Which Drugs are Most Effective in the Management of Atopic Dermatitis and What's New?

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Canine atopic dermatitis is a chronic non-curable but manageable inflammatory disease of the skin. Cats also develop allergic skin disease, but its features are unique to cats in most cases. Medications we use to treat allergic skin disease mask symptoms, but do not change the disease process. Most dermatologists would agree that taking a multi-modal approach provides the best management of this disease. Avoidance of allergens when possible (particularly foods and fleas), immunotherapy to change the immune response, infection control (focus on topical therapy with the use of systemic antimicrobials when necessary), skin barrier repair, and control of itch and inflammation are the tools we use to manage these dogs. Here we focus on the drugs used for itch and inflammation for which we have the best evidence: two older drugs, glucocorticoids and cyclosporine (Atopica), and one new one, oclacitinib (Apoquel).[1-5] In addition, an exciting biologic approach to itch management, using a monoclonal antibody directed against the itch molecule, Interleukin 31 (IL - 31), is on the horizon.

Glucocorticoids

Glucocorticoids have been effective in the management of atopic dermatitis for years.[6] Glucocorticoids affect many pathways of inflammation and their major effect on itch is through the rapid control of inflammatory pathways. They also have immunomodulatory and anti-proliferative effects. Dosing is determined by the glucocorticoid used and the severity of the disease.

Prednisone or prednisolone are the steroids used most commonly. We often start with 0.5 to 1 mg/kg orally divided BID with a slow taper to the most effective maintenance dose. In cats, the use of prednisolone has been advocated and in general, starting doses are double those used in dogs, as it has been suggested cats have lower numbers of glucocorticoid receptors, with lesser affinity for the glucocorticoids.[7] Methylprednisolone (Medrol) can be used as well. It is often desirable as it is less likely to cause increased water drinking and urination, and it is slightly more potent.

Injections of dexamethasone can be used to rapidly reduce itch and this method has been termed "crisis buster". Recommended doses vary from 0.5 to 1 mg/4.5 kg intravenously (dexamethasone sodium phosphate) or subcutaneously (either dexamethasone SP or dexamethasone). Relief is variable: 24-72 hrs. depending on the severity of the itch.

Oral dexamethasone can be used for short term itch relief, but it is not ideal for long term use due to its potency. Oral triamcinolone can also be used for short term itch relief and we find it particularly useful to open up ear canals that are swollen shut and to treat very itchy cats, but it is not ideal for long term use due to potency.

Trimeprazine 5 mg/prednisolone 2 mg (Temaril-P, Zoetis) can be a very useful aid in treating itch and inflammation. We find that the combination of the antihistamine trimeprazine seems to potentiate the steroid, allowing us to get comparable relief with lower steroid doses. Initially it is dosed at 1 tablet per 4.5 kg twice daily, then tapered according to the needs of the patient. This medication has also been used for cats, usually at the dosing regimen of 1 tablet twice daily then tapered per patient need.

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Topical steroids have been shown to have efficacy in atopic dermatitis. Triamcinolone spray (Genesis, Virbac)[8] and hydrocortisone aceponate (Cortavance, Virbac)[9-12] have been used effectively in dogs. General recommendations for dosing are twice daily use for 7 days, then once daily use for 7 days, then every other day or as needed. Although not licensed for use in cats, hydrocortisone aceponate has been shown to be effective and safe for use.[9]

Key Points:

