



# Which Drugs Are Most Effective in Managing Atopic Dermatitis?

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Part 1 of this series, published in the January 2016 issue, presents an overview of glucocorticoid therapy as used to treat canine atopic dermatitis (AD). Part 2 covers additional drugs used in the management of this condition.

## Alternative Immunomodulatory Strategies (Systemic)

### Overview

Alternative strategies for systemic control of AD include use of oral cyclosporine in dogs and cats and oclacitinib in dogs.

**Cyclosporine** → A highly recognized viable treatment option for AD and allergic dermatitis, cyclosporine has offered an alternative treatment in dogs and cats with disease refractory to glucocorticoids because of unacceptable side effects or concomitant disease (ie, diabetes mellitus, hyperadrenocorticism, arthritis requiring NSAID treatment).<sup>1-7</sup>

**Oclacitinib** → The only Janus kinase (JAK) inhibitor approved for veterinary use, oclacitinib specifically targets cytokines involved in itch and inflammation in dogs with AD; it is not approved for use in cats.<sup>8</sup>

### Cyclosporine

Modified cyclosporine is a cyclic polypeptide that exerts anti-inflammatory and antipruritic effects and preferentially inhibits activation of T lymphocytes following antigenic stimulation, impairing production of interleukin-2 (IL-2) and other T cell-derived cytokines.<sup>9</sup>

- Binds to cyclophilin, which inhibits the enzyme calcineurine and blocks the nuclear transcription factor (ie, NFAT) involved in the synthesis of IL-2 and other cytokines<sup>10</sup>
- Can block<sup>9</sup>
  - Eosinophil recruitment and activation
  - Production of cytokines by keratinocytes
  - Functions of Langerhans cells
  - Degranulation of mast cells and release of histamine and proinflammatory cytokines
- Relatively poorly absorbed<sup>9</sup>
  - Bioavailability is widely variable, even with modified cyclosporine.

—In cats, bioavailability is highly variable but drug absorption is not significantly changed when cyclosporine is administered with or mixed in food.

- Use of modified cyclosporine highly recommended because it is more uniformly absorbed<sup>9</sup> and therefore more reliable

**Formulation** → Oral (capsule, liquid [cats])

**Dose (dogs, label)** → 5-7 mg/kg once a day for 4 to 6 weeks to determine if medication is effective, then taper slowly to dose and frequency that control disease<sup>9</sup>

- Tapering individualized to each patient
  - Some patients may require daily cyclosporine for maximum efficacy.
- Extralabel using modified cyclosporine: Modified cyclosporine combined with ketoconazole can be given to some patients to reduce dose of cyclosporine (cost factor) while increasing cyclosporine blood concentrations.<sup>9</sup>
  - Ketoconazole at 2.5 mg/kg once a day, modified cyclosporine at 2.5 mg/kg once a day (varies according to weight)
  - Use cautiously, as both ketoconazole and cyclosporine can interact with many other drugs.

**Dose (cats)** → 7 mg/kg once a day for minimum 4 to 6 weeks or until clinical signs resolve; taper slowly to decrease frequency to every other day or twice a week for therapeutic effect<sup>9,10</sup>

- Administer directly by placing with small amount of food or PO immediately after feeding.<sup>11</sup>

### Key Points

- In one study, cyclosporine was shown to be as effective as methylprednisolone for treatment of canine AD.<sup>12</sup>
- In addition to use of modified cyclosporine (as licensed in the United States and Europe), a bioequivalent form has been shown to be effective in dogs.<sup>6</sup>
- Common short-term side effects include nausea and vomiting.<sup>9</sup>
  - Can be prevented by initially administering with food or, in dogs, by short-term use of maropitant or metoclopramide

**Some patients may require daily cyclosporine for maximum efficacy.**

AD = atopic dermatitis, IL = interleukin, JAK = Janus kinase, NFAT = nuclear factor of activated T cells, NSAID = nonsteroidal anti-inflammatory drug



**Alternative Immunomodulatory Strategies (Systemic)**  
*(continued)*

- Common long-term side effects include gingival hyperplasia, soft stools, diarrhea, weight loss, lethargy, and (cats only) drooling.<sup>9,10</sup>
  - Rarely, cats have developed fatal infections caused by *Toxoplasma* spp or *Mycobacterium avium*.<sup>13-16</sup>
  - Dogs have developed cutaneous fungal infections.<sup>17</sup>
  - A small number of dogs and cats have developed psoriasiform lichenoid dermatitis.<sup>18</sup>
- Modified cyclosporine is not recommended for use in dogs or cats with a history of neoplasia.<sup>10</sup>
- **Cats:** Modified cyclosporine use<sup>10</sup>
  - FIV and FeLV testing recommended to ensure negative status
  - Safety not evaluated in cats younger than 6 months of age, breeding, pregnant, or lactating
  - Recommended for indoor-only cats (ie, prohibited from hunting)
  - Not recommended for cats fed raw diets
- **Dogs:** Modified cyclosporine use<sup>10</sup>
  - Safety not evaluated in dogs younger than 4 months of age, breeding, pregnant, or lactating
  - Author recommends not administering to dogs younger than 1 year of age.
  - Not recommended for dogs fed raw diets
- Although product label recommends administering to dogs on an empty stomach,<sup>10</sup> a recent study has shown clinical benefit when administered with or without food, at least in cats.<sup>19</sup>

### Oclacitinib

Oclacitinib is a synthetic JAK inhibitor selective for JAK-1. Cytokine receptors using JAK-1 in combination with JAK-3 mediate the function of several cytokines, particularly those involved with allergic itch and inflammation (ie, IL-2, IL-4, IL-6, IL-13, IL-31). Cytokine has minimal activity against JAK-2, the kinase involved in hematopoiesis and antigen presentation.

