



UNIVERSITY OF CALGARY FACULTY OF VETERINARY MEDICINE

This review accompanies the relevant episode of the Cutting Edge veterinary podcast. In each episode of this podcast, 3rd year students in the University of Calgary's veterinary medicine program fill you in on the most up-to-date literature and evidence-based practices on topics that matter to you, the practising veterinarian.

Immunotherapy as an Alternate Long-Term Solution for Pets with Allergies

STUDENT: Ciara Milicevic

FACULTY MENTOR: Dr. Johnathan Canton

EXTERNAL MENTOR: Dr. Becky Valentine

Introduction:

In this review I will be discussing immunotherapy as a long-term solution for pets with allergies. Before we get into immunotherapy, I'd like to touch on environmental allergies. More specifically, I'd like to talk about atopy or atopic dermatitis. Who gets it, what is it, and how?

Atopic dermatitis:

Both canines and felines are affected by atopic dermatitis (AD). I have listed the numerous breeds that are predisposed to developing AD among both species, however it is important to note that any dog or cat of any breed can be allergic. Typically, the age of onset is anywhere between 6 months and 3 years of age.

Atopic dermatitis (AD) is a genetically predisposed, chronic inflammatory skin disease. It involves the patient having abnormal skin barrier function and cutaneous inflammation, developing secondary staphylococcal and Malassezia skin/ear infections, and characteristic clinical features commonly associated with IgE antibodies to environmental allergies. The clinical features of AD include: the presence of pruritus and associated skin lesion that have a characteristic distribution. In particular, we see lesions around the mouth, eyes, ears, flexor aspect of the elbow, carpal and tarsal joints, digits and interdigital skin, ventral abdomen, perineum, and ventral aspect of the proximal tail. These clinical features can be seasonal, non-seasonal (most commonly), or nonseasonal with seasonal exacerbation. Additionally, AD is relentlessly progressive.

A healthy skin barrier will keep the skin hydrated and prevent skin penetration by allergenic and microbial proteins. With a disrupted skin barrier, as we see in cases of AD, it allows allergens, irritants, and other triggers to penetrate the skin and activate an immune response. The

pathogenesis of AD is complex and not fully understood, however there is likely a defective skin barrier that is allowing microbial adherence and penetration of allergenic proteins, which initiates an abnormal inflammatory and allergic response. The acute itching and inflammation we see in AD is associated with cytokines produced by Th2 lymphocytes, such as IL-4, IL-5, IL-10, IL-13, and IL-31.

No diagnostic test exists for this disease, therefore atopic dermatitis is a **diagnosis of exclusion**, meaning that clinicians will need to rule out the other main causes of pruritus before diagnosing a patient with AD. The other main causes include parasitic infections, pyoderma or yeast infections, and food allergies. Signalment is important for factors such as age of onset and breed of the patient, as these can raise our index of suspicion for AD if the patient is predisposed. However, although AD is heritable, there is also interaction with environmental factors at play. Such as: allergen exposure, pollutants, and urban vs. rural lifestyle. For this reason, history is incredibly important. When did the onset of itch occur? What is the lifestyle of the pet like? Are the allergies seasonal? What medications have/are being tried and what was the response? These are all critical pieces of information that can help a veterinarian conclude a diagnosis. As for clinical signs, itching is the most typical sign. When the pet scratches, it can lead to secondary signs of wounds, scabbing, skin and ear infections, hair loss, and scaling. Other signs include licking or chewing the paws and rubbing the face and eyes.

Current treatment options:

Here are some of the current medications used to manage AD. They have been developed to target cytokines that drive pruritus and inflammation in dogs with a allergic dermatitis, including AD. Glucocorticoids are very effective and cheap, however it is only meant to be used for short term and seasonal use. This is due to the side effects of steroids: PUPD, polyphagia, hyperadrenocorticism, obesity, muscle atrophy, and behavioural changes just to name a few. Cyclosporin is also very effective for treatment, but it has a slower onset of action and is more expensive than glucocorticoids. That being said, it is safe for long term use, unlike glucocorticoids. As for adverse effects, we can see things like vomiting, diarrhea, anorexia, weight loss, hypertrichosis, cutaneous papillomatosis, and gingival hyperplasia. Oclacitinib (Apoquel) is fast acting, has a high safety profile, and is also more expensive than glucocorticoids. As for adverse effects, these are uncommon, but we can see anorexia, vomiting, and diarrhea. Finally, Lokivetmab (cytopoint) is fast acting, safe for long term use, and is more expensive than glucocorticoids. As for adverse effects, we can see signs like sleepiness, vomiting, diarrhea, and pain at the injection site. It is important to note however, that no one treatment, including newer pharmacological interventions, has 100% efficacy in canine cases of atopic dermatitis.

Allergen-Specific Immunotherapy (ASIT):

In 1941, Fred Wittich was the first to publish a report of using ASIT for the successful treatment of allergies in a dog. So, what is ASIT? Currently, it is the only therapeutic option that has the

ability to reduce clinical signs of AD and potentially prevent progression of disease by modifying or reversing its pathogenesis.

So, how does ASIT work? First, allergy tests must be conducted on the patient to identify offending allergens. This is done either through intradermal allergy testing or IgE serological testing. Once these allergens are identified, they can be formulated into ASIT as either an injectable form (SCIT) or allergy drops (SLIT). Then, ASIT is administered to the patient with increasing volume and concentration of the allergens over a few weeks to months, depending on the protocol. In doing this, we train the immune system by introducing a microdose of allergens into the body, and over time the immune system learns to not have an exacerbated or inappropriate inflammatory response to them. I know you might be thinking, but why should we use ASIT if we have highly effective drugs? Well, while those drugs control clinical signs very well over long periods of time, they are still treatments that require lifetime administration. They also reduce clinical signs, but they do not reverse the pathogenesis as ASIT has the potential to do.