- Glucocorticoids have widespread anti-inflammatory effects and metabolic effects.
- Glucocorticoids have multiple modes of action.[6,13,14] Genomic effects are mediated by the binding of glucocorticoids to an intracellular glucocorticoid receptor (GR) allowing it to dimerize, become activated, and bind to DNA where it serves as part of a transcription factor complex to activate or repress gene transcription. In general, ligand-bound GR activates the transcription of anti-inflammatory genes and represses the activation of pro-inflammatory genes. But the specific mechanisms of action may be cell type and context specific; there is much we don't know about glucocorticoid function.[13] Their metabolic effects include gluconeogenesis in the liver, mobilization of amino acids from extrahepatic sources, inhibition of glucose uptake in muscle and adipose tissue, and lipolysis in adipose tissue.
- Common side effects include polyuria, polydipsia, and polyphagia. Behavioral changes are also common. Long term side effects include hepatic enzyme elevations, catabolism of muscle and fat, potbellied appearance, osteoporosis secondary to decreased calcium uptake and inhibition of bone formation, and delayed wound healing. Skin effects include thinning of the skin with increased dryness, the development of comedones, striae, and milia, and calcinosis cutis. Increased susceptibility to urinary tract infections and skin infections has also been noted. In cats, diabetes mellitus and the development of acquired fragile skin syndrome are of concern.
- A phenomenon observed commonly when glucocorticoids are used is a loss of efficacy over time. This has been attributed to tachyphylaxis, the mechanism of which in dogs is not known. Glucocorticoid resistance is real, but the mechanisms are quite complex. Postulated mechanisms include the production of alternative GR that bind up the GC but lack anti-inflammatory function, and reduced levels of an enzyme called histone deacetylase-2, critical for the anti-inflammatory function of GC.[15,16]
- Topical steroids can have considerable side effects as well. Topical medications containing betamethasone should be restricted for short term use, as they induce thinning of the skin, increased skin fragility, comedones, milia, and calcinosis cutis. Low concentrations of triamcinolone in Genesis spray are less likely to have these effects, but its use in small dogs should be monitored. The use of the "soft" steroid hydrocortisone aceponate is preferred because while it is potent in the skin, it is metabolized to hydrocortisone by the time it reaches the bloodstream.
- A useful tool for monitoring glucocorticoid use in dogs is the concept of the safe steroid dose equation popularized by Candace Sousa.[6] The body weight in kg is multiplied by 30 to get the milligram dose of steroids PER YEAR. For a 10 kg dog this would yield 300 mg per year. If Temaril-P is used, this equates to 150 tablets per year or roughly 1 every other day. This dose appears to be associated with minimal risk of serious steroid side effects. Temaril-P containing a combination of the antihistamine trimeprazine and the steroid prednisolone is believed to control itch at a lower dose of glucocorticoid than using glucocorticoid alone.
- It is important to optimize the success of glucocorticoid treatment by recommending rigorous flea control, and by treating cutaneous infections effectively using topical therapy and when necessary systemic

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antimicrobial medications. The presence of fleas, staphylococcal pyoderma, or Malassezia dermatitis will often induce flares in otherwise well controlled patients. Controlling ectoparasites and infections can assist in keeping steroid doses low.

Cyclosporine

Cyclosporine revolutionized the treatment of atopic dermatitis in dogs and later, feline allergic skin disease.[17-23] Cyclosporine provides a viable option for patients whose disease has become refractory to glucocorticoids, who have developed unacceptable side effects, or whose associated diseases (diabetes mellitus, hyperadrenocorticism, arthritis requiring NSAIDS) make their use contraindicated. It is critical that modified cyclosporine be used as it is more uniformly absorbed. Modified cyclosporine is approved for use in dogs and cats and produced as the brand drug Atopica (Novartis Animal Health).

We recommend dosing modified cyclosporine at 5-7 mg/kg/day for 4-6 weeks to determine if the medication is effective, then the medication is lowered slowly to the dose and frequency that controls the disease. Ketoconazole can be given to reduce the dose of cyclosporine in some patients. It is recommended to use 2.5 mg/kg of each medication.