- IL-31 is one of the major cytokines mediating itch. Its signaling is particularly sensitive to the inhibitory effects of oclacitinib.
- Pruritus is rapidly controlled because IL-31 binding to its receptor on nerves does not induce signaling.

**Formulation** → Oral (tablet)

**Dose (dogs, label)** → 0.4-0.6 mg/kg twice a day for up to 14 days, then once a day thereafter if used for long-term maintenance therapy.

- Oclacitinib can be used in the short-term to treat the flares of any allergic dermatitis, including flea allergy and food allergy.
- Can be used to manage atopic flares for dogs taking allergen-specific immunotherapy (ASIT), as well as during the induction period of ASIT to control itch

ASIT = allergen-specific immunotherapy,  
FDA = Food and Drug Administration,  
FeLV = feline leukemia virus,  
FIP = feline infectious peritonitis,  
IL = interleukin, JAK = Janus kinase

- Approved for use in dogs 1 year of age or older<sup>8,20</sup>
- Off-label use: A small number of canine patients may need twice-a-day administration for periods longer than 2 weeks.
  - Off-label administration requires careful monitoring, particularly of blood cell counts, as anecdotal (clinical) evidence of anemia, leukopenia, and thrombocytopenia have been observed by veterinary dermatologists.

**Dose (cats)** → Not FDA approved for use in cats<sup>20</sup>

### Key Points

- Shown to be at least as effective as glucocorticoids or cyclosporine<sup>21,22</sup>
  - However, appears to be very effective in dogs with disease refractory to glucocorticoids or failed cyclosporine therapy
- Exclude ectoparasites and infections as contributing factors to AD.
  - Critical to rule out because oclacitinib represses allergic pruritus<sup>20</sup>
- No safety studies conducted in breeding, pregnant, or lactating dogs
  - Safety studies in dogs 4 to 6 months of age using 3 and 5 times recommended doses reported demodicosis, sepsis, and pneumonia.<sup>20</sup>
- Most common side effect reported is upset stomach, seen in <5% of dogs.<sup>23,24</sup>
  - Additional reported side effects included diarrhea, lethargy, increased nodules (eg, sebaceous adenomas, follicular cysts, lipomas), and pododermatitis.
- Some patients may experience increase in pruritus when dose is reduced from twice a day to once a day. In most cases, this is mild and can be managed by bathing with nonirritating shampoos (eg, fatty acid, phytosphingosine, ceramide-containing products).<sup>24,25</sup>
- Oclacitinib should be given in the evening to maximize benefits.
- Recent long-term study followed 247 dogs receiving daily oclacitinib for up to 630 days<sup>25</sup>
  - Study not placebo controlled, but most common side effects cited were vomiting, diarrhea, otitis externa, pyoderma, and urinary tract infection
  - Sixteen dogs developed neoplasms, but study authors could not attribute tumors to oclacitinib.
- Anecdotal evidence of outbreaks of demodicosis and histiocytomas have been reported in low numbers by dermatologists.
- **Warnings**
  - Do not use in dogs with serious infections.<sup>20</sup>
  - Oclacitinib administration may increase patient susceptibility to infection (including demodicosis) and may exacerbate neoplastic conditions.<sup>20</sup>

**Dexamethasone injection can be used to rapidly reduce pruritus.**

### Author Insights

Allergic dermatitis and AD are chronic, incurable diseases that require a multimodal approach to treatment. Before initiating therapeutic strategies, clinicians should perform a thorough dermatologic workup.

### Bridging the Gap



**Bridging the Gap** →  
*(continued)*

Furthermore, successful management of the disease involves more than specific use of the medications discussed here and in part 1. Success also depends on rigorous flea control and effective topical treatment of cutaneous infections, along with systemic antimicrobial treatment as necessary.

- The presence of fleas, staphylococcal pyoderma, or dermatitis caused by *Malassezia* spp infection will often induce flares in otherwise well-controlled patients.
- Of note, pruritus associated with these complications may be glucocorticoid-resistant, and controlling ectoparasites and infections can assist in keeping steroid doses low.
- Likewise, although cyclosporine may not be an effective treatment in all patients with AD and with allergic dermatitis, the presence of fleas, staphylococcal pyoderma, or dermatitis associated with *Malassezia* spp infection can induce flares.
- In addition, if response to oclacitinib treatment is poor, clinicians should consider occult scabies, uncontrolled fleas, and/or untreated infections caused by *Staphylococcus* spp, *Malassezia* spp, or both.

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AD = atopic dermatitis

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