Allergen-Specific Immunotherapy

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Allergen-specific immunotherapy (ASIT) is the preferred term for what has been called hyposensitization, desensitization, allergen therapy, specific immunotherapy, and immunotherapy. ASIT is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the signs associated with subsequent exposure to the allergen. An allergen is an antigen that favors the development of a hypersensitivity reaction. It usually also involves giving the allergens by an alternate route of exposure, which in dogs is usually the subcutaneous route. Allergen extracts are generally solutions containing proteins from the pollens, molds, epithelia, and insects that cause allergy. Effective ASIT is more economical than many antihistamines and other treatment options, especially in large dogs. Once maintenance therapy is reached, it is usually less labor-intensive than oral and topical treatments. The greatest disadvantages are the need for subcutaneous administration and that it is not a cookbook or static therapy. Clinicians must learn to manage and make changes to optimize efficacy. Failure to understand ASIT and how to modify it lead to frustration, and clinicians may abandon this effective and valuable treatment method.

Efficacy

ASIT is considered to be efficacious and is recommended for control of chronic atopic dermatitis (AD) in dogs. It has also been recommended for seasonal disease when other anti-inflammatory therapies are ineffective or associated with side effects. It has been reported to be the only therapy that may cure canine AD and modify development of further allergies, although the data were from retrospective surveys. Some state that 10% may be cured. A blinded, placebo-controlled study demonstrated ASIT is effective in dogs. This study showed greater than 50% improvement in 59% of the allergen-treated dogs and only 21% of placebo treated dogs. An open study that evaluated venom immunotherapy with end-point titration and results when dogs were again stung by hymenoptera showed ASIT to be effective for preventing hymenoptera-induced anaphylaxis. Numerous open studies have demonstrated similar results, with most showing good to excellent results in about 60% (50%-80%) of the study population. Some studies have shown lower percentages and others have reported higher percentages, over 90%, when ASIT protocols are adjusted based on patient response. When combined with other nonsteroidal treatments, it has been stated that over 75% of atopic dogs having ASIT treatments can avoid systemic glucocorticoids.

Mechanism of action

Numerous changes reported in humoral and cellular tests in humans treated with allergen immunotherapy may contribute to its efficacy. These have been extensively reviewed; however, studies in dogs demonstrating in vitro changes associated with efficacy are limited. The study on hymenoptera ASIT showed a decrease in intradermal sensitivity, as determined by end-point titration, associated with a favorable response. Another study in dogs successfully treated with ASIT demonstrated an increase in interferon gamma and a shift to a Th1 cytokine profile based on the interferon gamma/IL4 ratio, but not due to a lowering of IL4. The level of IgG1 also increases after 6 months of ASIT therapy in treated dogs compared with non-treated atopic dogs and compared with healthy dogs on good parasite control. One study correlated clinical response in dogs on ASIT with increases in T reg lymphocytes as well as increases in IL 10, which have recently been considered the most consistent change in responsive humans.

Factors affecting efficacy

Although we do know that ASIT is effective, we do not know the optimum way to hyposensitize or how to maximize efficacy. In humans, there has been some work in humans but the typical protocols are very different from what is routinely done in veterinary medicine. Most studies have been with mono or limited allergen therapy, and in these types of protocols it has generally been shown that the response is allergen specific and that mid to high-dose therapy is more effective than low-dose therapy. In contrast, mixed therapies are routinely used in dogs and dose is controversial. This evidence supports that mixes may be preferred, although the optimum mix is unknown.

It is also important to choose allergens for ASIT to which the pet is sensitive as well as those that are likely to be in the pet's environment. There has been no work to evaluate this recommendation. A study comparing a standard treatment with a treatment based on targeting positive reactions only showed a significantly better response in the specific treated group. Results in the standard groups were similar to those of the placebo groups in another study by the same authors (Willemse 94), although comparing what is picked from the positive reactions has never been evaluated. It is difficult to determine what is logical if we factor in cross-reactivity, threshold, and summation. There are also no data regarding how frequently allergen injections should be given. In both human and veterinary medicine, the goal appears to be to inject at intervals as wide as possible, or at least to strive for monthly injections. This may have evolved strictly for convenience and compliance issues, but is it the most effective method? Another issue that is considered potentially important with allergen mixture is the effect mixing may have on other allergens. This has been a concern with mold allergens. In fact, in human medicine where mixes are used most often they do not include mold allergens because the proteases in

