
   c) Performance of allergen-specific intradermal and/or IgE serological tests to identify possible environmental allergen flare factors
   d) Possible implementation of house dust mite control measures, if relevant and feasible
   e) Evaluation of use of antimicrobial therapy if signs of infection or colonization with bacteria or yeast are present on the skin or in the ears

2. Improvement in skin and coat hygiene and care:
   a) Bathing with a nonirritating shampoo or an antiseborrheic/antimicrobial shampoo, depending on the skin lesions seen
b) Dietary supplementation with essential fatty acids

3. Reduction of pruritus and skin lesions with pharmacological agents:
   a) Treatment with topical glucocorticoids or tacrolimus, especially for localized lesions, as needed to control signs
   b) Treatment with oral glucocorticoids, cyclosporine or subcutaneous interferon, especially for widespread or severe lesions, as needed to control signs. These agents would not normally be combined together.
   c) Use of steroid-sparing agents, such as essential fatty acids, Chinese herbs and antihistamines, if glucocorticoids are being used as a long term treatment option.

4. Implementation of strategies to prevent recurrence of signs
   a) Avoidance of known flare factors, as identified above
   b) Consideration of preventive pharmacotherapy, if feasible and relevant
   c) Implementation of allergen-specific immunotherapy, if feasible. This can be used alongside all the above treatment options in an attempt to provide long term amelioration of the aberrant immune response

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