

# Cytopoint, Apoquel, and Atopica, Oh My! How Do We Decide Which Systemic Drugs to Use?

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Mollie Mesman, DVM, DACVD  
Greenville, SC, USA

\*\*\*This set of notes is not a comprehensive dermatologic drug review but does provide pertinent information as it applies to allergic itch treatment. The clinician is advised to consult his or her preferred drug manual for complete drug details.

## **Allergen-specific immunotherapy**

Allergen-specific immunotherapy (ASIT) is a foundation treatment for canine atopic dermatitis. There are few studies that have documented its effectiveness in dogs (likely due to the cost and time requirement for performing controlled studies for a complex disease that may take a year or more to help). Still, ASIT is the only current treatment for allergies that can partially modify, or reverse, the pathogenesis of the condition, reduce clinical signs, and prevent progression of the disease.

Conventional ASIT approaches consist of either subcutaneous or sublingual administration. Other routes that are less commonly used but may be promising include intralymphatic and transdermal administration (Allibre TVIT transdermal immunotherapy).

There are many positives to communicate to owners regarding the use of ASIT including: minimal adverse effects, lack of long-term effects that may accompany the use of a lifetime of allergy medications, and the potential for long-lasting effectiveness. A quality of life (QoL) study from 2023 showed that the QoL of dogs treated with ASIT and their owners seemed to improve significantly compared to dogs that are not treated with ASIT.

Based on the available studies, the response rates of canine ASIT (typically quoted as percentage of dogs that experience at least 50% improvement in clinical signs) are quoted as 60-70% (with many dermatologists experiencing even greater efficacy).

The mechanisms of action for canine ASIT have not been fully elucidated although it is suspected that they parallel those for humans: early reduction in effector cell activity (eosinophils, basophils, mast cells) followed by a long-term immunologic shift from a T helper 2 (Th2) cell to a T helper 1 (Th1) cell response and development of immunological tolerance. Additionally, there is an increase in regulatory T cells and increase in certain cytokines such as IL-10. This leads to an increase in IgG (especially IgG4) and with extended treatment a decrease in IgE (the “allergy immunoglobulin”). The end result is immune tolerance. With sublingual administration, at least in humans, there are additional effects by oral dendritic cells, which are the key cells in oral tolerance.

ASIT protocols for dogs [and cats] lack standardization and are subject to significant variation. Different allergen dosage regimes with different allergen compositions and potencies are used. Research supports that immunotherapy is more effective when managed by a veterinary dermatologist, and this is likely due to advanced knowledge of pollination periods, dosage

regimens and modifications, better compliance by owners, and reliable systems for refilling immunotherapy (most general practices have been found to have a large percentage of new immunotherapy sets that are never refilled which means these pets are never making it to a full year).

Rush immunotherapy is the process of administering increasing doses of immunotherapy over the course of 4-8 hours while being monitored for reactions in the clinic. One specific rush administration schedule has been examined in dogs and found to be equally effective to a conventional injection protocol. The benefit of rush immunotherapy is better owner compliance, potentially faster improvement, and likely better tolerance by the pet given that the pet goes home on the weekly or biweekly dose of immunotherapy (bypassing the induction phase).

Despite the fact that ASIT may be costly and take a year or longer to become effective, it should still hold an important place in the allergy therapy “tool box.” Unfortunately, it is often looked at as a “last resort,” but it should be viewed as a foundational and early treatment for patients that can may reverse the pathogenesis of disease and potentially provide a cure for allergies rather than only masking the clinical signs. It is important to note that, while we do have several newer allergy medications that are highly effective, these drugs may not work long-term for chronic allergies and they unfortunately allow the disease to progress over time.

### **Antihistamines**

Strong anecdotal evidence supports that antihistamines do have some effect (perhaps 20% of pets experience improvement), either as a monotherapy or as an allergy drug-sparing agent. Limited studies support the efficacy of one antihistamine over another in veterinary patients.

