The Low Down on Apoquel and Cytopoint:
Making Sense of Allergy Control Medications

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Key Point #1: Allergies are NOT the result of an underactive or suppressed immune system, but a trigger-happy one. Allergies are (probably a genetically-based) abnormal response to "normal" proteins / agents. E.g., chicken meat, cedar pollen, grass pollens are not pathogens (not expected to cause disease), but there are plenty of pets and people who react to these things. This is an "abnormal" response to a "normal" item present in our daily life.

More in-depth details: The exact pathogenesis of allergies, how and why they get started, is not 100% known and likely there are different pathways for different individuals. However, a key player in allergies is the production of *IgE*, an immunoglobulin or antibody, to an allergen. The involvement of IgE in the immune response triggers a cascade of events that leads to allergy symptoms (redness, itch, swelling, altered skin barrier, etc.). For example, the dog who has an allergic reaction to a vaccine has made IgE against the vaccine after a previous vaccinations. With subsequent vaccination, the IgE attaches to mast cells in the skin, the mast cells degranulate (explode) and release histamine and other cell proteins causing the allergic symptoms (hives, facial swelling, dilated blood vessels and red skin). We also believe part of the pathogenesis of allergies is an imbalance in the regulation / production of T-lymphocyte helper cells, an imbalance that favors forming lymphocytes that promote excessive and perpetual inflammation.

Key Point #1 Summary: In simplistic but relatable terms, chronic allergies are basically a trigger happy immune system that is stuck in a traffic circle firing at an armored car in front of it. And *to control allergies, we have either avoid the allergens (don't be exposed to other cars), calm down / suppress the immune system (take away the gun), or try to divert the immune system* (give it something else to do – get out of the traffic circle).

Key Point #2: Allergy "testing" is too inaccurate to use it to tell us what to avoid. The major allergies are food, flea and environmental triggers. Skin and blood tests for food allergies are very inaccurate, and skin / blood tests for environmental and flea allergy are, at best, moderately accurate. In an allergy work up, we start by "controlling what we can control" (food, flea) and see how much that helps. If at least one (preferably 2) different food trials have failed to help, we resign ourselves to the diagnosis of environmental allergies (also called **atopic dermatitis**; allergies to pollens, house dust mites, molds, etc.). Once we have this diagnosis, we have committed this pet to a life of management of allergies because avoidance is almost impossible. The best hope is to minimize long term medication use is to do *desensitization*, or *allergen immunotherapy (see notes below)*.

More in-depth details: Details of food trial are beyond the scope of this talk, but in short, there is no one perfect food; we have to consider previous diets, owner preference, need for treats, canned food. Owners need detailed instructions and encouragement during food trials. And many pets have both food and environmental allergies, such that we see only partial improvement during a food trial, complicating our assessment.

More in-depth details: *Allergen immunotherapy* ("AIT"; aka allergy shots, allergy vaccine, allergy serum) is giving to a pet, in a controlled and graduated fashion, the allergens to which they are allergic, trying to retrain their immune system, just as is done for people. We are not sure how this works, maybe by turning off IgE production, or altering the types of T-helper cells produced by the immune system, or maybe creates a diversion for the immune system.

Key Point #2 Summary: Diagnosis of allergies (food vs environmental vs flea) is a process of elimination. Avoidance of environmental allergens is almost impossible. Allergy testing is done to help us do allergen immunotherapy.

Key Point #3. Allergen immunotherapy (AIT) can be technically challenging, takes a dedicated pet parent, and often takes months (if not more than a year) to work. About 65% of pets started on AIT respond. Response rate is lower for pets with years and years of allergies. AIT is indicated for the relatively young (< 7-8 yrs of age) and cooperative pet. *All the negatives aside, AIT is the best chance of controlling allergy symptoms yet minimizing use of medications.*

More in-depth details: AIT involves either giving SQ injections 1-3 x /week or oral drops twice day. Not all pet owners have the skills or patience for this. Oral administration is usually easier for most owners, except for (most) cats.

So, for pets who do not improve with diet changes and flea control (which is >50% of our allergy patients), we have to find a way to control the pets' symptoms. Owners would like control without medications, which means AIT, but this is not right for everyone. For years, all we had were steroids and Atopica (cyclosporine), both with their pros and cons. In the last 5 years, we have 2 new exciting medications (Apoquel and Cytopoint) to help control canine allergic dermatitis. What do you as a technician need to know about these medications (how fast they work, how they are given, potential side effects, costs, etc.)?

Apoquel (oclacitinib):
This is a unique immune suppressive medication (a janus kinas inhibitor) used for control of allergy symptoms. It affects less of the immune system than prednisone, more than cyclosporine, more than Cytopoint. It works by affecting the production and function of some cytokines (chemical signals between immune cells).

Onset: Rapid onset, decreasing itch in 24 hrs or less. Effectiveness: 95% of dogs respond to BID Apoquel; 75% to once a day.

Route of administration: Oral pill; usually easy to give; give twice a day for up to 2 weeks, then DECREASE to once a day. Note: Apoquel should NOT be given BID long term.

