How to treat atopy in cats?

E. Vidémont [1], *D. Pin*[1]

SUMMARY

Therapy of atopic dermatitis (AD) can be a challenge to the clinician's therapeutic skills and selecting the best treatment plan for individual situations is an art. Cats diagnosed with AD are treated in a variety of ways depending upon the severity of clinical signs, duration or owner preference. Treatment options include allergen avoidance, treatment of aggravating factors, allergen specific immunotherapy (ASIT) and symptomatic therapy of pruritus. This article presents an update of these different options.

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Introduction

AD in cats is not well known and its pathophysiology is unclear. Some authors consider feline atopy to be similar to the human and canine form while others have obtained contradictory findings. There may be particular differences relating to cats but investigation of these has not been performed. There have been very few controlled studies in cats. Such studies that have been carried out must be examined critically partly because they often involve only small numbers of cats and partly because of differences in approach to diagnosis. For example, in some studies, there is confusion between flea bite hypersensitivity and AD. As in the dog, it is important to consider the hypersensitivity threshold concept. Each animal has its own pruritic threshold, the level of stimuli resulting in pruritus. Once this threshold is reached, additional stimuli will increase pruritus and other clinical signs. It is therefore important to reduce or eliminate additional stimuli. Infections must be searched for and treated. Strict flea control must be maintained.

Allergen avoidance

In practice, only food allergens can really be avoided. Avoidance of aeroallergens is only practical if the allergens concerned are in a limited area from which the allergic cat can be excluded. The most important allergens for cats in Europe are house dust mites and although various measures aimed at reducing their number can be recommended, these are only likely to be effective if combined with other procedures: very regular ventilation of the cats' surroundings, frequent aeration of duvets, mattresses and blankets, use of a vacuum cleaner fitted with special filters, treatment of resting areas with a combination of insecticides and insect growth hormone regulators, and steam cleaning of sleeping areas [24].

Treatment of aggravating factors and disease

Microbial proliferation

Although bacterial [24] and *Malassezia* [22] overgrowth are less common in cats than in dogs, they can be observed in allergic cats and cause additional pruritus. These complications should be searched for by taking tape strip impressions and, treated, if present, with appropriate antimicrobial or antifungal therapy. Antiseptic shampoos, particularly those containing chlorhexidine, could help prevent relapse. In cats, shampoos are rarely used because cats have a reputation (often unjustified) for not liking being washed. However, shampoos, when it is possible to apply them easily, form an effective adjunctive therapy. Antiseptic solutions can now be applied in a spray formulation. Canine shampoos containing quaternary ammonium compounds and phenols can be toxic in cats and must be avoided.

Dry skin

Dry skin is associated with atopic dermatitis. The functional integrity of the epidermis relies particularly on intercorneocyte sheets of lipids. Disorders of epidermal lipid metabolism account for the defect in barrier function in atopic dog [23]. If we assume that a similar phenomenon occurs in the cat, several approaches can be used to restore epidermal barrier function.

- Essential fatty acids (EFA)

The used of EFAs is proposed for several reasons:

- They seem to contribute to the restoration of skin barrier function [23],
- They have been shown to exert anti-inflammatory effects in various in vitro and in vivo models, and
- They seem to have positive effects on the quality and luster of the hair coat.

1) Emilie Vidémont and Didier Pin, Unité Dermatologie, Ecole Nationale Vétérinaire de Lyon, France
E-mail: e.videmont@vet-lyon.fr

EFA products generally contain a mixture of gamma linolenic acid and eicosapentaenoic acid. EFAs can be administered in food as a capsule, oil or spray. For several years, EFAs have also been supplied in some dry pet foods. There are few reports on the effectiveness of fatty acid supplements to control pruritus in the cat [Table 1]. In several open trials [10, 11, 12, 19], cats with pruritus, eosinophilic granuloma complex (EGC) and miliary dermatitis secondary to flea bite hypersensitivity or atopy were treated with various combinations of evening primrose oil and fish oil. These studies suggest that cats respond favorably to EFA with variable efficacy. A double-blinded study by Logas et al. showed no significant difference between two groups of cats receiving either evening primrose oil liquid or olive oil [15].
Side-effects of EFA are very uncommon (occasional vomiting) but palatability is, often, considered to be poor.
To summarise, EFA supplementation may improve coat condition but its true clinical efficacy remains uncertain.

- Moisturisers and emollients

They are useful in the treatment of dry skin. Products with propylene glycol, glycerine and urea can be used in cats.