molds inhibit the effects of other allergens (Nelson et al 2009, Esch 2006). The optimum number of allergens needed to hyposensitize an animal is not really known; by convention, most protocols are limited to 10 to 12 allergens in a formula. However, a report indicates that hyposensitizing with more allergens (11 to 20) in allergic dogs with more than 10 positive reactions increases the response rate, although another report indicated that dogs with 2 to 10 allergens did better than dogs with 11 to 20, and yet in an another report it made no difference. Anecdotal reports and two retrospective studies have suggested that dogs that are allergic to mold may have a suboptimum response to ASIT.

The effects of age, breed, severity, and types of allergy may affect the response to ASIT. Most studies are too small to show which factors play a statistically significant role in their effects on allergy. One study indicated dogs older than 5 years of age or who have had signs for more than 3 years before ASIT was instituted had a significantly poorer response to therapy. Another report showed no relation to age but that dogs who have had over 61 months of signs had a poorer response. Another report indicated that West Highland white terriers and boxers have a poorer response. Since most studies have few breeds with large enough numbers in them to adequately evaluate breed predispositions, clinical impressions are often all we have on which to base our recommendations. My experience suggests that not only West Highland white terriers, but Cairn and Yorkshire terriers as well as bichon frise may be poor-responding breeds. In contrast, St. Bernards, golden retrievers, and Chinese Shar-Peis may respond well.

The most important factor in obtaining the best possible results with ASIT is case management. Over 70% of the cases I manage do not follow the standard protocol, and most protocols need to be altered within the first 4 months. In one report, 48% of dogs entered into an ASIT protocol were withdrawn in the first 6 months and only 2% of the withdrawals were due to persistent adverse reactions. Of the dogs that remained on therapy for more than 6 months, 50% had their treatment changed from the standard protocol. More impressively, the response rate was excellent in 96% of the modified cases and excellent in 77% of dogs that followed the standard protocol. This study demonstrates how close monitoring and adjusting therapy for each case can affect results.

Administration, training, and adverse reactions

It is easiest to have clients give ASIT at home by subcutaneous injection. Despite some reluctance on the part of veterinarians as well as owners, this method is easier for most clients and is readily tolerated by most dogs and cats. Because injections are usually initially given every other day and then eventually every 7 to 30 days, this regimen is certainly less demanding than treatment of a diabetic pet. The different vials are shown and explained to the client, who is then taught how to accurately draw up the appropriate amount of antigen solution. One-ml syringes with 27-gauge needles are used to inject into a pocket of subcutaneous tissue formed by raising and folding the skin. This technique and the small needle size make aspiration to determine whether the needle is in a blood vessel unnecessary because it is very unlikely that a vein in the pocket will be hit, and drawing back on the plunger with a needle this size does not readily show any blood unless a larger vein is penetrated. The technique I prefer is to lift the skin with the thumb and second finger and then use the first finger to indent the fold of skin into the shape of a Y or V. The needle is inserted parallel or up to 30-degree angle from the plane of the back or neck. The needle is inserted rapidly, and the solution is injected by pressing the plunger. Caution owners about putting pressure on the plunger until the needle is located subcutaneously. This is sometimes easier by having them hold the syringe like a dart and only touching the plunger after the needle is inserted through the skin. Also, they need to insert the needle directly into the center of the pocket because an angled direction may pierce the entire fold of skin and result in injecting the solution outside the skin.

Many clients are initially concerned and should practice this with a technician or veterinarian present. Techniques to alleviate unwanted pet reactions include drawing the solution up into the syringe then letting the solution come to room temperature before injection, and training the pet that receiving the injection is good. This is especially helpful when owners are concerned and nervous about giving the injections, because the dog may sense this apprehension. Training is accomplished by daily taking the hyposensitization formula out of the refrigerator, acting as if the solution is drawn up, positioning the dog and making a fold of skin, touching the fold with a covered needle, and then giving a reward. The actual injection is only given every other day. Many dogs can be trained to happily anticipate receiving the injection instead of hiding when the refrigerator is opened. For some dogs, it is best to give treats or rewards only after the dog has sat still for a practice shot one to multiple times a day. An excellent reference for owners and veterinarians on instructions and technique is available.

