Newer therapies for canine atopic dermatitis: the IL-31 inhibitors

Introduction:
Canine atopic dermatitis (cAD) is now known to be an extremely complex and multi-factorial disease. For this reason, a single “magic bullet” therapy which ameliorates the itch, inflammation, and recurrent secondary infections associated with cAD has been elusive. Many intrinsic abnormalities have now been identified within the skin and circulating immune cells of atopic patients (both human and canine). The old theory that the pathophysiology of atopic dermatitis (AD) could be adequately explained as an excessive IgE response against environmental allergens is now seen as simplistic and naïve. While excessive production of allergen-specific IgE is still recognized as part of the “atopic cascade” of events leading to inflammation in some patients, there are many other patients for whom this response cannot be demonstrated by either intradermal allergen testing or serum ELISA.

Currently, two major pathways which contribute to development of AD are recognized:
1. defects in stratum corneum barrier function which allow allergen penetration into the skin, and
2. aberrant T-lymphocyte (T-cell) responses to allergens, which produce a host of pro-inflammatory and pruritogenic cytokines and chemokines (and activate other cells which also participate in the atopic cascade). In the atopic patient, these two factors likely act in synergy to perpetuate the itch and inflammation (and secondary infections) associated with AD. Therefore, combination therapies have long been the rule, but require customization to each individual patient. Options continue to include a host of topical and oral therapies:

Topical therapies:
Topical products marketed for treatment of cAD focus either on restoring stratum corneum barrier function (through lipid replacement spot-ons or use of moisturizers available as rinses, sprays, shampoos and cream rinses) or on delivering active pharmaceutical ingredients to the skin’s surface to combat itch +/- inflammation (eg, antihistamines, anesthetics, steroids or calcineurin inhibitors – available in many formats).

Systemic therapies:
These focus on interrupting one or more components of the atopic cascade, and run a broad gamut of risk and benefit.

a. Glucocorticoids shut down most of the inflammatory pathways that are activated during the atopic response, but produce a host of unacceptable side-effects, making them unsuitable as the sole therapy for a chronic life-long disease. In addition, the effect of steroids generally wanes with chronic use. Steroids are best utilized for rescue therapy as brief “itch buster” tapers.

b. Oral drugs and supplements with minimal risk for side-effects include anti-histamines, essential fatty acids, and Vitamin E. These may be used successfully in combination for some dogs with very mild cAD, but are marginally effective for most. They may be useful for steroid sparing effect.

c. Higher-order drugs with mild to moderate anti-inflammatory properties (but little risk for upsetting immunoregulation) include pentoxifylline and misoprostal. These work best when used in synergistic combinations with other topical and systemic therapies.

d. Cyclosporine A (Atopica®; Elanco, Greenfield, IN) is a much more effective anti-inflammatory drug with proven efficacy equivalent to steroids in many patients with cAD. It carries some risk for global immunosuppression, but is very useful in patients for whom recurrent staphylococcal infections (especially pedal furunculosis) and/or hyperplastic otitis externa are prominent features. It has a slow onset of action.
e. For decades, a main-stay for therapy of cADs has been allergen-specific immunotherapy (ASIT). This is an extremely safe modality based on identifying allergens to which the patient mounts an excessive IgE response, and then administering these allergens (as a mixture) at extremely high concentrations intended to mitigate the aberrant immune response against them. ASIT is now available for either subcutaneous or sub-lingual administration. However, it works for only a portion of patients (50-65% according to several authors) and requires a long-term commitment from the pet owner (a beneficial response may take up to 12 months to be realized). Patients on ASIT will require “bridge therapy” with other modalities while awaiting a response. When effective, ASIT can also mitigate the occurrence of recurrent infections.

In addition to anti-inflammatory and anti-pruritic therapy, a very important part of controlling cAD successfully is treatment and prevention of secondary bacterial (staphylococcal) and yeast (Malassezia) skin infections and infectious otitis externa. For some pets, this is indeed the greatest challenge as the itch is treatment and prevention of secondary bacterial (staphylococcal) and yeast (Malassezia) skin infections and infectious otitis externa. For some pets, this is indeed the greatest challenge as the itch is 

The role of IL-31 in cAD:
Interleukin-31 (IL-31) is cytokine produced by a subset of skin-homing T-cells that are known to participate in the initiation and exacerbation of the atopic cascade of inflammatory events. Receptors for IL-31 occur on skin cells (keratinocytes), inflammatory cells (eosinophils, macrophages) and small nociceptive neurons. When IL-31 binds to its receptor on peripheral nerves, it appears to directly signal neuro-transmission of the sensation of itch. Receptors for IL-31 invoke cellular responses by activating a Janus-kinase (JAK) -mediated signal transduction pathway.

Oclacitinib (Apoquel®, Zoetis, Kalamazoo, MI, USA):
Oclacitinib is a JAK inhibitor which interrupts signal transduction after IL-31 binds to its receptor. Other allergy-associated cytokines (IL-2, IL-4, IL-6, and IL-13) are also independently inhibited through the JAK mechanism. Oclacitinib therefore has both anti-pruritic and anti-inflammatory properties. It produces a very rapid effect on pruritus (within 4 hours) and significantly reduces skin lesions as assessed by standardized scoring metrics. Oclacitinib produces anti-pruritic effects equivalent to prednisone and cyclosporine (although the latter is slower in onset). It is labeled for use in dogs greater than 12 months of age (due to risk for demodicosis) at a dosage of 0.4-0.6mg/kg twice daily for 14 days, then once daily for maintenance. An extended use study (up to 630 days) in 247 client-owned dogs reported no adverse effects on serum chemistry values or blood cell counts. Vomiting, diarrhea, and infections (urinary tract, pyoderma, otitis externa) occurred at rates thought to be typical of dogs with cAD. For more prescriber information, see the clinician brief by Faulk & Ferrer (available open-access).