Psychogenetic factors

A link has been established in man between anxiety and atopy, with stress aggravating the clinical signs. It is possible that a similar link exists in the cat. Severe, prolonged pruritus can induce a state of anxiety and behavioural problems. When cats have extensive lesions, especially on the face, marking is decreased. Moreover, owners are sometimes reluctant to stroke their pets. If anxiety or behavioural problems are suspected, behavioural therapy or treatment with pheromones or psychotropic drugs may be given. Several sedating antihistamines also have anxiolytic properties. It may be speculated that this is the reason for some of the beneficial effects of this group of drugs in atopy.

Allergen-specific immunotherapy

Allergen-specific immunotherapy is defined as the practice of administering gradually increasing quantities of an allergen extract in order to reduce or eliminate the signs associated with subsequent exposures to the causative allergen. Few studies have been performed in feline atopic patients and most information is anecdotal. The mechanism of action in both the canine and feline atopic patient has not been fully elucidated.

For an effective response to ASIT, the relevant allergens must be selected, typically by identification of high levels of allergen-specific IgE in the sera and/or by positive skin test results to the allergen. One of the major problems in the cat is the low level of accuracy associated with these tests. [see previous article in this issue]

The injection schedule is borrowed from canine medicine and depends on the company that prepares treatment. No standardisation exists in cats. The schedule involves injecting a gradually increasing amount of allergen over a period of several weeks (induction phase). This is then followed by a gradual reduction in the frequency of injections but leaving the amount of allergen constant (maintenance phase). Current recommendations [33] are to encourage owners to continue ASIT for at least 1 year before discontinuing therapy. Improvement may be monitored by the dose and frequency required of additional medications and the pruritus scores that owners have assigned to their pet during the course of the therapy. In cats that exhibit only minimal to moderate improvement during the first year of ASIT, the clinician and owner have to decide whether or not continuing ASIT provides therapeutic benefit to the patient. In patients that exhibit good to excellent response to ASIT after 6 months to 1 year, the recommendation would be to reduce gradually the frequency of the injections over the subsequent year. If, after one year, the cat's allergies are controlled with no clinical signs attributable to allergy or need for other medications, the recommendation would be to discontinue the injections and monitor the patient for recurrence of clinical signs. Although immunotherapy is usually continued lifelong, it may, in a few cases, be discontinued after some years without recurrence of clinical signs.

Reported success rates [Table 2] range from 50 to 100 % in feline atopic patients [3, 4, 9, 16, 25, 26]. However, a placebo-controlled trial demonstrating unequivocally that cats respond to immunotherapy would be useful. In the majority of studies,

Tab. 1 Trials reporting treatment with EFA in management of feline AD.

Study	Product	Patients	Results
Harvey 1991 [10]	Evening Primrose oil + fish oil (Efa-Vet 2 capsules)	8 cats with military dermatitis	6 cats good response with absence of papules, decrease of pruritus and improvement in coat condition
Harvey 1993 [12]	Evening primrose oil (6 cats) or sunflower oil (5 cats)	11 cats with military dermatitis	Improvement of all cats, better efficacy of evening primrose oil
Harvey 1993 [11]	Various combinations of evening primrose oil and fish oil	14 cats with military dermatitis	Improvement with evening primrose oil. No effect of fish oil alone
Miller 1993 [19]	DVM Derm Caps Liquid™ 1 mL/9.1 kg once daily 14 days	28 cats with various pruritic dermatosis, military dermatitis and EGC	Complete resolution in 13 cats At least 50 % improvement in 3 cats
Logas 1993 [15]	Double-blinded study. Evening Primrose oil versus olive oil	15 cats	No significant differences between the two groups

Studies and their result on ASIT in the cat	Number of cats	Response rate (%)
Reedy 1982 [26]	20	55 % response
McDougal 1986 [16]	13	69 % : good response 23 % : moderate response 8 % : bad response
Carlotti 1988 [4]	6	66 % excellent response
Prost 1992 [25]	28	78 % response
Bettenay 1996 [3]	29	Overall success rate of 50 %. Success rate decreases after 3 years of follow-up
Halliwell 1997 [9]	42	Improvement ranges from 53.3 % (hair loss) to 100 % (linear granuloma) according to the dermatologic signs

Tab. 2 Trials reporting results of ASIT in the management of feline AD.

period evaluation is short, generally under a year and it is interesting that success rate decreases when the follow-up period is longer. In a study by Bettenay [3], success rate after one year is similar to than in other studies but it decreases significantly after 3 years of treatment.