Side effects: Uncommon unless given BID long term, which can be very immune suppressive. May increase predisposition to viral papillomas, some skin growths (histiocytomas). Question of association with cancer development is unproven / no association recognized at this time. Occasionally see behavior changes (increased aggression).

Okay for long term use? Yes, but not our "soundest medical advice" for a young dog

Cost: Variable – not cheap; mostly over $50 / mon. All 3 tab sizes cost the same but some dogs need a half of one size

No-Nos: Not labeled for dogs < 1yr of age, pregnant or lactating dogs; cautionary use if history of neoplasia or ongoing serious infection such as pneumonia. Do not use ID long term unless no other option.

What about cats? Not labeled for cats but there are several case reports using it in cats. They do not respond as well as dogs; often need a higher dose and more often. We have no long term safety data on its use in cats.

Cytopoint (lokivetmab):
This is a monoclonal antibody against IL (interleukin)-31. IL-31 is a cytokine whose only function, to our knowledge, is to generate itch and inflammation. The function of Cytopoint, an antibody to IL-31, is to bind or

lock up all the IL-31 in the dog's body. Cytopoint is considered an "immune modulator", *not* an immune suppressive therapy.

Onset effectiveness: Rapid, usually decreased itch in 24-48 hrs and works for, on average, 4 weeks (some longer some less). ~60-70% response rate

Route of administration: subcutaneous injection. Warm to at least room temp before giving! (stings when cold)

Side effects: No predictable side effects; possible to have an allergic reaction to it; it is a protein. We watch our patients for 10 min after administration until they've had 5 injections.

Okay for long term use? Yes. Labeled to give up to every 4 weeks. Okay for dogs less than 1 year of age. Has not been testing in pregnant or lactating dogs

Cost: Depends upon body size; one injection in a dog over 70 lb may be $100 or more. Less expensive than Apoquel for small dogs.

What about cats? NO!! Dogs only. This is a DOG antibody; cats will develop a reaction to it.

In review / in comparison:
Corticosteroids (prednisone, prednisolone, dexamethasone, Depomedrol, etc):

- Onset / effectiveness: rapid; helping with 24-48 hrs. 90+% response rate
- Route of administration: Various (pills, liquids, injections, topical, transdermal)
- Side effects: Numerous. Short term: pu/pd, polyphagia, panting, behavior changes. Long term: "breaks the body down faster than it builds itself up" Can cause diabetes in cats
- OK for long term use? Not without at least some side effects – less at lower doses and most important to give every other day or less.
- Cost: cheap financially, but not physiologically
- Comments: Steroids have their place, such as in conjunction with other meds. And many owners are wise to steroids and don't want to use them or use them very much

Atopica (cyclosporine):
An immune suppressive medication (dampens the function of lymphocytes, alters cytokine production and function). It helps control foreign body rejection; used to prevent transplant rejection. It is a little more suppressive than Apoquel, less than prednisone (but dose-dependent). It is used in dogs and cats.

- Onset / effectiveness: Takes 2 to 4 weeks to work; ~80% response rate
- Route of administration: oral caps or liquid (injectable available but costly, can sting, and can cause abscesses)
- Side effects: GI upset (in 20-25%); gingival thickening; increased hair growth; increased susceptibility to some unusual infections. Fewer side effects than steroids, in general.
- Okay for long term use? Yes, if tolerated but like other meds, not ideal for the young patient as a long term plan
- No-No's: pets should NOT be on a raw diet and taking Atopica; use with caution in pets with history of neoplasia
- Cost: "not cheap" – Elanco has a rebate for repeat purchases; generic on human side less expensive (still not cheap).

If I have to use a medication long term for environmental allergy control, what would I use?
As is so often the case in veterinary medicine, "it depends." But on the whole, my best medical advice:

For the young dog: I would start allergen immunotherapy (ideally based on allergy testing). While waiting for that to work, I would start with Cytopoint because it has the least effect on the immune system and fewest potential side effects. If Cytopoint does not help, I would try Apoquel. If that fails, I reach for cyclosporine. If that fails, they should see a dermatologist! (All this is in conjunction with regular bathing, giving fish oils, using regular flea control, etc.) Our best controlled patients are ones on a combination of therapies (the *multi-modal approach*).

For the middle-aged to older dog with chronic allergies: I tend *not* to encourage allergy testing and immunotherapy but skip to the medications in the order list above.

Even though neither medication highlighted in this talk is labeled for cats, I will offer an opinion here: For younger cats, like dogs, I encourage allergy testing and immunotherapy. While waiting for this to work, my first choice is cyclosporine, if tolerated and the cat can be medicated orally. If this fails, I think the potential side effects of long term steroid use and the unknowns of Apoquel use in cats are about equal risks. I would use my judgment and educate the owner on pros and cons of both. If we elect Apoquel use, I do recommend monitoring blood work in 8 weeks and every 4-6 months thereafter if normal.

Resources:
https://www.zoetisus.com/conditions/dogs/itchcycle/home.aspx
https://www.apoqueldogs.com
http://www.cytopoint4dogs.com