

The Use of Allergy Serology and Allergen Specific Immunotherapy (ASIT) in the Management of Canine/Feline Atopic Dermatitis.

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Introduction

At the outset it is important to remember that allergy serology is not a diagnostic test used for the confirmation of a diagnosis of atopic dermatitis (AD). Diagnosis of atopy is based on meeting specific historical and clinical criteria (Favrot's criteria) and ruling out other possible causes of similar dermatological and clinical signs. Strict control of ectoparasites, exclusion of bacterial and/or fungal dermatitis and ruling out cutaneous lymphoma, forms part of the clinical workup of any atopic patient. In canine patients with perineum pruritus and/or concurrent gastrointestinal signs, running of elimination diet trials and/or performing the food reaction test (FRT) is indicated.

In an dog/cat with these historical and clinical criteria, the presence of allergen specific IgE is considered highly significant. Only once the clinical diagnosis of atopic dermatitis has been made, is allergy serology considered and then only as a test to identify potential triggering allergens to include in an allergen specific immunotherapy vaccine.

The first detailed description on the use of allergen specific immunotherapy in dogs, was described by Wittich in 1941. He demonstrated allergic sensitization to ragweed pollen and response to allergen specific immunotherapy (ASIT). So ASIT has been known as a therapeutic tool for canine atopic dermatitis for over 75 years and has become an important and foundational treatment for atopic dermatitis in dogs, cats and horses.

There are a growing number of studies that have documented the effectiveness of ASIT in allergic disease in animals. It remains currently the only therapy that can modify, or reverse part of the pathogenesis of CAD, both alleviating clinical signs and preventing progression of the condition. In addition, ASIT has minimal adverse effects with lifelong treatment and provides the possibility for long-lasting effectiveness.

The International Committee for Allergic Diseases of Animals co-ordinates and reviews scientific and clinical research into the following areas of atopic dermatitis

- Pathogenesis.
- Clinical Diagnosis.
- Allergy testing.
- Allergen Specific Immunotherapy.
- Evidence based treatment guidelines.

This highlights the scientific and clinical importance of allergy testing and ASIT in the effective management of atopic dermatitis in animals.

Allergy Testing

Atopic dermatitis is a common diagnosis in veterinary dermatology. A key factor in the pathogenesis of the clinical manifestations of atopy is the presence of high levels of allergen specific IgE. However, it should be appreciated that atopic dermatitis is a complex and multifactorial disease involving immune dysregulation, allergic sensitization, skin barrier defects, microbial colonization and environmental factors.

Only once the clinical diagnosis of atopic dermatitis has been made, is it decided whether an allergy test is required or not. Allergy serology should not be used as a front line diagnostic test for atopy, the clinical diagnosis of atopic dermatitis should have been made prior to testing. The following situations would warrant that allergy testing (allergy serology or intradermal skin testing) be performed.

- Severe clinical signs.
- Prolonged clinical signs that last for more than 3 months of the year.
- Poor control of atopic skin disease with symptomatic therapy.
- Side effects to drugs being used in the therapy program.
- Poor owner compliance.

The results of the allergy test are used to identify offending allergens to enable formulation of allergen specific immunotherapy vaccines. Allergy serology has several advantages over intradermal skin testing including no patient risk (as no sedation or general anaesthetic required), it is more convenient (for owner and animal), does not require repeated injections, serology is objective and reproducible and there is lower risk of drug interactions interfering with test results.

Evidence based studies have provided no evidence of for drug withdrawal prior to allergen-specific IgE serological tests for oral cyclosporine or prednisone / prednisolone. For intra-dermal skin testing on the other hand optimal withdrawal times are antihistamines (7 days), oral glucocorticoids (14 days), topical/otic glucocorticoids (14 days) and cyclosporine (0) days. It has been shown that the success rate of allergen specific immunotherapy (ASIT) based on allergy serology versus intradermal skin testing is not statistically different.

Various allergen specific IgE serology testing assays are available including monoclonal, mixed monoclonal and polyclonal anti-canine IgE assays plus the high affinity IgE receptor alpha subunit assay (Fc-epsilon receptor test/mast cell receptor test). Serum IgE levels are miniscule when compared to IgG, in fact for every IgE antibody there are more than 10 000 IgG antibodies. It should be appreciated that IgG also binds with allergens and therefore, there is huge opportunity for cross reaction. Hence, serological assays based on the use of monoclonal or polyclonal anti-IgE antibodies are complicated by cross reaction with IgG producing false positive results.

