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The Anti-pruritus Toolbox : Symptomatic Managing Allergic Skin Disease in Dogs

Prednisolone vs Cyclosporine vs Oclacitinib vs Lokivetmab

Introduction

Twenty five years ago, all we had available to effectively symptomatically manage pruritic dogs were corticosteroids (topical and systemic) and adjunct treatments with antihistamines and essential fatty acids that in some cases were able to lower the steroid burden of our patients.

In the early part of this century, cyclosporine emerged as the first non-corticosteroid option for symptomatic relief of pruritus with a high efficacy rate. In the last five years, we have seen the registration of new effective drugs modulating the JAK-STAT pathway (Oclacitinib Apoquel Zoetis and Lokivetmab Cytopoint Zoetis).

The purpose of this review is not to deal with the differential diagnosis of canine pruritus:

- Allergic (Atopic dermatitis, food related)
- Parasitic (fleas, mites)
- Infection (Bacteria, yeast and in some cases dermatophytes)
- Neoplastic and infiltrative skin disease (eg epitheliotropic lymphoma)
- Metabolic diseases (eg calcinosis cutis)
- Others

The multimodal management ESSENTIAL to dealing atopic dermatitis (AD) will not be discussed:

- Symptomatic treatment of itch
- Control of infections
- Repair barrier defects
- Deal with other allergies and parasites
- Allergen specific immunotherapy

The purpose of this article is to give some guidance as to how to choose the most effective anti-pruritic agent for your patient.

In terms of owner perception, clinical success is judged by:

1. How quickly and effectively can the itch be controlled
2. The avoidance of significant side effects
3. To a lesser extent, clinician's assessment of lesion score

Owner Quality of Life is negatively affected by pruritic dogs.
Studies indicate QoL scores are significantly correlated with pruritus scores and to a LESSER degree with veterinarian assessed lesion scores CADESI-3 Noli et al 2011

It is the author's experience, based on 42 years of clinical practice and 14 years of dermatology referral practice, that corticosteroid based management of canine pruritus (based on often misguided assumption that the client will not pay for anything better) leads to poor outcomes, client dissatisfaction and loss. To base stand of care for all on the financial willingness of the bottom 10% of clients is clinical and business folly.

Corticosteroids

Background and Pharmacology

Corticosteroids have actions on nearly every aspect of the immune system and are effective in many cases. In fact, in the case of uncomplicated atopic dermatitis, a lack of response to anti-inflammatory doses of corticosteroids should warrant an urgent rethink of the diagnosis.

The most commonly used corticosteroid in veterinary practice is prednisolone. Prednisone is not commonly used in this country and requires metabolism to prednisolone for activity. Of comparative interest, in the management guidelines for human atopic dermatitis, systemic corticosteroids are regarded as contraindicated due to unacceptable side effects.

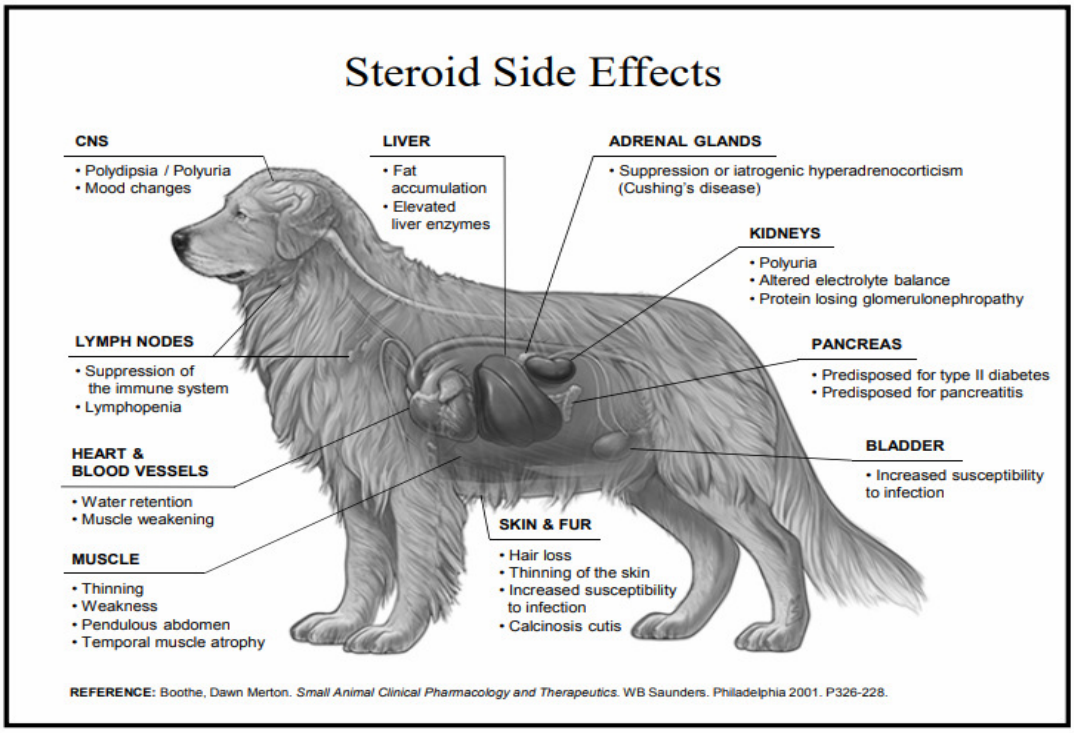
Glucocorticoid	Relative anti-inflammatory potency	Biological half-life	Relative mineralocorticoid effect
Cortisol/hydrocortisone	1	8-12 hrs	1
Prednisone/prednisolone	4	12-36 hrs	0.8
Methylprednisolone (not injectable)	5	12-36 hrs	0.5
Triamcinolone (not injectable)	3-5	24-48 hrs	0
Dexamethasone	29	35-54 hrs	0