Side-effects are rare and include worsening of clinical signs for a few hours to days, local reactions at injection site and anaphylaxis. Increased pruritus or local reactions can usually be managed by reducing the injection dose. The dose can later be increased gradually after a period of stabilisation. Even though life-threatening anaphylaxis is extremely rare, it is important to educate owners about this possibility. Anaphylaxis occurs within the first 30 to 60 minutes after the injection. Animals should be monitored during this time. If vomiting, diarrhoea, dyspnoea or collapse occur, the owner must seek immediate veterinary emergency care. The risk of inducing fibrosarcoma has never been investigated.

Rush allergen specific immunotherapy (RIT) is a technique of advancing an allergic patient to a maintenance dose of an extract over a shorter period of time than that required for the traditional induction period. RIT would minimise the owner's burden and may result in improved compliance. Typically, RIT is given over 8 hours as opposed to 25 days usually needed for induction. At present, RIT has been evaluated in 4 feline atopic patients [32] and in an experimental model of feline asthma [27]. Further studies are required.

Symptomatic therapy of pruritus

Therapeutic options include the use of glucocorticoids, antihistamines, EFA and cyclosporin.

Glucocorticoids

Until recently, corticosteroids were the mainstay of therapy for allergic cats.

Glucocorticoids can be administered by injection, orally or topically.

It is unusual to rely on topical therapy alone because cats are adept at grooming away topical products. Hydrocortisone aceponate, now commercially available, could be used. Its rapid penetration of the stratum corneum and metabolism in the skin are interesting.

Injectable preparations are popular, especially with cats that resent being given pills. Methylprednisolone acetate is often successful at a dose of 20 mg (or 4 mg/kg) every two to three weeks for a total of three injections [6]. Maintenance doses may be given every six to 12 weeks. Unfortunately, an initial beneficial response to injectable therapy can be followed by a reduced response and, consequently, a reduction in the interval between injections. Therefore, injectable methylprednisolone acetate should not be a standard therapy. Prednisolone or methylprednisolone are used orally at a dose of 1 to 2 mg/kg per day. After seven days, the dose should be reduced by 50 per cent for a further seven days followed by alternate day therapy and a search for the minimal effective dose. Some cats can be maintained on doses of 0.5-1 mg/kg on alternate day to alleviate pruritus. Cats have unpredictable absorption or metabolism (to the active form) of prednisone, which should not therefore be used in this species. Other oral steroids that may be useful in cases that fail to respond, or become resistant to the effects of the previously mentioned steroids, include oral triamcinolone (0.1-0.2 mg/kg/day) and dexamethasone (0.1-0.2 mg/kg/day). Their long duration of action requires an administration only every 3 days if they are used long-term [6].

Intralesional injections of corticosteroid have been described for severe refractory indolent ulcer (IU) and eosinophilic granuloma (EG) but benefit remains unproven.

Although glucocorticoids are effective and safer in cats than dogs, they are not without side-effects and often become less effective with time. Adverse effects include polydipsia, polyphagia, weight gain, diabetes mellitus, iatrogenic hyperadrenocorticism with fragile skin syndrome and urinary tract infections, dermatophytosis, demodicosis, and gastric ulceration.

Drug	Mechanism of action	Dosage	Comments	Study
Clemastine fumarate	H1-blocker antihistamine. Centrally mediated, synergistic with EFA	0.34-0.68 mg/cat PO BID	Diarrhea, lethargy, fixed drug eruption	Miller 1994 [20]: 10 cats 0.68 mg/CT, response in 5/10 cats
Hydroxyzine hydrochloride	Stabilizes mast cell membranes, centrally mediated	1-10 mg/kg PO BID or TID	Behavioral changes (hyperexcitability or depression), teratogenic	
Diphenhydramine		1-2 mg/kg BID to TID	Liquid form : alcohol base that cats strongly dislike	
Chlorpheniramine maleate	Centrally mediated	2-4 mg/cat PO SID to TID	Transient drowsiness, unpalatable (extremely bitter tasting)	Miller 1990 [18] 26 cats 2 mg/cat every 12 hours. Excellent response in 73 %
Cyproheptadine hydrochloride	H1-blocker antihistamine and serotonin antagonist	2 mg/cat PO BID (1 mg/cat, q 24h, to 8 mg/cat, q8h)	Polyphagia, behavioral changes, vocalization, sedation, vomiting, affectionate behavior	Scott 1998 [31] 20 cats, 2 mg, q12h, for 2 weeks. Good or excellent response in 9 cats (side effects in 8 cats, severe in 3)

Tab. 3 Trials reporting treatment with antihistamines in the management of feline AD.

Glucocorticoids can be considered a reasonable choice in animals with mild seasonal pruritus of only a few months duration but their long-term use should be undertaken with care.

Antihistamines

Several antihistamines have been used in cats [Table 3]. There are no placebo-controlled studies of antihistamines in cats, so the dosages recommended are empirical and based on open trials. Efficacy is often low and very variable with different authors reporting a success rate of 20 to 73 % [6, 18, 20, 31]. Administer the antihistamine for at least three weeks before evaluating a patient's response. If effective, antihistamines must usually be given once a day indefinitely. The success rate may be increased by trying several different antihistamines sequentially as patients may be responsive to one antihistamine but not to another.

The advantage of antihistamines is the rare occurrence of side-effects. The main side-effects are increased appetite and sedation, although paradoxically, there can be hyperexcitability. Gastrointestinal signs are uncommon. The frequent administration (two to three times daily) limits their long-term use in many feline patients.

Antihistamines may be synergistic with glucocorticoids or EFAs.

Essential fatty acids (EFAs)

See part 3.

Cyclosporin A (CsA)

CsA is a potent inhibitor of cell-mediated immunity, and a less potent inhibitor of humoral immunity. CsA also has a variety of anti-inflammatory effects on leucocytes other than lymphocytes, and on other types of cell, including keratinocytes and endothelial cells [28].

CsA is not licensed for use in cats. It is available as a solution or capsule. Dermatologists tend to use the microemulsion concentrate which is presumed to provide better absorption. It is not known if food affects the absorption of CsA in cats but a majority of authors recommend giving CsA at least 2 hours before or after meals. One study found no difference between the two formulations, although cats given capsules received a lower dose [34]. The liquid form allows more flexible dosing but is bitter tasting. Initial doses vary between 3.6 to 13.3 mg/kg but in the majority of cases are about 5 mg/kg or 25 mg/cat once daily. CsA must be administrated once daily until complete remission of clinical signs, then in an alternate day regimen for least two months and eventually a twice weekly administration for an unlimited duration. If it is stopped immediately after remission of clinical signs, relapse will probably occur [8]. Therefore, it is important to prolong maintenance therapy by increasing the interval between administrations and searching for the minimal effective dose.

In cats, successful use of CsA has been described principally in small, open and uncontrolled trials [Table 4]. Efficacy is generally very good. It is difficult however to compare the results of studies because formulation, clinical signs and evaluation period are different. Sometimes, the study period is too short [21], generally one month. This could lead to a lower success rate because remission of clinical signs may take longer than one month. In one study, pruritus and EG were the clinical signs which responded best, with a significant improvement seen after 10 days of treatment and complete remission after 30 days. However, it took 60 days to obtain complete remission of eosinophilic plaque (EP) lesions [8]. It is sometimes necessary to administer the drug once daily for two or three months before obtaining remission. Only one study compares the effects of prednisolone and CsA on skin lesions and pruritus in a double-blind pattern [36]. The effect of CsA is approximatively 70 % and

Study	Protocol	Outcome	Side effects
Guaguère 2000 [8]	12 cats with ECG. 25 mg CsA/cat once daily (4.9-12.5 mg/kg/day) for 2 months	By day 60, cats with EP and EG were completely cured. In 2 cases, relapse by day 90. In 3 cases of indolent ulcer, only partial regression	
Noli 2006 [21]	10 cats. 25 mg/cat once daily (3.6-8.3 mg/kg/day), preferably on an empty stomach, for one month	Good to excellent improvements was observed in 40 % of cats for pruritus, 57 % of cats for alopecia, 60 % of cats for erythema and 50 % of cats for the total lesions.	Mild diarrhea in one cat, which disappeared promptly with symptomatic therapy without the cessation of the ciclosporin therapy
Vercelli 2006 [34]	15 cats with EGC 5.8 – 13.3 mg/kg Solution once daily or caps twice a day, 2 h before or after meals, for one month.Then CsA continued every other day for 1 or 2 months until remission. Maintenance regimen: twice a week administration for an unlimited duration Study period: 6 months	Cure in all cats	In one cat, capsules caused diarrhea, disappeared with liquid formulation
Wisselink 2009 [36]	29 cats Oral therapy for 4 weeks with either one capsule of CsA 5 mg/kg SID (18 cats) or one capsule of prednisolone 1 mg/kg SID (11 cats) 2h before meals	No significant difference between the two groups. The effect of CsA is approximatively 70 %	11 cats treated with CsA involving intermittent vomiting, diarrhea or loose stools, hyperactivity, increased appetite, polydipsia

Tab. 4 Trials reporting treatment with cyclosporin A in the management of feline AD.

no significant difference was found between the two groups.

