ROYAL CANIN WEBINAR 2017: DIAGNOSIS AND MANAGEMENT OF THE ALLERGIC CAT

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Introduction

In 2015, the International Committee on Allergic Diseases of Animals (ICADA; www.icada.org) updated the guidelines for treatment of atopic dermatitis (AD) in dogs. These recommendations are generally made from evidence derived from previously published randomised controlled trials and systematic reviews. No such document exists for the treatment of allergies in cats. Evidence is predominantly limited to uncontrolled clinical trials or a consensus among authors for recommending a treatment intervention.

Using the framework of these published guidelines, this lecture is divided into three different sections: recommendations for i) the management of acute flares of feline allergic skin disease, ii) the treatment of chronic skin lesions of feline allergic skin disease, and, iii) the interventions to prevent disease relapses. These recommendations must be evaluated by veterinarians taking into consideration both patient and owner factors. Practitioners should always assess the benefit, side effects, practicability, cost and availability of the proposed treatments, which often will have to be combined for an optimal outcome.

ICADA has also considered the terminology for allergic skin diseases of cats. The consensus of the committee was to adopt the term "feline atopic syndrome" (FAS) which would specifically exclude parasitic causes but include environmental allergen causes and some manifestations of food reactions. The committee acknowledge that further refinement and standardisation is indicated for the terminology for feline allergic skin diseases.

1. Management of acute flares of feline allergic skin disease

A. Identify and avoid flare factors: acute flares of FAS can be caused by flea bites; a recent increased exposure to environment allergens (especially house dust mites and pollens) and the ingestion of food ingredients. Cats with allergic dermatitis are predisposed to secondary infections with bacteria and yeast and yeast otitis externa is a common complication.

i) **Implement flea control:** definitive evidence of flea infestation can be challenging in cats reflecting both grooming activity and prompt removal of fleas. Implementing flea control with a product that rapidly reduces flea feeding is important. Response to flea control is the best confirmation that fleas are a relevant flare factor. Useful products include spinosad (Comfortis ®) 50 to 100mg/kg PO q 14 days; nitempyram (Capstar ®) 1mg/kg PO q 24hrs or indoxacarb (Activyl ®) applied every 14 days.

ii) **Use antimicrobial therapy:** bacterial and yeast infections should be confirmed with cytological evaluation of skin and the external ear canal. Antimicrobial therapy is indicated, and in cats, injectable and oral antimicrobial therapies are more useful than topical medications, except for aural preparations.

B. Improvement of skin and coat hygiene and care

i) **Bathing with a non-irritating shampoo:** in allergic cats, shampoo therapy is not often used, however if cats will tolerate bathing then it can be a useful intervention for both physical removal of surface allergens and microbes and improved skin hydration. Emollient formulations containing either oatmeal and spherulites (Episoothe shampoo and conditioner ®, Resisoothe ® Virbac); or phytosphingosine, raspberry oil and lipids (Douxo Calm ®) have been shown to provide a modest effect on skin lesions and pruritus in dogs with mild AD. The intensity and frequency of bathing may be the most important factor in relieving pruritus. Wiping the patient with a damp cloth on a daily basis is an alternative to bathing that is often more practical in cats.

C. Reduction of pruritus and skin lesions

i) **Short-term treatment with topical glucocorticoids:** topical glucocorticoid sprays (Cortavance ®) are effective for treatment of flares of canine AD. Topical daily application of 0.0584% hydrocortisone aceponate (HCA) spray (Cortavance ® Virbac) is effective for reduction of skin lesions and pruritus in allergic cats. In cats that do not tolerate the application of the spray, the product can be wiped on lesional skin using cotton wool. Other medium potency topical corticosteroids that can be useful for local topical application include 0.1% mometasone or 0.1% methylprednisolone aceponate lotion. None of these products are registered for use in cats and caution should be exercised to avoid ingestion by grooming.

ii) **Short course of oral glucocorticoids:** oral prednisolone is typically dosed orally 1–2mg/kg per day to initiate therapy, then tapered to 0.5–0.1mg/kg every 48 hours for maintenance; dosing for glucocorticoids is generally higher in cats compared to dogs to achieve the same clinical effect. Adverse effects of oral glucocorticoids are normally proportional to drug potency, dosage and duration of administration. Treatment with long-acting injectable glucocorticoids is not recommended.

iii) **Short course of oclacitinib:** oclacitinib (Apoquel ®) at 0.4–0.6 mg/kg orally twice daily for up to 14 days rapidly reduces skin lesions and pruritus in dogs with AD and short-term treatment appears safe. Limited published studies are available reporting the pharmacokinetics or clinical use of JAK inhibitors in cats and the drug is not registered for use in this species. Oclacitinib administered at 0.4–0.6 mg/kg q 12hrs for 14 days tapering to q 24hrs for 14 days improved pruritus scores in less than 50% of 12 cats in a small pilot study. There may be a potential role for oclacitinib in the treatment of feline allergic dermatitis but prospective studies in cats are needed before this medication can be recommended for clinical use

2. Treatment of chronic feline allergic dermatitis

A. Identify and avoid flare factors

i) **Implement a flea control regimen:** in geographic regions where flea infestation is endemic, all cats with allergies should be treated with year-round flea adulticides combined with relevant environmental measures. Insecticides that demonstrate long effect and fast residual speed of kill are more effective in flea allergic cats.