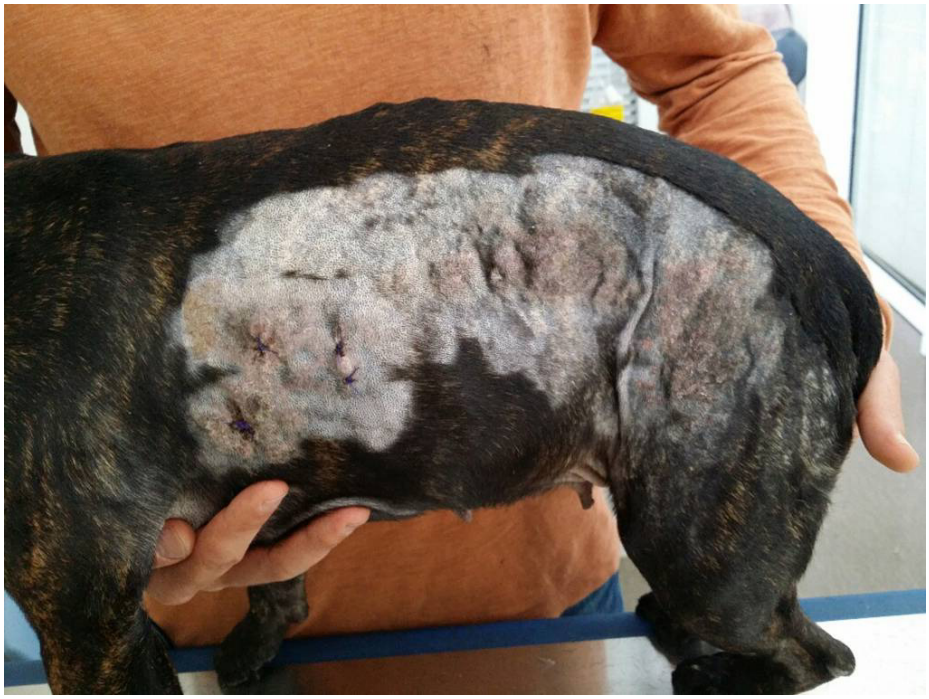
Source: Boothe DW. *Small Animal Clinical Pharmacology and Therapeutics*. Philadelphia, Pa: WB Saunders Co, 2001;313-329.

Prednisolone has a convenient biological half life that often supports every 2nd or 3rd day maintenance therapy. Indicative anti-inflammatory doses are 0.5-1mg/kg. Onset of action is within 30 minutes and there is no benefit in using injectable dexamethasone to initiate prednisolone therapy. Depot corticosteroid injections have no role whatsoever in veterinary dermatology; their clinical action is short and their side effect action is long

Should prednisolone not be effective at 1mg/kg, the dose should NOT be increased to those used to treat immune-mediated diseases (1.5-3mg/kg). Rather, the diagnosis should be reassessed

The side effects of corticosteroids are well recognised and are dependent on the dose, duration and individual variation. Calcinosis cutis is not uncommon in iatrogenic Cushing's syndrome and is highly pruritic. The side effects are both severe pan-immune system suppression and metabolic from endocrine effects.