Pros and Cons of ASIT:

In 2020, there was a survey conducted in the US that determined the perceived barriers and motivating factors of veterinarians for specialty referral and ASIT recommendation. 70% of veterinarians in the study said they were likely to recommend ASIT to their clients for the following reasons:

1. A strong desire to avoid complications associated with pharmacological management of AD, which includes risk of adverse drug reactions and recurrent pyoderma with antibiotic resistance.
2. Even with medications on board, many veterinarians in this study believe that AD still had a negative impact on the quality of life for their patients and clients. The constant scratching and secondary infections associated with AD can greatly strain the bond between affected animals and their owners, sometimes to the point where these animals may be relinquished to shelters or euthanized.
3. Lastly, many vets said they were likely to recommend ASIT as it had a high safety profile and carried the potential to modify the course of disease.

While 70% of veterinarians in the study said they were likely to recommend ASIT, this still leaves 30% who said they were unlikely to recommend it. Why is that? Let's take a look at some concerns veterinarians have attributed to this. The biggest concern, by far, was cost. Allergy testing and ASIT formulation can be pricey. Another concern regarded the efficacy of ASIT. Some veterinarians stated that they believed ASIT was rarely able to reduce concomitant therapy. Lastly, some vets voiced that their clients had concerns about having to give injections. All very fair concerns – but let's break them down.

As for cost, several studies have demonstrated that cost may not have to be the deciding factor in a client's decision to pursue ASIT. With pharmacological management of AD, these are lifelong costs. Not only including the price of medications themselves, but also necessary

laboratory work for drug monitoring, and potential adverse events that may arise which need to be medically managed and paid for. As for efficacy, there was a study conducted in 2020 where 109 dogs went through a 12-month course of ASIT treatment. Of those 109 dogs, 87% experienced a significant drug sparing effect and 52% of that group required no concurrent medications after their course of ASIT. This is just one study, but there are numerous studies that echo the same results. Lastly, regarding administration concerns, this is quite simple to address! If clients are uncomfortable with doing the injections, ASIT can be formulated as allergy drops. So, no injections need to be given! But rather, they would have to give oral drops, 1-2 times per day.

Many studies have accredited ASIT failure to owner compliance. On average, when treating AD with ASIT, we see clinical improvement within 3-9 months. However, very commonly, it can take up to a year to see improvement. Therefore, many owners will discontinue ASIT before the 12 months is up. To me, this is understandable – clients are giving an expensive treatment for months and months and not seeing improvement, and their pets are still itchy. In addition, their pets can experience side effects like anxiety or hyperactivity. With all that combined, it's not hard to understand why many owners will discontinue.

How to Optimize ASIT Treatment:

When dealing with AD, it is best to avoid repeated, intermittent polypharmacy without a diagnosis. This can result in chronic inflammation of the skin, antimicrobial resistant infections, as well as owner fatigue and financial exhaustion. If you're unsure, refer! Along the same lines, ASIT has historically been viewed as a "last resort" after all other efforts have been exhausted. By the time the patient is finally referred for evaluation for immunotherapy, the patient is often chronic, and unremitting disease is challenging for any treatment. Instead, ASIT should be an early choice for AD as modifying the clinical signs and course of disease over a patient's lifetime should be a primary goal. Referral may be ideal for young, affected animals (1-2 years old) and have non-seasonal, moderate to severe allergies. As I previously mentioned, severe environmental allergies can negatively affect the QoL of both clients and patients. Knowing this, it is extremely important that clinicians make sure their client does not feel alone. Once they feel alone, that's when we start to see these owners pull out of treatment. To combat this, frequent communication with the client by all veterinary staff and appropriate owner education are crucial for successful disease control. And appropriate owner education starts with our wonderful clinicians. And finally, we want to make sure our patients are not uncomfortable during treatment. When beginning ASIT, it is important to utilize concomitant and adjunctive therapies to keep the patient comfortable while ASIT takes time to work. For instance, using apoquel or cytopoint can help calm the "cytokine storm" caused by active disease, thus allowing ASIT to work more effectively. The key to a successful long-term outcome is combining treatments to maximize benefits and minimize adverse effects.

The Future of ASIT:

What is in store for the future of ASIT? I wanted to include this because during my research, I found this study that was pretty interesting. In 2016, there was a small pilot study conducted. It was a double-blind, placebo-controlled, randomized clinical trial that tested the efficacy of food allergen-specific sublingual immunotherapy (FA-SLIT) in patients with adverse food reactions. All subjects in the study experienced up to a 20% reduction in pruritus and anywhere from a 40-80% improvement in clinical lesions. While more research needs to be done to collect data on best protocols and optimizing pruritic relief and improvement in clinical lesions, it's things like this that make me really excited for the future of ASIT and veterinary dermatology.

Conclusion:

To finish off, we'll do a quick recap. Environmental allergies affect a significant number of pets. The number of pets affected each year is only expected to increase, as that has been the trend for decades. There is no perfect treatment for environmental allergies and AD. ASIT is a very effective treatment with a high safety profile, that has the potential to modify disease outcomes. As for our veterinarians, there is a responsibility to remain well informed about environmental allergies and ASIT, so that we are able to impart realistic expectations to clients about ASIT and to know when to recommend ASIT to patients. And lastly, if you aren't sure – refer!

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