Clients must also be educated about what they need to watch for. The client should be around and able to observe the pet for at least the first 30 minutes and preferably for 1 hour after the injection. Any reactions should be noted and communicated to the veterinarian. Reactions that require contacting the veterinarian immediately include hives, facial swelling, vomiting, diarrhea, weakness, or collapse. The last three may be signs of anaphylaxis, a potentially life-threatening situation. However, anaphylaxis was only seen in 1 of 185 ASIT dogs in one study. In another study using alum precipitated allergens, 18.5% had adverse effects, of which 7.4% was urticaria or angioedema, although none had anaphylaxis. In humans, risk for a serious reaction requiring hospitalization is 8.4% with hymenoptera venom immunotherapy. If clients are aware of this, they may be more concerned than necessary. It is also helpful to point out that the anaphylaxis target organ in humans is the respiratory tract whereas in dogs it is the gastrointestinal tract, and this difference changes the life-threatening nature of severe reactions. In dogs, anecdotally there will be less severe reactions in

the shots preceding the development of anaphylaxis. Rosser reported adverse reactions as early as 6 days after the start of therapy or as late as day 142. I have seen reactions but not anaphylaxis even with the first injection.

Milder allergic reactions that should be reported to the veterinarian before injections are continued are increased itching, listlessness, sleepiness, and anxiousness. Pain or swelling at the injection site is infrequent and minimal if shots are done correctly and animals are trained to accept the shot as a reward situation. Intradermal injections are a cause for some of these reactions. In rare cases, after many injections some animals develop subcutaneous or dermal swelling, and in these cases using different injection sites may alleviate the problem. Other reactions that have been anecdotally reported include panting, hyperactivity, increased bowel sounds, changes in urinary habits, and frequent swallowing. Most reactions occur relatively rapidly after injection, but changes in activity and pruritus may occur 1 or 2 days later. Dogs should be observed for patterns of pruritus in relation to when shots are given, as this is often the basis for adjusting the treatment protocol. It is helpful to have client's grade and note locations of pruritus. Grading from 1 (no pruritus) to 10 (most severe pruritus for this dog prior to ASIT) should be done before therapy is started and as frequently as possible during the first few months of therapy. Some clients will keep a diary, which may be very helpful in determining allergen adjustments.

Protocols

ASIT is based on giving the allergens to which the pet is allergic in a controlled manner. The allergens are available as a sterile liquid that is an extract of the allergenic material and contains protein. The actual allergen is part of this protein, and the volume of allergen in the solution is therefore related to the amount of protein in the liquid extract. Most commonly in the United States, the protein content is expressed as protein nitrogen units with higher numbers supposedly equated with more allergen protein in the solution. Weight to volume is another common method of reporting the level of protein. ASIT therapy begins by injecting the most dilute or lowest-protein concentration allergens first, then gradually increasing the volume of injections, followed by an increase in the concentration of protein until a maintenance dose is reached. The maintenance dose is usually reached by following an injection protocol. Many protocols will have the initial injections given frequently, such as every other day to weekly, then as the maintenance dose is reached the intervals between injections become longer, such as every 10 to 30 days. Companies that supply allergens will supply an ASIT treatment protocol. Numerous protocols for ASIT are used. The schedules should emphasize what clients should watch for and remind them of recheck evaluations (Table 1). For dogs, I use different protocols, one for large dogs (Table 2) and modified versions for small dogs (under 20 pounds), and cats. Regardless of the protocol, the important thing to remember is it is just a starting point and adjustments may, and often should, be made based on the pet's response.