Iatrogenic Cushing's Syndrome and severe calcinosis cutis in a 3yo dog receiving 0.5mg/kg prednisolone every 2nd day

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Choosing systemic corticosteroids to symptomatically control pruritus

Indications:

1. 3-10 days when a primary cause (eg flea allergy, acute insect bite reaction or adverse reaction to food) has been identified, action taken to eliminate the primary cause and no metabolic contraindication to corticosteroid use exists
2. If the dog can be maintained on 0.5mg/kg or less twice a week or 1mg/kg daily for 3 days and at least 14 days before next pulse AND regularly monitored for side effects
3. Where immediate anti-inflammatory action is needed to reduce swelling, particularly in the case of ear disease. JAK-STAT inhibitors are not very effective in ear canal swelling and the lag phase of cyclosporine is too long for acute cases.
4. For 14-21 days when initiating cyclosporine therapy and awaiting the effects
5. In a closely monitored situation where JAK-STAT inhibitors and cyclosporine have proved to be ineffective, all treatable differentials have been eliminated (food reactions, parasites, infection, barrier issues etc) and always in combination with steroid sparing agents
6. Where economic considerations are such that the only alternative is euthanasia

Contraindications:

1. Metabolic disease eg diabetes, Cushing's disease, liver disorders, immune-deficits, history of pancreatitis etc
2. Neoplasia
3. If allergen testing for immunotherapy is contemplated
4. Where owners have not given informed consent (documented) to the risks
5. For more than 4 weeks on a tapering basis unless absolutely no other alternative exists

Causes of pruritus that do NOT respond well to corticosteroids

- Sarcoptic mange - nearly all
- Adverse food reactions (food allergy) -50% of cases
- Flea allergy - part response only
- Pruritus from infection (yeast, bacteria and dermatophytes)
- Pruritus of calcinosis cutis

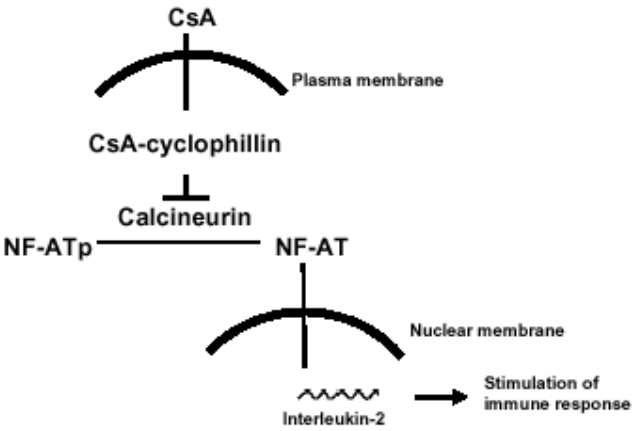
Cyclosporine A (CsA)

Background

Since the 1980's, CsA has been extensively used in humans for prevention of transplant rejection and for the treatment of immune-mediated disease. Atopic dermatitis is a T-cell driven disease. CsA's action is on T-cells, significantly through preventing T cell activation and proliferation through inhibition of interleukin-2 prodution (see below)

For the last 20 years, CsA has been used initially off label and for the last 12 years as a registered canine medication. Many dogs have benefited from CsA in the control of atopic dermatitis and for off label use in the treatment of immune-mediated diseases.

Mode of action



Lasilla , 2000 writes "*CsA binds to cyclophilin to inhibit phosphatase calcineurin, and thereby prevents the dephosphorylation of nuclear factor of activated T-cells. CsA interferes with the synthesis of many cytokines, particularly interleukin-2, (native T-cell activation, T-lymphocyte proliferation and maturation) and interferon- γ, (critical for macrophage activation).*"

CsA in the dog has a bioavailability of 25-43%, the rest being excreted unchanged in the faeces. Bioavailability of oil based generic or compounded CsA formulations can significantly vary from the more consistent absorption of the Novartis ultramicronised products (Neoral – human; Atopica – veterinary). There is considerable variation of the half life of CsA between individuals. Absorption is reduced by failing to give on an empty stomach but it has been shown that giving with food does not alter clinical outcomes

