

## **SUBLINGUAL IMMUNOTHERAPY FOR PETS: A GUIDE FOR VETERINARIANS**

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Canine atopic dermatitis (AD) is a common diagnosis in veterinary dermatology, affecting as much as 3-10% of the canine population.<sup>1</sup> Though many treatments currently exist for AD, many have drawbacks and none are universally effective; there is clearly a need for additional therapeutic options. Allergen-specific immunotherapy (ASIT) via subcutaneous injection – “allergy shots” – has efficacy in as many as 70% of treated patients; however, it requires weekly to twice-monthly injections. Owners who find injections difficult to administer, or who are frightened of needles, can be averse to use of this therapy.

Allergen-specific immunotherapy has been used in human beings for over 100 years, supported by well-controlled studies showing its effectiveness with both environmental and venom allergens. ASIT has been used in dogs, cats and horses for over 40 years. Unlike ASIT in people, there are very few randomized, controlled scientific trials available to determine the efficacy, optimal dose and frequency of injections for ASIT in companion animals. Recent reviews and commentary on treatment of AD in animals stress the lack of controlled studies on injection ASIT, yet there exists substantial empirical evidence from open trials that immunotherapy is beneficial for AD in animals.<sup>2,3</sup>

Sublingual immunotherapy (SLIT) or “allergy drops” is a form of ASIT that historically has been favored in Europe more so than in North America. Like injection ASIT, SLIT has been used in humans for over 50 years. A growing body of evidence and research supports the use of SLIT for human allergy, and the World Allergy Organization endorses its use.<sup>4</sup>

The formulation of SLIT treatment sets is different than that of injection ASIT. Allergy “shots” use phenol-saline based allergen extracts as the starting material, whereas SLIT is formulated with glycerin-stabilized extracts prepared in a vehicle that augments uptake through the oral mucosa. In the United States, allergenic extracts for human injection are FDA-registered, and therefore SLIT represents “off-label” use. This is concerning to some physicians, and is a major factor that has limited the use of SLIT for human beings in the USA. The situation is much different in Europe, where many extracts and specific products, even including oral lozenge-type products, are registered for use in SLIT. Some of these products are undergoing regulatory review in the USA for human use, and may be available here in the near future.

Allergenic extracts sold in the USA for veterinary use are licensed by the USDA, much like a vaccine or other biological product. Because registration for veterinary extracts is not via the FDA, the same limitations on “off-label” use do not apply. The prospect of using SLIT treatment in animals represents an exciting and valuable new therapy option for AD in animals.

### **SUBLINGUAL IMMUNOTHERAPY IN HUMANS**

#### *Review of Mechanism*

Over the last several years, a great deal of understanding has been gained on the mechanisms involved in humans, specifically the sublingual route. Sublingual immunotherapy allows specific antigens placed under the tongue to induce immunologic tolerance. Multiple mechanisms are involved and include the production of anti-inflammatory cytokines such as IL-10 and the induction of regulatory T-cells.

The mucosal area under the tongue is a privileged immunologic site with unique characteristics. It consists of a physical barrier with integrated immunologic elements that allow the uptake of antigens while preventing the invasion by pathogens.<sup>5</sup> Local immune cells must constantly differentiate between harmless antigens and harmful pathogens and must tolerate a broad range of food antigens for normal function. There is a high concentration of dendritic cells and T-cells and a low concentration of mast cells, basophils and eosinophils. Dendritic cells present in the oral cavity appear to have unique functional properties as well as differences in cell surface markers compared to other dendritic cells, which may explain part of the difference in response between injection immunotherapy and SLIT.<sup>6</sup> Both immediate and delayed allergic responses at this site are muted, which contrasts with other mucosal surfaces. The oral cavity is a unique, immunologically active area which tolerates foreign antigens and thus is ideal for immunotherapy.

During sublingual immunotherapy, a small portion of the antigen is taken up by dendritic cells in the mucosa. IgE bound to high affinity receptors on dendritic cells facilitates antigen uptake and has the effect of concentrating the antigen 100–1000 fold in sensitized individuals. Dendritic cells partially mature and migrate to the basal lamina where the antigen is presented to T-cells, directly inducing an effector response. Dendritic cells also migrate to regional lymph nodes where they prime naive T-cells and induce regulatory T-cell formation.<sup>7</sup>

Regulatory T-cells modulate Th1 and Th2 responses directly and indirectly through cell-cell contact and by cytokines including IL-10 and TGF- $\beta$ . Very early effects of immunotherapy are related to mast cell and basophil desensitization.<sup>8</sup> Non-specific effects of sublingual immunotherapy may be seen within the first 4 weeks of treatment and are mediated by IL-10 produced by dendritic cells and regulatory T-cells. An important observation from Marogna's study on multiple- versus single-antigen sublingual immunotherapy was that suppression by IL-10 was non-specific; treating a major allergen sensitivity also resulted in some symptomatic benefit even to allergens that were not included in the treatment mixture.<sup>9</sup>