I highly recommend at least starting with antihistamines in mildly pruritic patients. I do not recommend jumping immediately to a stronger allergy medication. I also find that antihistamines can be helpful in patients once their allergies are better controlled and when used in a multimodal approach.

I typically recommend choosing an antihistamine based on cost, convenience of administration, and availability of milligram size (some antihistamines are not possible in smaller pets, like fexofenadine [Allegra]).

If after 14 days there is minimal to no improvement, prescribe another antihistamine until each of the antihistamines has been tried for 14 days or an effective one has been found.

### **Steroids**

Historically, prior to the emergence of our newer allergy drugs, steroids were the most widely used and abused drugs in veterinary medicine, especially in reference to management of chronic allergy disease.

The pharmacology of steroids is complex. These agents affect almost all body systems. Metabolically, steroids promote protein catabolism, gluconeogenesis, glycogenesis, lipolysis, and decrease peripheral glucose utilization.

\*\*\* Steroids are not a diagnostic test for allergic disease. Glucocorticoids suppress inflammation and pruritus and therefore improve the clinical signs of many dermatologic conditions. Because of this broad anti-inflammatory effect, a positive response to steroids does not confirm an allergic etiology.

A common misconception is that if a dog improves with steroid therapy, the condition cannot be a food allergy. This is incorrect. Adverse food reactions can be steroid responsive, and improvement following glucocorticoid administration does not rule out food allergy.

Steroid response should therefore never be used as a diagnostic tool when evaluating pruritic dogs. Accurate diagnosis of allergic disease requires a systematic approach that includes ruling out parasites and infections, implementing appropriate flea control, and performing a strict elimination diet trial when food allergy is suspected.

### **Dermatology pearls:**

1. Steroids are incredibly helpful for inflamed and/or stenotic ear canals. If you have an inflamed ear, if the dog is healthy otherwise, use high end anti-inflammatory dosing (at least 1 mg/kg/day) x 14 days then recheck the ear. There is no medication that will open an ear canal like steroids will.
2. If prednisone causes intolerable side effects, try methylprednisolone.
3. If one steroid does not work well, especially for cats, consider a different steroid like dexamethasone or methylprednisolone.
4. Consider using dexamethasone sodium phosphate (DexSP) (\*use 3 mg dexamethasone/mL as the concentration when calculating\*) orally for cats at 0.2 mg/kg PO SID and then tapering down from there. The volume is significantly smaller than prednisolone 15 mg/5 mL solution and cats seem to better appreciate this.

### **Oclacitinib (Apoquel®)**

Apoquel is an anti-itch medication with some anti-inflammatory properties. The drug mitigates the clinical effects of canine atopic dermatitis through its action on the signaling pathways of Janus kinase 1 (JAK1) enzymes, which modify production of several interleukins, including IL-2, IL-6, IL-4, IL-13, and IL-31.

Dogs must be >1 year of age to use. Zoetis does not recommend the usage of Apoquel in cats. There are studies demonstrating safety in cats, however the drug is not reliably effective in cats, requires a higher dosage, and can lead to severe adverse effects.

Apoquel is not labeled for use with other drugs, though there is a study demonstrating the safety of concomitant use with cyclosporine for 3 weeks. This is a nice option to use together (off label) when you are changing over to cyclosporine and are waiting for it to take effect. Another study shows a better effect of Apoquel when a short course of steroid is used as Apoquel is started.

\*\*\*If you find that combination therapy is required or that long-term twice-daily dosing of oclacitinib is necessary to control pruritus, it is important to recognize that an underlying issue may not have been fully identified or addressed. While these medications can be highly effective at controlling itch, they should not be relied upon to mask unresolved disease. In these situations,

further diagnostic investigation is warranted, and consultation or referral to a veterinary dermatologist should be strongly considered to help identify the underlying trigger and develop a more targeted long-term management plan.