CsA at 5mg/kg once a day has been shown by numerous trials to produce significantly decreased pruritus and improvement of clinical signs in 75-80% atopic dogs by four weeks of therapy with full benefit after six weeks. About 36% of dogs, once stabilised, can be maintained on an alternating day basis and about 25% can be maintained on every third day or less. The author prefers to begin dose reduction to 2 days on and on day off for 3 weeks before attempting every other day maintenance

During the lag phase of approximately four weeks before the benefits of CsA are seen, protocols of prednisolone have been described (authors protocol 1mg/kg daily for 8-10 days then 1mg/kg every other day up to day 25). A study in 8 dogs with concurrent short term oclacitinib during the initiation of CsA therapy (0.4-0.6 mg/kg twice daily for 14 days then once daily for seven days) showed no adverse effects. CsA does NOT interfere with intradermal allergen testing

The long term concurrent use of other immuno-modulators with cyclosporine is off label and requires the most extreme caution. The author at this point does not advise long term use of concurrent CsA and oclacitinib; both have actions on interleukin-2 and interferon γ and profound immunosuppression is potentially possible.

Side effects

In humans, severe nephrotoxic and hypertensive side effects limit it's more widespread use. In dogs, the principal side effects are:

- Gastrointestinal especially vomiting and cramps which may be temporary or persistent. Some cases can be managed by freezing the capsules before administration and the short term use of anti-emetic premedication
- Immunosuppression resulting in opportunistic infections (eg fungal osteomyelitis) and potential loss of anti-tumour immunity. Dogs which "hyperabsorb" CsA or have innate or drug-induced prolonged half-life of elimination are at an increased risk. CsA blood level monitoring is strongly advised, especially those dogs on daily or 2 days on/1 day off regimes. CsA is contraindicated in dogs with neoplasia.
- Drug interactions. Cyclosporine is actively pumped out of cells (eg intestinal enterocytes or endothelial cells of the blood-brain barrier) by P-glycoprotein and is metabolised by cytochrome P450 3A. Important interactions are listed below; a more full list is available from Archer, 2014 and potential interactions should be researched when medications are combined with CsA

Examples in increased drug levels due to competitive inhibition of excretory pathways

Fluoroquinolone antibiotics eg enrofloxacin	Oestrogens	Azole antifungals (ketoconazole, itraconazole)
Metoclopramide	Fluoxitine	Ivermectin, moxidectin and doramectin
Calcium channel blockers	Digoxin	Certain antihistamines esp. H2 blockers

Examples of drugs that decrease cyclosporine levels through induction of increased excretion

Phenobarbitone	Sulphadiazine	Terbinafine
Clindamycin	Some proton pump inhibitors (famotidine)	Trimethoprim

Indications for cyclosporine use

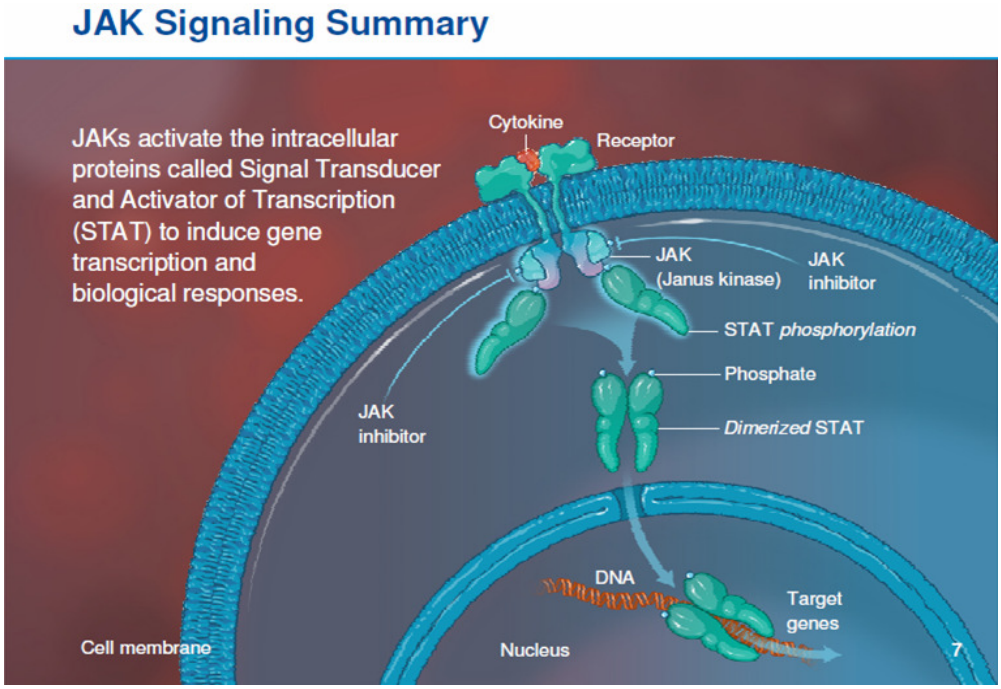
1. Failure of or intolerance to JAK-STAT pathway inhibitors. For example:
   - Oclacitinib associated bone marrow suppression.
   - Non-response to oclacitinib and lokivetmab
2. Where owners prefer an oral agent that has a reasonable chance of every other day or less frequent dosing and understand the lag phase before the onset of benefits
3. Dogs that are currently stable on CsA at a dose of 5mg/kg every 2nd day or less and 24 hour post dose blood level is within the reference range

Contraindications

1. Neoplasia
2. Infection (especially through immunosuppression)
3. If 24 hour post dose blood levels are above the reference range and dose lowering results in relapse
4. Persistent gastrointestinal side effects
5. Concurrent drugs that alter CsA metabolism and/or have their metabolism altered by CsA

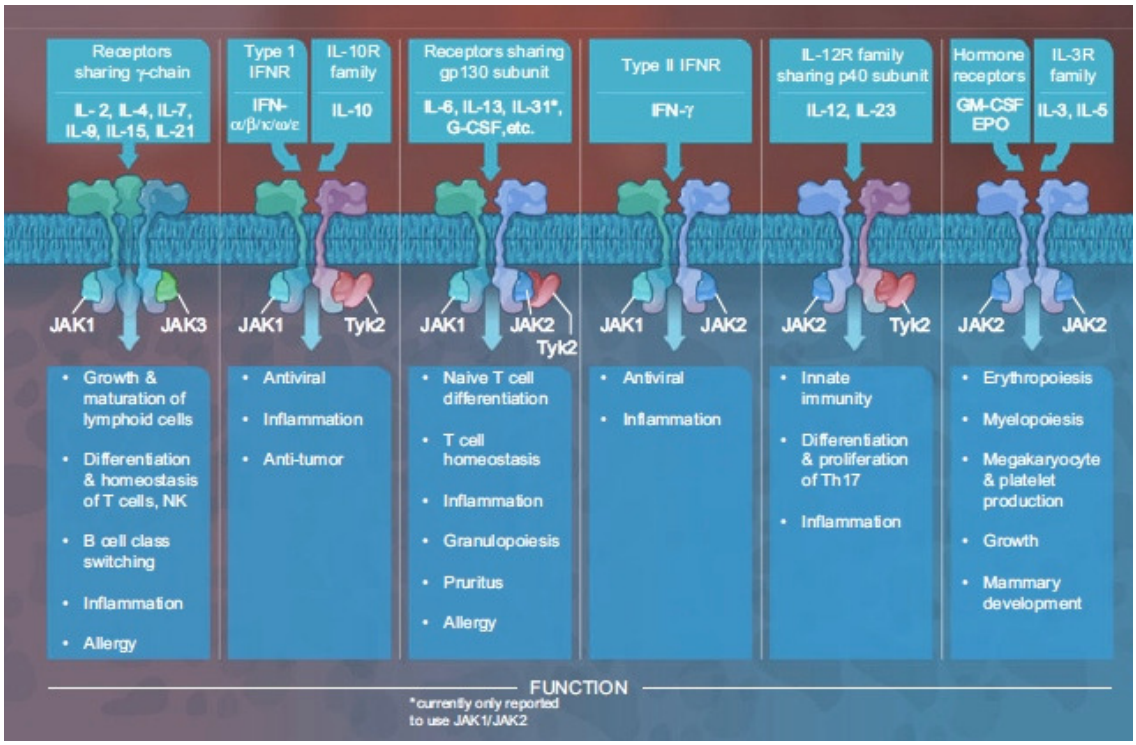
Drugs acting on the JAK-STAT pathway: Oclacitinib and Lokivetmab

The JAK-STAT pathway is best illustrated below.