IgG4 induced by immunotherapy is thought to act as blocking antibody to antigens and is associated with immunologic tolerance.<sup>10</sup> Secretory IgA may play a crucial role in the immunologic benefits of sublingual immunotherapy at lower doses where changes in IgG4 and IgE are not seen.<sup>11, 12</sup>

A decrease in end-organ sensitivity, such as to bronchial and nasal provocation, is seen at all ranges of sublingual immunotherapy doses. As treatment progresses, increases in IgA and IgG4 induced by immunotherapy may require an increase in antigen dosing. IgE may be transiently increased during the early phase of sublingual immunotherapy, before the IgE levels eventually decline. With higher doses of immunotherapy, clonal deletion and anergy among reactive T-cells are seen.<sup>13</sup>

Allergen-specific immunotherapy has been shown to sustain disease-modifying effects even after discontinuation of active treatment. IgG4 develops throughout the course of treatment and has shown persistence for an additional year after SLIT (as well as SCIT) has been stopped. IgG antibodies appear protective with ability to block IgE.<sup>14,15</sup>

#### *Review of Evidence for Efficacy*

Efficacy of sublingual immunotherapy depends on antigen choice, frequency, and dose, as a variety of studies over the past several decades indicate. Since 1999, more than 80 double-blind, placebo-controlled studies on SLIT were published in peer-reviewed journals, though most were European. The studies showed SLIT to be safe and effective for adults and children, indicated that SLIT reduced asthma symptoms, sometimes prevented asthma from developing, and showed lasting benefit after treatment was stopped. Research began in the USA in 1995, with Peter Creticos of Johns Hopkins publishing a study on oral immunotherapy for ragweed. In a 1998 position paper, the World Health Organization endorsed SLIT as a "viable alternative to injection therapy." The Allergy Rhinitis and its Impact on Asthma Guidelines (ARIA) endorsement of SLIT followed in 2001.

In 2003, a Cochrane Report panel of experts reviewed 22 "grade A" clinical trials on SLIT involving 979 patients. The experts reviewed six SLIT studies on dust mites, five on grass pollen, five on *Parietaria* (a common European pollen), two on olive pollen and one each on ragweed, cat dander, tree pollen, and cypress pollen. Each study was double-blind and placebo-controlled. The conclusion: for these allergies, SLIT significantly reduced symptoms and need for symptom-relieving medication. Across all trials, SLIT reduced symptoms by 42 percent and reduced medication need by 43 percent. No adverse reactions occurred. SLIT's benefits persisted for at least three years after treatment stopped.

An update to the Cochrane review was completed in 2011. This confirmed the efficacy and safety of SLIT.<sup>16</sup>

A comparative effectiveness review on allergen-specific immunotherapy was prepared by Johns Hopkins University Evidence-based Practice Center,<sup>17</sup> funded by the Agency for Healthcare Research and Quality. It was published in March 2013 ([www.effectivehealthcare.ahrq.gov/allergy-asthma-immunology.cfm](http://www.effectivehealthcare.ahrq.gov/allergy-asthma-immunology.cfm)). Only studies using allergen extracts in the form of drops (not tablets) were included for review: 74 randomized controlled trials (RCTs) on the efficacy and safety of subcutaneous immunotherapy (SCIT), 60 RCTs on the efficacy and safety of sublingual immunotherapy (SLIT) and 8 RCTs on head-to-head comparison between SCIT and SLIT. They concluded there was sufficient evidence to support the effectiveness and safety of both SCIT and SLIT for treating

allergic rhinoconjunctivitis and asthma. There was not enough evidence to determine if either SLIT or SCIT was superior.

Studies on SLIT in human allergic disease have focused mostly on allergic rhinitis and asthma, and less on atopic dermatitis (eczema) – perhaps because historically there has been a feeling among physician allergists that immunotherapy in general is not useful for atopic skin disease. However, several recent studies have re-examined the possibilities for SLIT in human atopic dermatitis and have concluded that it can be clearly effective.<sup>18-21</sup>