To specifically identify only IgE in serum, one needs to make use of IgE's unique affinity for binding to mast cells and basophils, no other class of immunoglobulin is able to perform this.

This Fc-epsilon receptor test (mast cell receptor test), shows a strong and highly specific affinity for canine and feline IgE and a complete lack of cross reaction with IgG. This system is specific for the detection of IgE only, it will not identify any other Ig class. Due to this higher sensitivity and specificity plus the absence of IgG cross reaction of the Fc-epsilon receptor test, the use of the monoclonal, mixed monoclonal and polyclonal anti-canine IgE assays have decreased. The complete absence of any IgG cross-reaction in the Fc-epsilon receptor test enables this test to detect IgE in serum down to extremely low concentrations, making it ideally suited for the purpose of allergen selection in an immunotherapy vaccine.

Allergy serology only measures circulating allergen specific IgE, it does not measure other allergic pathways and positive reactions are documented in non-allergic dogs, hence restricting the use of allergy serology to **only** patients with confirmed clinical atopic dermatitis.

Quantitative assessment of serum IgE levels can only be achieved with the IgE specific Fc-epsilon receptor test. A test is considered positive if it is above a certain cut-off level. These positive results are then correlated to

- History of exposure of the patient to the allergen in question.
- Cross reactivity of allergens within botanical groups of related weed, tree or grass pollens.
- Level of IgE if more than 12 allergens positive.

There is still a lack of standardization of the currently employed allergy tests (allergy serology, intradermal skin testing) and it is suspected that false negative and false positive results do occur. Allergy testing is also unable to detect dogs with atopic like dermatitis, which is a condition clinically identical to canine atopy, but in which an IgE response to environmental or other allergens cannot be demonstrated.

Allergen prescription formulation.

Selection of allergens for inclusion in an allergen specific immunotherapy vaccine involves interpretation of the medical records of the particular dog/cat, especially as regards seasonality and animal's habitat (i.e. presence of specific allergens in the animal's environment) in conjunction with IgE levels of individual allergens achieved with allergy serology.

- Non-seasonal – environmental allergens, indoor moulds.
- Seasonal – spring (trees / ectoparasites), summer (grasses / outdoor moulds / ectoparasites), autumn (weeds / outdoor moulds)
- Seasonally non-seasonal – seasonal and non-seasonal allergens involved concurrently. (Seasonal atopy complicating adverse food reaction / Ectoparasites complicating non-seasonal atopy).

Mold extracts should not be mixed in the same vials as pollen extracts, as the pollen allergens will be degraded by the mold proteases during storage. Therefore, mold extracts should be in a separate vial and administered as a separate injection.

Allergen Specific Immunotherapy (ASIT).

Although numerous treatments exist for atopic dermatitis, many have significant side effects and drawbacks and not all are universally effective. Allergen specific immunotherapy (ASIT) is the only proven treatment for atopic dermatitis that works through reversing the underlying immunopathogenesis of the disease with the added advantages of being virtually free of serious adverse effects, even with prolonged use, offering substantial, long-lasting relief in many patients.

ASIT vaccines are available in two forms namely an injectable form given by subcutaneous injection every 2-4 weeks (SCIT) and a sub-lingual immunotherapy (SLIT) vaccine, which is applied orally under the tongue on a daily basis.

ASIT has emerged as an important and useful tool in the long-term management of skin disease in atopic patients. Allergen avoidance, prevention of allergen contact, antimicrobial therapy, pharmacotherapy and / immunotherapy are crucial in the therapeutic management of atopic patients. Pharmacotherapy is frequently needed when a rapid and short-term response is required or when allergen avoidance is difficult or impossible to implement, while ASIT is utilized as a long-term therapy that reduces or eliminates the need for pharmacotherapy.

Mechanisms of action of ASIT demonstrated in humans include early reduction in effective cell (eosinophils, basophils, mast cells) activity, followed by a long-term immunological shift from a T helper 2 (Th2) cell to a T helper 1 (Th1) cell response and the development of immunological tolerance. These changes are accompanied by increases in immune regulator cells and certain cytokines. This all results in an increase in allergen specific IgG (especially IgG4) which impairs the effector functions of IgE and with extended application initiates a decrease in allergen specific IgE.