Key points:

- It is critical to use modified cyclosporine. Brand name Atopica (approved for use in dogs and cats) is recommended whenever possible.
- Modified cyclosporine is not recommended for use dogs or cats with a history of neoplasia.
- It is recommended that cats taking Atopica be tested for Feline Imunodeficiency (FIV) and Feline Leukemia Virus FeLV, that they be indoor cats, that they be prohibited from hunting, and that they not be fed raw diets. Dogs should not be fed raw diets while taking modified cyclosporine.
- Modified cyclosporine has not been evaluated for safety in dogs less than 4 months of age, or cats less than 6 months of age, or breeding, pregnant, or lactating dogs or cats. In the opinion of this author, this drug should not be used in dogs less than one year of age. Young dogs have immune systems that are still developing and this medication could affect that development.
- The most common short term side effects include nausea and vomiting. These can be prevented in most patients by initially giving the medication with food, or by short term use of maropitant (Cerenia, Zoetis). Long term side effects of cyclosporine include gingival hyperplasia, soft stools, diarrhea, weight loss, lethargy, and in cats, drooling. In rare cases, cats have developed fatal infections with toxoplasmosis or M. avium.[24-26] and dogs have developed cutaneous fungal infections.[27]
- It has been recommended to give this medication on an empty stomach, but a recent study has shown that the clinical benefit was the same whether the medication was given with or without food, at least in cats.[28] Giving with food may help reduce the Gastrointestinal (GI) side effects.
- Tapering of cyclosporine is not automatic and needs to be individualized to each patient. It is best to do a slow taper until the frequency is found that controls the disease. Some animals require daily cyclosporine for maximum efficacy.
- While cyclosporine is not effective for all pets with atopic dermatitis/allergic skin disease, it is important to optimize the success of treatment by recommending rigorous flea control, and by treating cutaneous infections effectively using topical therapy and when necessary systemic antimicrobial medications. The presence of fleas, staphylococcal pyoderma, or Malassezia dermatitis will often induce flares in otherwise well controlled patients.
- See package inserts for more detailed information.

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Oclacitinib

Oclacitinb (Apoquel, Zoetis) is a new targeted drug available for the treatment of canine atopic dermatitis. Its mechanism of action is as an inhibitor of Janus kinase, (JAK) and is selective for JAK-1, with effects on JAK-3; in general, it spares JAK-2, the kinase involved in bone marrow production of blood cells. Upon binding of the allergic cytokine to its cell surface receptor, the receptor dimerizes, which results in JAK phosphorylation and activation. Activated JAK phosphorylates STAT proteins, which dimerize and enter the nucleus to activate gene transcription. Thus, inhibition of JAK-1 interferes with the ability of allergic cytokines to transduce their signal into the cell and clinical signs are ameliorated. Cytokines known to be affected by oclacitinib include IL-2, IL-4, IL-6, and IL-13, among others.[29] The itch cytokine, interleukin 31 (IL-31) is particularly sensitive to inhibition of JAK signaling, and thus itch is rapidly controlled following administration of the drug because the binding of the cytokine to its receptor on the nerves does not trigger itch in the presence of oclacitinib. The recommended dose is 0.4 to 0.6 mg/kg twice daily for up to 14 days, then once daily thereafter for chronic use.

Key points:

- Oclacitinib, because of its highly targeted mechanism of action, may be the safest and most effective pharmacologic agent we currently have for the treatment of the itch associated with allergic dermatitides in dogs. Its mechanism of action is such that it will only repress allergic itch and thus a workup to rule out ectoparasites and infections as contributing factors is critical. It has been shown to be at least as effective as glucocorticoids or cyclosporine[1,2]; however, it appears to be very effective in many dogs whose disease has become refractory to glucocorticoids or who have failed cyclosporine.
- It is approved for use in dogs of one year of age or older, and has not been studied in breeding, pregnant, or lactating dogs. In safety studies performed in dogs 4-6 months of age, using dosing 3 and 5X the recommended dosing, demodicosis, sepsis, and pneumonia were observed in some of the animals.
- The most common side effect observed in the clinical trials was upset stomach, seen in less than 5% of dogs.[14,30] Additional reported side effects in less than 5% of dogs included diarrhea, lethargy, increased cutaneous lumps, and pododermatitis These clinical signs were observed in placebo-treated dogs at the same rates. A recent publication followed 247 dogs taking daily oclacitinb for up to 630 days.[31] The most abnormal clinical signs seen were vomiting (10%), diarrhea (6%), otitis externa (9%), pyoderma (9%), and urinary tract infection (11%). Since this long term study was not placebo controlled, it is difficult to determine whether the signs are referable to the drug or the atopic state. Sixteen dogs developed neoplasms, but it is important to note that except for one 6 year old, these dogs exceeded 9 years of age, three of the dogs were Golden retrievers considered a tumor-prone breed, and no one tumor type was identified. A tumor rate of 6.5% is not higher than the tumor rate in the aging canine population at large. The conclusion is that the tumors could not be attributed to the oclacitib. Anecdotal reports of outbreaks of demodicosis and histiocytomas are being reported by dermatologists in low numbers of patients (less than 5%). There are anecdotes of neutropenias, anemias, and thrombocytopenias as well, although these observations are rare. It is prudent to have a Complete Blood Count (CBC) and chemistries done during the treatment. This author takes blood for a CBC and mini-chemistry panel 3 months after daily administration of the drug; if all is well, then annual bloodwork as part of a well dog check is sufficient
- Although not approved for use in cats, many dermatologists are using it for the treatment of allergic skin disease in cats, and a recent paper supports it use off-label in this species.[32] Cats may metabolize this drug differently from dogs, though, so it may take some time to determine the best dose and dosing interval for this species.
- To date there are no known contraindications for use of oclacitinib with other medications, although its use has not been studied with glucocorticoids or other immunomodulatory conditions.

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- As for any patient with atopic dermatitis, it is important to advocate for rigorous ectoparasite and infection control as flea infestations and infections will create flares in otherwise controlled patients. Oclacitinib will not replace the need for a thorough dermatologic workup. If response to oclacitinib is poor, consider occult scabies, uncontrolled fleas, and untreated infections with Staphylococcus or Malassezia or both.
- Oclacitinib can be used effectively to control itch during the induction of immunotherapy.
- Some patients will develop an increase in itch when the dose is reduced from twice daily to once daily. In most cases, this is mild and can be managed with bathing. The dogs stabilize with time. A few patients seem to need oclacitinib twice daily for periods longer than 2 weeks. This is an off-label use; careful monitoring, particularly of blood cell counts, is recommended if dogs take this medication twice daily.
- See package insert for complete information.

Canine Atopic Dermatitis Immunotherapeutic (CADI)

The newest treatment for the itch of canine atopic dermatitis is a caninized monoclonal antibody that binds the itch cytokine Interleukin 31. When IL-31 is bound by the antibody, it can't bind to its receptor and activate itch. Because only IL-31 is affected, there is no anti-inflammatory activity. This approach may be best for dogs with itch but not extensive inflammation.

Monoclonal antibodies are usually made by injecting mice with the protein of interest, in this case canine IL-31. The mice make antibodies against this foreign protein. The antibody-producing lymphocytes from their spleens are fused with a tumor cell called a myeloma. These hybrid cells (hybridomas) can then be maintained in culture forever to produce the desired antibody. If we tried to inject mouse antibodies into dogs multiple times, they would eventually reject these antibodies and the product would no longer work. So genetic engineering is used to replace most of the mouse parts with dog antibody. This is what we mean by caninized antibody. CADI can be injected multiple times without inducing an allergic response and without becoming less effective over time.

Key Points:

- Because this is not a drug, it is very specific and does not cause side effects.
- It can be used in dogs of any age.
- It is given subcutaneously by injection at 2 mg/kg; effects can last for 4 weeks. Reduced itch is experienced within 24 hrs. and appears maximal at 72 hrs.
- This product should not be used in cats.
- This product is conditionally licensed at this time by the USDA and is currently available through veterinary dermatologists; however, when full licensure is obtained all veterinarians should be able to use it.
- For more information about monoclonal antibody technology, please visit Itch Cycle.com, Antibody Science. https://www.zoetisus.com/apoquel_dvm/antibody-science.html
- For more information about CADI, see http://www.drugs.com/vet/canine-atopic-dermatitis-immunotherapeutic.html

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