## **SUBLINGUAL IMMUNOTHERAPY IN VETERINARY MEDICINE**

### *Evidence for Efficacy*

Studies on SLIT and other non-injection methods of ASIT for use in pets are only just being reported. One early study in an experimental model of canine AD failed to show evidence for efficacy of orally-administered allergen in laboratory beagles experimentally sensitized to dust mite; however in this study the allergen was fed to the dog rather than applied to the mucosa.<sup>22</sup> A further study by the same investigators with allergen extracts applied to the mucosa of experimentally-sensitized laboratory beagles showed only slight clinical response, but significant increases in cytokines such as TGF $\beta$  and IL-10, which are associated with successful therapy.<sup>23</sup> Another small open trial of atopic canine clinical patients with dust mite allergy treated with SLIT reported clinical benefit in 80% of dogs, and that clinical benefit was usually accompanied by measurable immunologic changes, including significant increases in allergen-specific IgG and decreases in allergen-specific IgE.<sup>24,25</sup>

Based on the initial success of these pilot trials, a larger-scale clinical study of SLIT in canine atopic dermatitis was undertaken, and results have been preliminarily reported.<sup>26</sup> This study involved 21 veterinary dermatologists throughout the USA, and used the formulation and dosing schedule equivalent to a current commercial product (Heska Allercept<sup>®</sup> Therapy Drops). Though an uncontrolled open trial, the results provide further evidence of the effectiveness of SLIT in canine AD. In this trial, 59% of 77 dogs with no prior immunotherapy had a “good to excellent” final global assessment rating, while 23% were rated as “fair” and 18% “poor.” These numbers are similar to what has been reported for subcutaneous injection immunotherapy in dogs. Even more encouraging was the fact that, in the same trial, 49% of 47 dogs that had failed injection immunotherapy responded favorably to SLIT. This is consistent with experimental evidence that shows that the mechanism of SLIT is somewhat different than that of injection immunotherapy. SLIT is not just a different route of administration to produce the same effect, it’s actually in some ways a different treatment altogether.

There are many reasons why discrepant results have been reported with non-injection ASIT methods, but central to them may be the same principle that has plagued SLIT research in human beings for decades: different studies use widely differing protocols for dosing, frequency, treatment set vehicle and preparation, etc. These protocol differences are the most obvious explanation for differing results; it makes empirical sense that variations in dosing and formulation of the treatment sets may impact effectiveness. It remains for future trials to determine if one particular SLIT formulation, dose, or administration schedule is superior for control of AD in dogs.

### *Advantages and Disadvantages of SLIT*

One big advantage of SLIT is in ease of administration. We’ve found that though many owners “don’t mind” giving injections to their pets, most owners clearly don’t relish it, and are delighted to be presented with an alternative to giving injections. Most dogs accept administration easily, even viewing it as a treat, which increases compliance. On the other hand, we believe that successful SLIT requires faithful twice-daily administration, and owners with busy travel schedules may find it much more convenient to give an infrequent injection. “Head-shy” dogs may also resist treatment.

In human beings, anaphylactic reactions to SLIT are rare to nonexistent, and SLIT can be used in humans with a prior history of reaction to allergy shots. In our experience, the same is true for dogs; we’ve treated numerous patients with SLIT who have had anaphylactic reactions to allergy shots, with no adverse effect.

Additionally, with some SLIT formulations, one can include mold extracts with pollens in the same vial without fear of losing efficacy of non-mold allergens, and SLIT treatment bottles can be stored at room temperature for a shelf-life of 6 months; refrigeration may not be necessary.

We encourage veterinarians to try SLIT in patients who simply have not improved after a year of allergy shots. We've had remarkable response to SLIT in some of these "shot failures."

#### *Recommended Protocol for SLIT in Dogs with AD: A Practical Guide*

*Testing.* In summary, do what you have always done! Dogs should be evaluated for different sensitivities in exactly the same manner that the individual clinician is comfortable and familiar with for treatment using injection ASIT. Following establishment of a firm clinical diagnosis of AD, any combination of serologic or intradermal testing techniques may be used to establish the individual sensitivities of each patient.

*Prescription Formulation.* Following careful testing, again, principles for choosing the allergens in the prescription mirror those employed for choice of allergens for injection ASIT mixtures, and are completely familiar to every veterinary dermatologist, including:

- History of exposure of the patient to the allergen in question
- Cross-reactivity of allergens, including consideration of botanical groups of related weed, tree, or grass pollens
- Empirical observations on the significance of a particular allergen in relation to others, such as may be suggested by the "score" of serologic or intradermal tests

A few considerations that may be unique to formulating a SLIT prescription include the following:

- SLIT prescriptions in human beings tend to follow a "less is more" principle. There is much greater use of "mixes" of related allergens rather than combining many different individual extracts that are antigenically-related, and use of fewer allergens in the mix rather than a greater number. Consider limiting the number of allergens in your prescription to a maximum of the 10-12 you believe are most important for the patient. Remember, there is substantial documentation in other species that part of the mechanism of SLIT is allergen-specific, *and part is nonspecific.*
- Generally, on the prescription just indicate a list of the relevant allergens; the correct dose of these allergens will be included in the final prescription. Typically the prescriptions do not "double-up" on a particular allergen that is felt to be more "important" than others; all treatment sets are prepared with a uniform and standard dose of relevant allergen.
- If you believe molds or fungi (including *Malassezia*) are important allergens for a patient, it is possible that they can be included in the mixture – there may be no need to give them by separate administration. Check with the specific SLIT supplier for further information.