There is no definitive recommendation for blood work monitoring for Apoquel. I typically recommend baseline CBC/chemistry panel to monitor overall health, and then I will monitor blood work in 1-3 months and then every 12 months thereafter.

Apoquel should not be used in the face of neoplasia or papillomas. If I diagnose neoplasia during Apoquel usage, I am typically changing therapies. Cytopoint may be a good option.

Remember that Apoquel is not a completely benign medication. Secondary infections, *Demodex*, increased ALT and ALP, azotemia with resolution after d/c drug, anemia, leukopenia, increased creatinine, histiocytoma, polyphagia, weight gain, bronchopneumonia, aggression, seizures, occult UTI, and papillomas have been reported.

Apoquel is an excellent option in dogs over 1 year of age with acute pruritus. The goal is ideally to not use Apoquel (or any drug) long-term for allergies but we know realistically a medication is often needed. New uses for Apoquel (literature review): Perianal fistulae, sebaceous adenitis (along with low dose prednisolone), pemphigus foliaceus, ischemic dermatopathy, hyperkeratotic erythema multiforme, cutaneous epitheliotropic T-cell lymphoma, ear tip ulcerative dermatitis; the list is growing!

Remember that at least 20% of dogs do not respond to Apoquel.

If Apoquel appears to “stop working,” check for infections, scrape for *Demodex*, check for fleas/flea dirt, and consider the possibility of disease progression rather than decreased efficacy of the drug.

### **Ilunocitinib (Zenrelia®)**

Zenrelia is an FDA-approved JAK inhibitor for the management of allergic pruritus in dogs 12 months and older. It differs from Apoquel by targeting JAK1/JAK2/TYK2 rather than JAK1/JAK3. It is classified as an immunomodulatory drug and can be given once daily with or without food.

- A head-to-head study with Apoquel and Zenrelia showed Zenrelia may be equal or superior in efficacy compared to Apoquel. In this study, Zenrelia was more likely to put a dog into clinical remission of itch compared to Apoquel.
- Often more cost-effective, especially in large breed dogs.
- Side effects are similar to Apoquel. Common side effects include mild GI upset and lethargy.

**FDA Warning:** Avoid administration for 28 days before or after vaccination. This warning is based on one study involving 8 young, unvaccinated, and unwell dogs who received a daily overdose of the drug. Follow-up studies in healthy, previously vaccinated dogs did not show compromised vaccine responses. Zenrelia is best used in healthy, adult dogs who are up-to-date on primary vaccines. Understand that outside of North America, there is no statement on the

label regarding vaccinations and dogs are being vaccinated regularly on Zenrelia.

**Dosing:** 0.6–0.8 mg/kg PO SID. A dosing chart is available for convenience.

### **Lokivetmab (Cytopoint®)**

Cytopoint (Canine Atopic Dermatitis Immunotherapeutic [CADI]) is labeled for reducing clinical signs associated with “allergic dermatitis and atopic dermatitis” in dogs of any age. Cytopoint is NOT safe for use in cats.

\*\*\*It is important to understand that this works for all types of allergic itch, not just environmental allergies. Cytopoint CANNOT be used as a diagnostic tool because it is NOT specific for only environmental allergies.

Cytopoint is a monoclonal antibody that blocks itch caused by IL-31. It is labeled for injection subcutaneously every 4-8 weeks. The level and duration of response varies in individual dogs. Onset of efficacy is within 1 day and may persist for up to 2 months in some patients. Elimination is via protein-degradation pathways.

The label lists no contraindications or precautions. It is safe for any age, even in dogs with concomitant diseases and medications. It has not been tested in pregnant, lactating, or breeding animals.