A post-marketing epidemiological surveillance study has now documented a higher incidence of histiocytomas in older dogs taking oclacitinib than cyclosporine A and there are many anecdotal reports of papillomatosis occurring at higher rates in dogs on oclacitinib (not yet confirmed by appropriately designed case-control studies). These finding suggest some degree of impairment of immunoregulation. However, a prospective study has shown no increased risk for urinary tract infections, and routine urine culture is not required. As stated on the label, oclacitinib should not be used in dogs with a history of neoplasia or with serious pre-existing infections.

Lokivetmab (Cytopoint®, Zoetis):
(Formerly known as Canine Atopic Dermatitis Immunotherapeutic [CAD]): Lokivetmab is a monoclonal anti-canine IL-31 antibody that binds directly to circulating IL-31, thereby preventing it from binding to its neuronal receptor and inducing neurotransmission of the itch sensation. In published studies, lokivetmab significantly reduced itch (compared to placebo injections), with an onset of efficacy within 1 day and persisting for at least 30 days. It is labeled for use at a minimum dose of 2mg/kg and supplied as single-use vials containing 10mg, 20mg, 30mg, or 40mg doses. Injections may be repeated "as needed" (Q30-60 days) for mitigation of pruritus. A published study documented no clinical pathology or health derangements in 162 dogs after two monthly doses (followed for 42 days).
Lokivetmab is a “caninized” monoclonal antibody (mAb), of which 95% of the genetic sequence is canine (5% is murine). This should minimize immunogenicity, although development of blocking antibodies against any
mAb is possible. In the two published clinical trials (456 client-owned dogs) no anaphylactic reactions were noted. However, treatment-induced immunogenicity was documented for 2.5% of 245 dogs as characterized by development of anti-lokivetmab antibodies. Average lokivetmab concentrations were 90% lower on days 28 and 42 in these patients than in dogs without antibody development. This may be appreciated clinically as a dog that does not respond as well to subsequent doses of the product after showing an initially favorable response. In the author’s experience, this is rare.

**Newer therapies for ectoparasitisms: the Isoxazolines**

The isoxazolines are a novel and relatively new class of anti-parasitic agents with activity against insects and arthropods. Three products are licensed and approved for the treatment/prevention of fleas and ticks on dogs in the United States, and one of these is approved for use in cats:

1. Afoxolaner (NexGard®; Front Line Vet Labs, Merial Inc., Duluth, GA): Labeled for once monthly oral dosing at 2.5mg/kg in dogs 8 weeks of age or older and weighing 4 pounds or greater, for treatment/prevention of the cat flea and four species of ticks.
2. Fluralaner (Bravecto®; MSD Animal Health, Kenilworth, NJ): Labeled for oral dosing at 136.4mg/kg in dogs 8 weeks of age or older and weighing 2 pounds body weight or greater (also in breeding, pregnant, and lactating dogs) for treatment/prevention of the cat flea (3 months) and three species of ticks (variable durations – see product insert). In some countries, it is also approved for treatment of demodectic mange (3 months), sarcoptic mange (1 month), and ear mites (1 month). Bravecto is labeled for topical application to cats (40mg/kg) at 6 months of age or older and weighing 2.6 pounds or more, for treatment/prevention of the cat flea (12 weeks) and two species of ticks (variable durations).
3. Sarolaner (Simparica®; Zoetis): Labeled for once monthly oral dosing at 2mg/kg in dogs over 6 months of age, for treatment/prevention of the cat flea and 5 species of ticks. A topical product for cats is approved in the European Union.

Soon after commercial launch of each product, anecdotal reports began to surface regarding their efficacy against a variety of other arthropods (mites). They have revolutionized therapy for canine generalized demodicosis; a disease for which off-label use of avermectins has become the standard (imidacloprid-moxidectin topical spot-on is an approved treatment in some countries, but not in the USA). Due to their ease of use and safety (effective against *Demodex canis* at the label dose used for fleas & ticks), these products are rapidly replacing veterinarians’ reliance on avermectins (eg., daily oral ivermectin, milbemycin, or topical moxidectin) for the treatment of demodicosis. Three recent studies have illustrated efficacy:

1. Fourie et al (2015) compared efficacy of fluralaner to imidacloprid/ moxidectin (Advocate®; applied q28 days) in 16 dogs (eight dogs per group). After a single oral dose of fluralaner, mite numbers in skin scrapings were reduced by 99.8% on Day 28 and by 100% on Days 56 and 84.
2. Beugnet et al (2016) compared efficacy of afoxolaner (given at the recommended dosage on days 0, 14, 28 and 56 to eight dogs) with topical imidacloprid/moxidectin (Advocate®, Bayer). The percentage reductions of mite counts in the afoxolaner group were 99.2%, 99.9% and 100% on Days 28, 56 and 84, respectively.
3. Six et al (2016) compared efficacy of sarolaner (2 mg/kg given orally on days 0, 30, and 60 to eight dogs) to topical imidacloprid/moxidectin (applied once weekly). In the dogs treated with sarolaner, pretreatment mite counts were reduced by 97.1% at 14 days and 99.8% by 29 days after the first dose. No live mites were detected after day 29.

Published reports also describe the isoxazolines to have excellent efficacy against a variety of other mites:
- Sarolaner for *Sarcoptes scabiei* and *Otodectes cynotis* in dogs.

The author’s clinical group has also used afoxolaner to successfully treat canine scabies and fluralaner to treat feline demodicosis. Many more clinical reports and clinical trials can be expected.
References: