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How I treat Atopy with cyclosporine
Dra. Chiara Noli, DVM, Dip ECVD
Servizi Dermatologici Veterinari
Peveragno (CN), Italia

Cyclosporine
Cyclosporine is a polypeptide derived from the fungus *Tolypocladium inflatum*. Its mode of action is by inhibiting the enzyme calcineurin. It has a variety of immunological effects on multiple members of the skin immune system and is active in the acute and chronic phase of atopic dermatitis. In the acute phase, cyclosporine acts against the initiators of the immune response (inhibiting Langerhans antigen presenting cells and inhibiting lymphocyte proliferation and cytokine production from Th2 cells and keratinocytes). The effector cells of the acute phase are also inhibited. Cyclosporine inhibits mast cell degranulation and the production of mast cell inflammatory mediators and cytokines. Eosinophil function is inhibited through reduced mast cell products and by direct inhibition of eosinophil degranulation and inflammatory mediator production/release. In the chronic phase of atopic dermatitis cyclosporine inhibits both the production of and the response to Th1 cytokines (e.g. interleukin-2) and inhibits cytokine production by macrophages. Cyclosporine has lesser affect on B-lymphocytes.

Cyclosporine has the same efficacy rate as prednisolone in the control of symptoms of atopic dermatitis. A lag period of about 2-3 weeks, in which no response is seen, occurs after cyclosporine treatment is started. Significant reduction in pruritus is expected in over 85% of cases within one month of treatment. To maximize absorption, cyclosporine should be administered two hours before a meal. However, there has been recent data suggesting that giving cyclosporine with food does not alter clinical outcomes.

The metabolism and excretion of cyclosporine is an active process involving active pumping of the drug through the cell membrane via microsomal cytochrome P-450. Ketoconazole and erythromycin actively compete for cytochrome P-450, increasing bioavailability levels of cyclosporine by up to 200%, hence reducing the dose of cyclosporine required by up to 75%. The effect of ketoconazole on cyclosporine blood levels is dose dependent. Ketoconazole at 5mg/kg SID has been shown to reduce cyclosporine dose rates needed for steady blood levels by average of 38% while doses of 13.6mg/kg SID reduced cyclosporine doses by 75%. Within the groups of dogs studied there as considerable individual variation in the effect of ketoconazole.

The frequent hepato/nephrotoxic side effects seen in humans are not recognized in dogs. Side effects reported are transitory vomiting (controlled by metoclopramide, temporarily reducing the dose or giving the drug with food), reversible gingival hyperplasia, hyperkeratosis and hirsutism. Humans with cyclosporine-induced gingival hyperplasia respond to antibiotics, especially azithromycin. A retrospective study on 51 dogs receiving cyclosporine therapy for atopic dermatitis (Radowicz and Power, 2005) showed 71% owner satisfaction with the treatment. Two dogs developed gingival hyperplasia, three dogs developed hirsutism and 78% of owners reported no adverse events in their dogs during the treatment period. Before the drug can be declared safe for long term use, further follow-up studies are required. Cyclosporine can be used in cats at 5mg/kg SID but sporadic cases of toxoplasmosis have been reported in cats receiving cyclosporine.

Cyclosporine in canine atopic dermatitis
Suggested protocol for cyclosporine therapy in atopic dogs is the following:

- Daily administration at a dose rate of 5mg/kg for a period of four weeks.
- Concurrent use of other symptomatic control medication (prednisone 0,5mg/kg), on a scaling-down basis, for the two to three weeks.
- If after four weeks of daily cyclosporine therapy there is a reduction in pruritus, begin to scale back the dose. About 50% of responding dogs can be reduce to every second day therapy while 25% of dogs can be reduced to every third day or less.
- If there is no response to daily administration of cyclosporine by 40 days, the drug may not be effective in that patient or concurrent pruritogenic factors (dietary allergy, secondary infection or ectoparasites) may not have been controlled.
- Once a stable base line dose of cyclosporine has been achieved and cost is a factor, a trial with ketoconazole (initially 10mg/kg SID or divided BID) can be undertaken to further reduce the dose or frequency of administration.
- The patient should be monitored for secondary infection or any side effects.
- In seasonal cases, cyclosporine therapy can be suspended for part of the year and restarted before the expected onset of clinical signs.

A significant minority of atopic dogs treated with cyclosporine may go into remission when treatment is suspended. In a recent study using cyclosporine or prednisolone for four months, 38% of dogs treated with cyclosporine were in remission two months after therapy was stopped (in comparison to 13% for the prednisolone group).

**Cyclosporine in allergic cats**

Cats should be tested for toxoplasmosis before the beginning of the therapy, because several cases of fatal toxoplasmosis induced by cyclosporine have been described. Toxoplasma-negative cats should not be fed raw meat and should not be allow to hunt. Furthermore it is important to test for viral diseases (FIV and FeLV) before starting the therapy and consider advantages and disadvantages of treatment in case of positivity.

The most prevalent use of cyclosporine in cats is for the symptomatic relief of signs of allergy and lesions of the eosinophilic granuloma complex.

The first report describes six cats with eosinophilic plaque, three cats with oral eosinophilic granuloma and three cats with lip (indolent) ulcer treated with 25mg/cat cyclosporin for 60 days. The cats with eosinophilic plaque and oral eosinophilic granuloma experienced a complete recovery, while in the other three cats with lip ulcer only a partial remission was achieved.

In another more recent retrospective study cyclosporine was given at the dosage of 50mg/cat (average dosage 5,8-14,2 mg/kg) per day for 30 days, then every 48 hours for one or two months thereafter, to seven cats with eosinophilic plaque and/or oral and/or cutaneous eosinophilic granuloma and/or lip ulcer, and eight cats with idiopathic pruritus. All cats were cured within 60-90 days and maintained in remission on alternate day therapy.

A prospective open pilot study evaluated the efficacy of cyclosporine at the dosage of 25mg/cat (3,6-8,3 mg/kg) in 10 cats with signs of allergic skin disease including pruritus, various degrees of self-inflicted alopecia, erythema, miliary dermatitis, and eosinophilic plaques. Fifty percent of the animals responded well or were cured after 30 days.

Very recently a double blinded, randomised, prednisolone-controlled study found no difference between 18 cats with presumed atopic dermatitis treated with 5 mg/kg per day of cyclosporine to 11 cats treated once daily with 1 mg/kg prednisolone for one month. In this study pruritus decreased in 61% and clinical scores decreased by at least 50% in 55% of the cats treated with cyclosporine.

These data taken together suggest that cyclosporine is effective in improving or healing the clinical manifestations of feline allergic skin diseases at the dosage of 5-10 mg/kg (25mg/cat) once daily for a minimum of 1-2 months (once daily for one month, then every-other-day treatment).

As an alternative to long-term use of corticosteroids, cyclosporine at the dosage of 7mg/kg once daily has been regularly used also in cats. A lag period of about 2-3 weeks, in which no response is seen, occurs after cyclosporine treatment is started. Sporadic cases of toxoplasmosis have been reported in cats receiving cyclosporine, thus testing for this disease before starting the therapy is highly recommended.

**Selected references**

**Review articles**


Other references not cited in the review articles