In canine atopic patients a shift from Th2 to Th1 cell response, increases in immune regulator cells and certain cytokines plus increases in IgG levels, have all been demonstrated and suggests that mechanism of action in dogs is similar to that in humans.

Subcutaneous immunotherapy (SCIT) is available as two methods based on availability and regulatory approvals in North America versus Europe. SCIT vaccines produced in North America are aqueous, saline phenol preserved extracts. The protocol begins with frequent injections of dilute extract, progressing to less frequent injections of concentrated extract as a maintenance therapy. In Europe alum precipitated allergen extracts are utilized, with absorption of the allergen molecules to an aluminum hydroxide adjuvant, which provides a slower release product which has the advantage of less frequent injections.

Time to efficacy with SCIT varies from up to 8 months with aqueous allergens and 9 months with alum-precipitated allergens. Those dogs which have not responded by this time are unlikely to.

These **sublingual immunotherapy (SLIT) vaccines** have an excellent safety record due to the unique nature of antigen capture at this sublingual site. This oral immune site comprises various antigen presenting cells (Langerhans cells, myeloid and plasmacytoid dendritic cells) with a distinct location in the mucosa and sub-epithelial lamina propria. These dendritic cells are tolerogenic being key in the induction of immune tolerance, resulting in induction of peripheral (skin, respiratory tract) tolerance to allergens. The oral mucosa also contains limited numbers of mast cells and eosinophils mainly located in the deep submucosa explaining the good safety profile (lack of adverse reactions) of SLIT.

SLIT shows a far more rapid clinical response with some dogs showing significant improvement in 3 months, while many have substantial improvement by 6 months.

Modifications of the standard SCIT protocol are emerging and include rush immunotherapy and intra-lymphatic immunotherapy.

Rush immunotherapy has the advantage of limiting the number of injections that an owner must apply during the initiation phase of ASIT as maintenance levels are achieved rapidly. Dogs must be hospitalized and increasing doses of allergen extract or injected subcutaneously every 30 minutes for 7 hours. Animals are then discharged and continue on maintenance therapy. Therefore, with rush immunotherapy maintenance doses are achieved within one day compared to weeks or months with conventional immunotherapy.

Intra-lymphatic immunotherapy is a recent modification of ASIT vaccine application, is reported to be associated with fewer and less severe adverse reactions than encountered with SCIT and to be effective for several years after only 3 intra-lymphatic injections. Alum precipitated ASIT vaccines are administered monthly into 1 of the popliteal nodes (alternating sides with each subsequent injection), under ultrasound guidance over 3 to 5 months. The number of intra-lymphatic injections (4 to 6) is based on the clinical improvement of the individual dog. In most instances, no sedation is required. In various studies complete remission was documented in 13% to 24% of dogs.

Trouble shooting allergen specific immunotherapy (ASIT).

Subcutaneous immunotherapy (SCIT).

- Be alert to anaphylactic reactions, most likely during the initial loading phase.
- Monitor for increase in pruritis and flare ups of otitis or pyoderma.
- If pruritis initially decreases after each injection but then slowly increases prior to the next injection, the interval between injections should be decreased.
- If pruritis initially increases after each injection, followed by improvement prior to the next injection, the allergen dose is too high. Decrease the dose by 25%. If pruritis still spikes after injection, reduce dose by a further 25%.

Sublingual immunotherapy (SLIT)

- A few dogs rub or scratch at their mouth following application and individual dogs will vomit. However, these effects are short lived and usually disappear

after a few applications.

- If signs persist or worsen lowering of the allergen dose may be required.
- Monitor for increase in pruritis and flare ups of otitis or pyoderma.

Some highly effective drugs such as cyclosporin and oclacitinib and biologicals (anti-IL-31 therapeutic monoclonal antibody), control clinical signs over a long period of time and may obviate some of the “need” for ASIT. However, these drugs and biologicals still require lifelong treatment and they only reduce clinical signs rather than reversing the pathogenesis of the condition as observed with ASIT. Long-term safety of these agents is not always known, and they carry no hope of permanent cure that can sometimes be achieved with ASIT. Use of these drugs and biologicals in conjunction with ASIT provides a template effective disease control in many instances.

Historically allergen specific immunotherapy has been viewed in general clinical practice as a last resort treatment option. With the growing knowledge of how and when to use ASIT, it has taken its place as a foundation treatment for the long-term management of canine atopic dermatitis.

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