*Dosing.* As with many injection ASIT protocols, dosing is typically done with a set of three bottles of gradually increasing concentration. For example, dogs start with the "A" (weakest) dilution, using the entire contents of the bottle. Then, the patient is escalated to the "B" (middle) dilution, and then again escalated to the "C" (strongest) dilution, which is the maintenance bottle. Each bottle is used until empty (and will last approximately 10 weeks) before progressing to the next dilution. The volume of allergen dispensed into the oral cavity is always the same, two 'pumps' twice daily, every day. The glycerin imparts a slightly sweet taste which many dogs view as a treat!

*If the patient has a history of prior anaphylactic reaction* to allergy shots, to be cautious we advise considering starting at an even weaker treatment dilution. This may or may not be advisable, depending on the situation. Please contact your supplier's medical consultants for advice on procedures to follow in these situations.

Ideally, the allergen solution should remain in contact with the oral mucosa for as long as possible. Humans are instructed to hold the solution under the tongue for 1 minute before swallowing. Obviously, we cannot request the same of our canine patients, but it is important that the solution is dispensed into the oral cavity, *not in food*, and that the pet refrain from eating or drinking for a short period after the dose is given.

We believe that a key difference with SLIT is this basic principle of treatment: *the allergen must be dosed regularly and frequently.* Multiple (TID) daily administrations are required for efficacy in human beings, and we strongly recommend that owners be counseled to administer the "allergy drops" TWICE DAILY, EVERY DAY. If they forget to give a dose in the morning, give one in the afternoon and one before bed.

This twice-daily dosing schedule is indefinite for the duration of therapy. The schedule does not “taper” to once daily, every other day, etc. Administration continues twice daily for the duration of treatment.

At this time, the ideal total duration of treatment is not known in dogs. In human beings, multiple-times daily administration is continued for a period of 2-5 years. After this time, if the patient is stable, the treatment can be discontinued *and the effect appears to be permanent in nearly all cases*. Whether this is true for a canine patient is yet to be determined.

**Adverse Reactions.** Mostly, these won't occur. From a “clinical experience” standpoint: we've seen a few dogs rub or scratch at their mouth after administration, perhaps analogous to the oral itch that some human SLIT patients experience. Almost always, this will disappear after the first few treatments. Likewise, occasional vomiting has been observed in a few dogs for the first few doses. In a few cases with very sensitive animals, we've seen worsening of clinical signs with SLIT administration – actually causing a flare of the disease. If any of these reactions occur or persist, it may require lowering the allergen dose. Please contact your supplier's medical consulting staff for specific instructions and advice on dealing with these potential reactions.

Information from one supplier (unpublished data, Heska Corporation) in a collection of several thousand dogs treated with SLIT indicated adverse reactions reported in approximately 4% of dogs. The most common reaction was transient worsening of pruritus, occurring in 3.1% of dogs, followed by GI upset in 0.4%. Most reactions occurred upon initial administration of treatment, or else just after escalation to the next-strongest bottle, and most resolved spontaneously after a short period. Reactions graded as “severe” occurred in 0.2% of dogs, and were most often just more severe instances of the above. No deaths have been reported, though one dog had hives and lethargy suggestive of a possible anaphylactic reaction. Thus, in general, SLIT appears to be very safe in dogs, even those with prior reactions to allergy shots.

**Follow-up Evaluations.** As with injection immunotherapy, it is important to re-evaluate patients on SLIT on a regular basis, for example after 3, 6, and 12 months on treatment. Our subjective clinical impression is that response to SLIT often occurs quite rapidly - some dogs are improved at 3 months, and most who will respond show at least some improvement, if not substantial improvement, by 6 months.

#### *In Conclusion*

Sublingual immunotherapy represents a new and potentially effective treatment for many dogs with AD. Client compliance with the regimen is unparalleled and response, though not universal, can be rapid and dramatic. As with all treatments for AD, SLIT is best used as part of a multimodal treatment plan that may also include allergen avoidance where possible, infection control and prevention, skin and coat hygiene, parasite prevention, and use of anti-inflammatory/antipruritic drugs if and when necessary.

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