The main disadvantage of CsA is its high cost. In cats, few adverse reactions to CsA have been reported [29]. Gastrointestinal signs (vomiting, diarrhoea and anorexia) are most frequently reported. Other adverse events include salivation, headshaking, intermittent soft faeces, gingival hyperplasia [14], hyperactivity, increased appetite and polydipsia [36]. Vomiting can often be overcome by giving the drug with a very small amount of food. To minimise vomiting, the dose can be gradually increased or metoclopramide can initially be given concomitantly.

A recent concern associated with CsA therapy is the increased risk of developing systemic toxoplasmosis and viral diseases. No publication exists at present concerning the association of viral diseases such as feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) with CsA treatment. In a study by Vercelli, no clinical expression of viral disease was apparent during the 6-month study period in the two cats found to be FIV-positive before CsA therapy [34]. Therapeutic doses of CsA have induced fatal toxoplasmosis in three cats following renal transplant surgery [2], two cats with atopy [1, 13] and one cat with immune-mediated haemolytic anaemia. Cats can develop systemic toxoplasmosis either by reactivation of latent infection or by primary infection. Precautions to consider during immunomodulatory therapy would include feeding only commercial cat food or other cooked foods, avoiding raw meat, poultry, viscera or bones and preventing hunting and scavenging. Monitoring of serological antibody status, for both IgG and IgM class antibodies to Toxoplasma gondii, both prior to initiation of immunomodulatory therapy, as well as during immunosuppressive therapy, might be helpful to detect seroconversion. When seroconversion occurs, or significant rises in toxoplasma antibody titres are observed in association with developing clinical illness in cats which were seropositive prior to initiation of immunosuppressive treatment, antitoxoplasma chemotherapy should be started immediately to prevent acute systemic toxoplasmosis.

These measures are difficult to apply in practice. It may be helpful to evaluate serological antibody status of cats for both

Tab. 5 General recommendations concerning the use of CsA in management of feline CsA.

- Before treatment: Check for FIV/FeLV and toxoplasmosis serological status
- In first intention: Microemulsion concentrate, capsules giving at least 2 hours before or after meal
- Induction phase: One capsule of 25 mg/cat once daily until complete remission of clinical signs (sometimes two to three months)
- Maintenance regimen: Increasing intervals between administrations and searching for the minimal effective dose.
- Whole blood level of 250 to 500 ng/mL is recommended. Whole blood levels higher than 1000 ng/mL can cause side effects. Measuring blood CsA concentrations in cats 2 h after oral administration [17].

Treatment	Dose	Mode of action	Side effects
Chlorambucil	0.1 to 0.2 mg/kg daily or every other day, in combination with steroids	DNA synthesis and inhibition of rapidly proliferating cells at all stages of the cell cycle	Vomiting, diarrhea, anorexia and, more importantly, bone marrow suppression
Gold salt therapy Chrysotherapy Sodium aurothiomalate	1 mg/kg intramuscularly every week, then every month	variety of influences on immune function including neutrophil migration, lymphocyte function and immunoglobulin production	glomerulonephritis, bone marrow suppression, thrombocytopenia and cutaneous eruption
Megestrol acetate		anti-inflammatory properties	polyuria, polydispsia, mammary gland hyperplasia, behavioral problems, potentially irreversible diabetes mellitus, iatrogenic hyperadrenocorticism and, possibly, mammary neoplasia

Tab. 6 Some of old treatments recommended in the literature in the management of ECG and pruritus in cats.

FIV/FeLV and toxoplasmosis before starting CsA. However, the risk seems to be low.

Others treatments

Several others treatments have been recommended in the literature, especially for the management of EGC lesions. All reports of these treatments are anecdotal with no proof of efficacy.

Old treatments include chlorambucil, aurothioglucose and progestagens [7]. These options are expensive, usually unlicensed, require careful monitoring and are not always effective [Table 6]. More recently, amoxicillin-clavulanate [35], an analogue of palmitolethanolamide called PLR-120 [30] and interferon α have been proposed [5] but further studies are necessary to evaluate these drugs.

Conclusion

Feline atopy is a disease recognised more frequently in recent years and there have been many studies concerning its management. In the majority of cases, a combination of treatments is needed. Topical treatments are often useful. The results of ASIT are very inconstant in cats. Antihistamines and essential fatty acids may be synergistic with others drugs but their efficacy is often low. Steroids, when used as long-term maintenance therapy, are associated with several side-effects. Cyclosporin may be a useful alternative therapy because it is safe and effective in most cases. However, the existence of a new antipruritic drug is no excuse for avoiding the difficult task of establishing a definitive diagnosis in the itchy cat!

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