Table 1. Information included on all protocols

Grade itch on a scale of 0 (none) to 10 (severe itch)

- Baseline should be determined when no infections or fleas are present
- Call in 4 weeks and report grade of itching
- Call if itch increases by more than 2 levels
- Call before giving any further injections if adverse reactions occur
    - Vomiting, diarrhea, anxiousness, and weakness are possible reactions
    - Reactions will usually occur within 1 to 2 hours after injection
- Recheck appointments should be made around day 60 and day 120
- Watch for pattern of itching in relation to the injection
    - Itch increases before or after the injection
    - Itch decreases after injection

Table 2. ASIT schedule for dogs 20 pounds and over

Day	Date/Itch	Volume (ml)	
Vial 1			
1			0.1
3			0.2
5			0.3
7			0.4
9			0.6
11			0.8
13			1.0
Vial 2			
15			0.2
17			0.3
19			0.4
21			0.6
23			0.8
25			1.0
10-day interval			
35			1.0
45			1.0
55			1.0
14-day interval			
69			1.0
83			1.0
97			1.0
111			1.0

Reasons for adjusting allergen therapy

Reasons to adjust ASIT vary but are related primarily to improving efficacy or decreasing adverse reactions, with improving efficacy being the most common reason for adjustment in my practice. There are two main scenarios in which attempts to improve efficacy are the basis for adjustments. The first is the recognition of only a temporary decrease in pruritus, whereby the pet improves after an injection but the improvement is not maintained until the next scheduled injection. In other cases, the pet improves when it is on the low dose or frequent injections but then the signs worsen as the intervals between shots or the volume of protein is increased. The second is when the pet shows no positive response to therapy.

Reactions indicating that adjustments are needed usually occur in the first month of therapy, and alternative treatments that may obscure observations of the response to ASIT should be avoided during this time. Most papers suggest that ASIT is a slow process, and as a result many dermatologists routinely use glucocorticoids or other therapies in the first month of ASIT to control the allergies. Unfortunately, these therapies make it difficult to determine the pet's response to ASIT and the subsequent need for any adjustments. For this reason, my preference is to avoid glucocorticoids during the induction phase of ASIT unless they are absolutely necessary. Antibiotics, yeast therapy, and shampoos are often used and can provide adequate control to preclude the need for systemic glucocorticoids. In severe cases, glucocorticoids or cyclosporine can be used for short periods and are discontinued during the ASIT induction phase so the response and reactions to therapy can be accurately gauged.

Adverse reactions are the next most common reason to adjust immunotherapy. The most common adverse reaction leading to adjustments are increased pruritus following an ASIT injection or worsening of signs after ASIT is initiated. However, any adverse reaction is a reason to adjust ASIT protocol by first reducing the volume. If volume reduction is not effective, then reducing the concentration of the allergen should be tried next. If a pet has a suspected reaction it is suggested that the owners bring the pet to the clinic for a repeated injection with veterinary observation to determine whether it is a true reaction or an ongoing phase of the pet’s AD. Cases should be examined prior to their antigen injection and kept for several hours and watched closely throughout the day for any signs of antigen reactions.

Less common reasons to adjust ASIT are client preferences for intervals or volume of injected material, or patient behavioral responses.

Basic rules on volume and interval adjustments

There is generally a relationship between volume of allergen injected and frequency of injections. My rule of thumb for injections is to try to keep your volume of allergen between 0.05 - 0.1 ml per day. For example if the initial injection frequency is between 10 and 20 days, then I will keep the dose at 1.0 ml (range of 0.05 – 0.1ml/d), unless injection-volume-related reactions occur. If reactions occur after the injection then less than 1 ml should be given, ie try 0.7ml. Dogs that receive shots every 5 days usually get 0.5 ml (0.1ml/d) or less, and dogs receiving shots at 7 day intervals get a maximum injection of 0.7 ml (0.1ml/d). I occasionally exceed this dose, but I build up to it and never start at that level. Reasons to try higher doses are to increase efficacy. Ultimately I try to achieve a maintenance dose of about 0.05 ml/day, and most dogs end up from 0.03 ml to 0.1 ml per day. In cases where antigens are not working or when the antigen injection does not last the full interval between injections, volume adjustments are correlated with reduce injection intervals. For example a dog on 1 ml every 14 days who starts to have symptoms after 8 days, may control with an adjustment of 0.5ml every 7 days.

By knowing the volume of antigen use on a per month basis the long-term cost of ASIT therapy can be calculated. On average a range of 1 to 3 ml per month is used. Thus, the cost of ASIT is whatever you charge per ml times the number of ml per month, plus the cost for syringes and a syringe disposal box per year. When the pet has an excellent response with total control then this cost plus the cost of one recheck per year is what the owners will spend on controlling their pet's atopic disease.

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