Zoetis.com

Cell membrane associated receptors bind specific cytokines resulting in the phosphorylation and dimerisation of STAT which acts on the DNA of target cells. JAK stands for Janus kinase; paired receptor complex to which groups of cytokines bind as shown in the image below



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Interleukin-31 has been demonstrated to be a most important cytokine causing pruritus in dogs

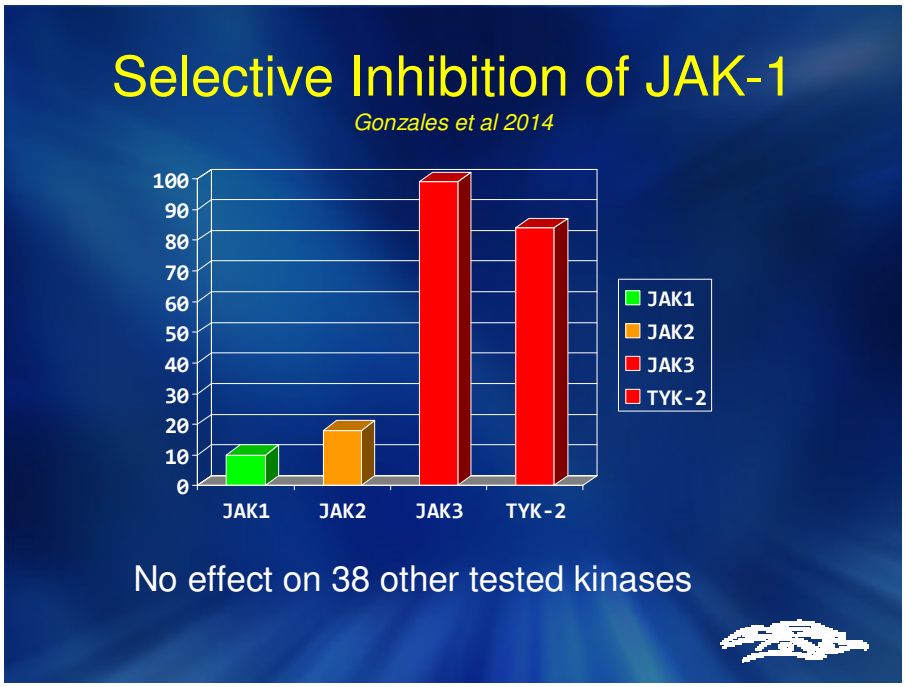
- Produced by activated T-cells as part of the inflammatory cascade associated with atopic dermatitis.
- Detectable in a high proportion of atopic dogs (and humans) and is not detected in normal dogs.
- Dogs injected with Il-31 will scratch! Pruritus does not occur when dogs are given histamine, IL-2, IL-6 and a variety of other known inflammatory cytokines.
- There are IL-31 receptors on nerve endings.
- Anti-IL-31 monoclonal antibodies are effective in reducing pruritus in the dog giving relief of pruritus for a period of weeks after injection.

Oclacitinib (Apoquel Zoeitis)

Background and pharmacology

Oclacitinib is the only registered veterinary JAK inhibitor. It has a very high affinity for the JAK-1 enzyme complex. At standard doses, it has a lower affinity for JAK-2 and very much lower affinity for the other JAK members: JAK-3 and TYK-2. Oclacitinib inhibition of receptor JAK1 containing receptor complexes

would appear to be on a cytokine to cytokine basis with a very high level of inhibition of Il-31



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Oclacitinib has a high efficacy rate. Short term, at least, equivalent to prednisolone and long term, at least, equivalent to cyclosporine. Oclacitinib is rapidly absorbed orally. The half-life of oclacitinib is only of the order of four hours. Abrupt withdrawal has been demonstrated in mice to show a rapid rebound type increase in pruritus

Oclacitinib failed to obtain registration in dogs under 12 months of age due to an increased number of cases of demodicosis and pneumonia when given at three times the registered dose, twice daily. The author speculates what would have been the outcome if this type of dosing were done with corticosteroids in puppies!