While Cytopoint appears to be quite safe, it is not without possible side effects. In a field safety study, reported adverse effects were noted as comparable with placebo. In rare cases, side effects include hypersensitivity-related reactions (anaphylaxis, facial edema, urticaria) and it may induce transient or persistent anti-drug antibodies which may reduce its efficacy. Transient vomiting, diarrhea, and lethargy may occur during the first few days. I have seen some profound lethargy after administration, and my own allergic Pug had an allergic reaction involving facial edema, hives, and severe pruritus.

Considerations:

- Cytopoint is potentially the best choice for a dog less than 1 year of age.
- Since Cytopoint may last up to 2 months, this should be considered when you are performing a diet trial since it may mask signs for too long when challenging the diet.
- Cytopoint, in my opinion, is *not* a good choice for severely inflamed ears and paws.

What do we do when Cytopoint runs out after 2-3 weeks?

1. Check for infection.
2. Check for fleas or other parasites.
3. Check dose of Cytopoint. Can you safely move up to next range?
4. Studies show subsequent monthly dosing of Cytopoint increases efficacy.
  - a. First injection: 65% treatment success
  - b. Second injection: 85% treatment success
  - c. Third injection: 93% treatment success

5. Consider progression of allergic disease.
6. Consider production of neutralizing antibodies.

### **Cyclosporine (Atopica®, Cyclavance®, Sporimune®)**

Cyclosporine acts by depressing induction of cytotoxic T-lymphocytes. Other effects include suppression of IL-2 and other cytokines such as IL-1 and blocking proliferation of activated T-lymphocytes.

Cyclosporine appears to be less commonly used than Apoquel, Cytopoint, or steroids, but it has an excellent place in our dermatology toolbox for certain types of animals, signs, and diseases.

The brand name Atopica® is reported to have better absorption in dogs. However, due to its expense, the generic alternative is often used for larger animals. When using the generic, it is imperative to use generic modified cyclosporine. There are many pharmacies that have less expensive options.

Cyclosporine is an excellent option for allergic cats and small dogs, dogs with severe pododermatitis (interdigital nodular furunculosis), allergic animals with recurrent infections, and generally in more inflamed presentations of allergies. I also prefer to use cyclosporine as my long-term medication in dogs with recurrent otitis as to reduce the need for long-term steroids.

Side effects: Cyclosporine can cause vomiting, diarrhea, anorexia, histiocytoma, secondary infection, and gingival hyperplasia. The GI effects are most common. Nephrotoxicity has been reported in humans. Side effects are rare in animals at the antipruritic dosing of 5-7 mg/kg/day. Side effects seen at higher doses such as 10-20 mg/kg/day include papillomatosis, lymphoplasmacytic dermatitis, malignancy, gingival hyperplasia, bone marrow suppression, insulin resistance, pyoderma, bacteriuria, nephrotoxicity, and hepatotoxicity.

The typical “goal” dose for canine allergies is 5 mg/kg once daily. The goal is then to put the animal’s signs into remission and then slowly taper the dose. I typically recommend starting off low and working up to 5 mg/kg/day over the course of 7-10 days. This helps to decrease the chances of GI upset. It is also recommended to put the entire box of capsules in the freezer. This appears to reduce GI upset while not affecting the efficacy of the drug.

Ketoconazole will decrease the metabolism of cyclosporine (i.e. raise the blood level). It is used deliberately to reduce the amount of cyclosporine needed. An equivalent of 5 mg/kg cyclosporine = ketoconazole 2.5 mg/kg SID + cyclosporine 2.5 mg/kg SID. Use a 5-10 mg/kg dose of ketoconazole if active fungal infection is present. I find that side effects are more likely when combining ketoconazole and cyclosporine so I would only recommend this for significant financial challenges.

Blood work monitoring: baseline CBC/chemistry panel, repeat at 1 month, then repeat q 6-12 months thereafter. Monitoring will also depend upon patient’s age, concurrent diseases, and concurrent medications.

It is prudent for the veterinarian to look up drug interactions when using cyclosporine due to actions on the cytochrome p450 activity.

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