The registered dose for dogs over 12 months of age is 0.4-0.6mg/kg twice daily for up to two weeks (or until pruritus is mild) then once a day. A proportion of dogs will show increased pruritus when reduced to once a day. Studies indicate that a significant proportion of these cases will return to acceptable control by 8 weeks of therapy. In the author's experience and that of dermatology colleagues, there are a significant proportion of dogs that will require a second dose, 12 hours later due to unacceptable pruritus. The author's preferred off-label protocol is to try to use a full dose in the morning (or evening if better results) and then to give half that dose 12 hours later. There are cases where a fine adjustment of the dose can give better results with these dogs responding to 0.6mg/kg and not responding to 0.4mg/kg. These is a small group of dogs that will not respond to any dose of oclacitinib despite elimination of infection and Sarcoptes differentials

Due to rapid elimination, oclacitinib is very useful during a dietary elimination trial (single novel protein, 7-8 weeks duration). Owners are instructed to attempt oclacitinib withdrawal at week 3. If pruritus returns, restart oclacitinib 2x day for 2-3 days then once a day (or as dosed previously) and a second oclacitinib withdrawal attempted at week 6-7 while the restricted diet is maintained. After 7 days without oclacitinib and markedly reduced pruritus, a diet rechallenge is performed. After a 7 week food trial, most diet related allergy cases can be identified. Very occasionally, diet trials need to be extended out to 8-10 weeks.

Oclacitinib has been shown to be effective against the pruritus of atopic dermatitis, food related allergy and flea allergy. Oclacitinib is not effective against the pruritus induced by yeast or bacterial infection. In fact, if a dog relapses while on oclacitinib, the most important differential is a reflare of infection.

Side effects

A single long term safety study indicated a favourable long term safety profile. Side effects relating to reduced T-cell function (possibly through inhibition of IL-2 and interferons α and γ) include occasional cases of papillomatosis, pyoderma, skin tumours and demodicosis. Very occasional cases of bone marrow suppression have been identified, potentially due to individual JAK-2 sensitivity to oclacitinib. Given this possibility, it is wise to advise a basic blood profile 60-90 days after initiating oclacitinib therapy and then every 6-12 months thereafter.

A limited study has shown oclacitinib does not interfere with intradermal testing for dust mite allergens. The author and several other colleagues prefer to withdraw the drug at least 4 days before intradermal allergen testing

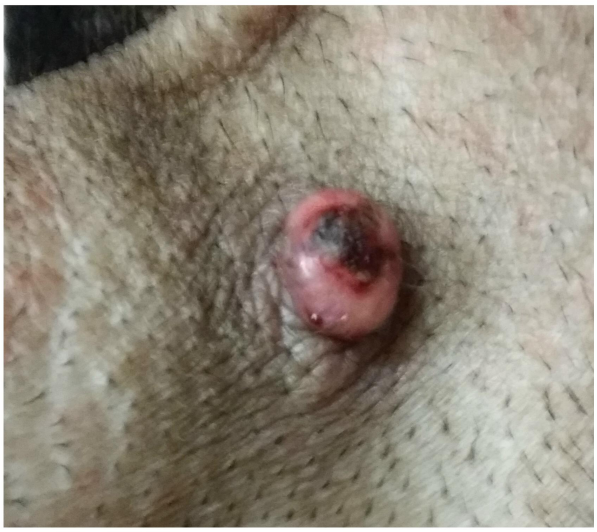
Indications for oclacitinib use

1. Short term pruritus control as a safer alternative to prednisolone
2. During dietary elimination trials
3. Long term if able to be used at the registered dose once a day and the owner is made aware of any potential risks
4. If allergen testing for immunotherapy is contemplated
5. If covered by an isoxazaline drug (fluralaner, afoxalaner, suralaner) to prevent demodicosis

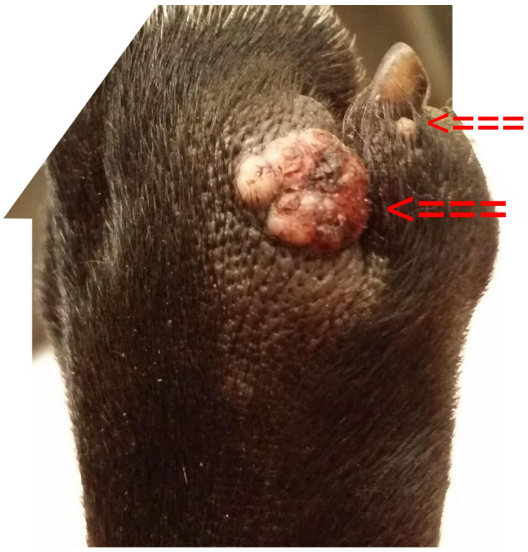
Contraindications

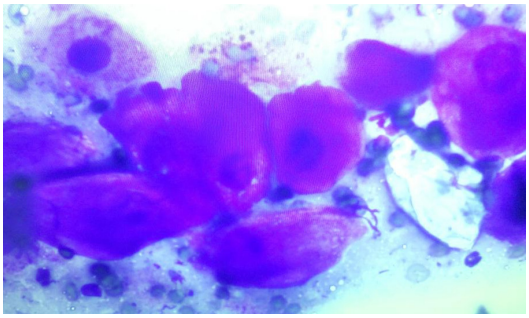
1. Neoplastic disease
2. Animals with a compromised immune system
3. Uncontrolled yeast or bacterial infection
4. If adverse effects or blood monitoring indicates significant bone marrow suppression
5. If no significant response to twice a day dosing at 0.6mg/kg

6. In dogs under 12 months of age. The author has used oclacitinib in younger dogs off label, short term (food trial) , with informed consent and under close observation in cases where no other reasonable alternative exists to relieve suffering
7. If an owner, after advice, prefers to use lokivetmab



Oclacitinib associated multifocal viral papillomatosis and fine needle cytology in a 2 year old dog. Note physical similarity of solitary mass to a “button tumour”. The lesions resolved after oclacitinib withdrawal and short term therapy with azythromycin, interferon-α and topical imiquimod.





Lokivetmab (Cytopoint Zoetis)

Background and pharmacology and side effects

Lokivetmab is the first and currently the only veterinary monoclonal antibody. Its name is based on standard nomenclature LO (identifier) KI (kinase acting) VET (veterinary) MAB (monoclonal antibody).

The antibody is directed specifically at interleukin-31 (see before) and not at an element of the JAK receptor complex.

Lokivetmab is of murine origin but has been caninised to over 90%. Immune rejection over time has been identified in a very small proportion of treated dogs.

No significant side effects other than possible pain at injection site, transient lethargy or mild gastrointestinal signs have been observed. In a controlled trial, side effects were not significantly different in the placebo group.

Efficacy studies

Dose rates trialled extend from 0.5-3.3mg/kg. Doses above 1mg/kg have a high level of efficacy for at least 4 weeks. This is the dose registered in Australia by the APVMA.

Higher doses are associated with longer duration of action. The author has observed that at 1-2mg/kg most dogs will have relief from pruritus for anywhere from 4-7 weeks.

The author's experience mirrors that of Souza et al , 2018 except to date the author has not personally identified any adverse effects. *"Pruritus improvement was achieved in 116 of 132 dogs (87.8%) following initial lokivetmab administration at 1.8 to 3.7 mg/kg ($P < 0.001$). A pVAS reduction of ≥50% was recorded in 104 dogs (77.0%).* ***Dogs with severe/very severe pruritus prior to treatment and large/giant sized dogs, had 2.7 and 2.8 times higher odds of treatment success, respectively. There were no significant associations between treatment success and age of onset of clinical signs, disease chronicity, lokivetmab dosage or age at initial lokivetmab administration. Dogs that did not previously respond to oclacitinib were less likely to respond to lokivetmab****. Adverse effects including lethargy, vomiting, hyperexcitability, pain at injection site and urinary incontinence were reported in 11 of 132 dogs."*

Importantly, a proportion of dogs refractory to oclacitinib WILL respond to lokivetmab. Lokivetmab, like oclacitinib, is unlikely to be effective in the presence of an uncontrolled yeast or bacterial infection.

It is unlikely lokivetmab will interfere with allergen testing for immunotherapy.

Neither oclacitinib nor lokivetmab have the significant drug interactions associated with cyclosporine. Furthermore, lokivetmab MAY be used with other immuno-modulating drugs

Indications for lokivetmab use

1. Owners wishing to have the agent with the best safety profile
2. Owners preferring injection every 4-6 weeks over daily oral medication
3. Where oclacitinib requirements exceed the registered dose
4. In cases of oclacitinib failure or adverse effects
5. Dogs under 12 months of age
6. Neoplastic disease or immuno-compromised animals
7. When allergen testing for immunotherapy is planned
8. In older dogs, lokivetmab may be a preferred option over oclacitinib. Older animals have age related declines in immune function. Oclacitinib is a highly selective T cell modulator but in animals with a declining immune capacity, the least immunosuppressive option may be preferable.
9. In combination therapy for the most refractory cases

Contraindications

1. During trials for food related allergy IF a clear drug withdrawal is needed at a specific date. If using lokivetmab during a diet elimination trial it would seem logical to maintain the test diet for at least 8-9 weeks after the last injection of lokivetmab
2. Non response to doses greater than 2.5mg/kg

Acknowledgments

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