ii) **Evaluate use of antimicrobial therapy:** topical and/or systemic antimicrobial therapy is indicated when a skin and/or ear infection with bacteria and/or yeast is diagnosed based on compatible clinical signs with or without supportive cytology or bacterial culture. Terbinafine or itraconazole can be prescribed once daily or for two consecutive days each week for three weeks to treat flares provoked or exacerbated by *Malassezia* skin infections in dogs with canine AD. The author has found this a useful strategy for in Sphinx and Devon Rex cats with FAS with relapsing *Malassezia* dermatitis.

iii) **Perform an elimination diet trial in cats with non-seasonal pruritus:** in dogs, as in humans, food allergy can manifest with clinical signs of AD. Food allergens can cause flares of clinical signs of FAS in cats. The current gold standard for the diagnosis of adverse food reactions remains a restriction trial with novel and/or hydrolysed diets followed by provocation with original food items once signs have abated during the restriction phase. An 8-week restriction-provocation dietary trial should permit the diagnosis of an adverse food reaction in a cat.

It is speculated that the presence of storage mites in dry dog foods might cause some relapses of canine AD because of their allergenic cross-reactivity with house dust mites. Freezing dry dog foods might reduce contamination with storage mites, but the impact of such freezing on the clinical signs of mite-hypersensitive dogs is unknown. To decrease excessive storage mite contamination, owners should be encouraged to avoid storing commercial dry dog foods in humid and warm areas, and they should be advised to store foods in clean and sealed containers. While there is no published evidence of the role of storage mites in dry cat foods, the same strategies are recommended for cats with FAS that are positive on allergy testing for house dust mite.

iv) **Intradermal and/or IgE serological allergy testing:** allergen-specific intradermal testing (IDT) and/or IgE serologies identify environmental allergens in cats with FAS. Positive immediate IDT reactions and IgE serology to environmental allergens can also be observed in cats without signs of FAS. As a result, these tests cannot be used to differentiate cats with FAS from healthy cats or cats with other pruritic dermatoses.

B. Improve skin and coat hygiene and care

i) **Bathing with a non-irritating shampoo:** if owners can bath cats with minimal stress, then weekly bathing with a mild non irritating shampoo and lukewarm water is likely to be beneficial for a direct soothing effect to the skin, the physical removal of surface allergens and microbes and an increase in skin hydration.

ii) **Supplementation with oral EFAs:** the benefits of EFA supplementation have been evaluated in several older studies on cats with allergic skin disease. Most of the studies, however, were not controlled nor randomised with unclear inclusion and exclusion criteria. Although the responses were variable among all of the studies, clinical improvement was reported for most cats with regard to lesion resolution and pruritus reduction although statistical significance was questionable. Whether clinical improvement from EFA supplementation in cats with FAS is related to improved barrier function, the anti-inflammatory effects of fatty acids, or simply an improved quality of overall hair coat is uncertain. The relative safety of EFA supplementation makes this option appealing as part of the management strategy, particularly in the mildly affected allergic cat.

At this time, there is no evidence of superiority for any particular EFA combination, dosage, ratio or formulation (including enriched diets) to improve skin and coat quality in cats with FAS. In general, EFA-enriched diets provide higher amounts of EFAs than oral administration of EFA supplements. Various dosing formulations exist, which may be added to the food (capsule, oil, spray); efficacy should be assessed after at least 6 to 8 weeks of administration. Side effects of EFA are uncommon but palatability for cats is often poor.

iii) **Application of topical EFA-containing formulations***:* topical lipid formulations can normalise existing stratum corneum lipid barrier defects in dogs with AD although there is still insufficient evidence for the benefit of lipid-containing topical formulations to recommend these as monotherapy for canine AD. The benefit of topical EFA-containing formulations is likely minimal in dogs already fed EFA-rich diets or EFA supplements. There are no studies evaluating the role of topical lipid formulations in cats.

C. Reduction of pruritus and skin lesions with pharmacological agents

i) **Topical glucocorticoids*:*** although topical therapy is used less frequently in allergic cats than in dogs due to their fastidious grooming behaviour, the availability of rapidly absorbed products makes this option appealing. 0.0584% hydrocortisone aceponate (Cortavance ® Virbac) spray is effective for the management of feline allergic skin disease. Care must be taken with frequent application as cutaneous atrophy has been reported with repeated use. Although the product is currently not licensed for use in cats, it appeared to be well tolerated, safe, and effective.

ii) **Oral glucocorticoids: prednisolone and ciclosporin:** these drugs are effective for treatment of chronic FAS, concurrently with or after control of known flare factors. Glucocorticoids lead to faster improvement than ciclosporin, but ciclosporin can be combined with oral prednisolone for the first three weeks to speed its onset of clinical improvement.

Oral glucocorticoids: prednisolone should be used at 1 mg/kg once to twice daily to induce remission of clinical signs of FAS. After such remission occurs, the dose of oral glucocorticoids should be tapered to the lowest dosage and frequency that maintains an absence of signs to minimize the risk of side effects in the long term. Long acting

injectable glucocorticoids should be avoided wherever possible as the lack of ability to taper their dose increases the risk of adverse events.

Oral ciclosporin (Atopica ® for Cats) should be administered at 7mg/kg once daily with food until satisfactory control of clinical signs, which will usually take 4 to 6 weeks. Higher dosages of 10 to 15mg/kg for up to 12 weeks can be required for some eosinophilic dermatoses, particularly oral eosinophilic granuloma. Thereafter, the dose required to maintain remission should be tapered by either decreasing the frequency of treatment from every day to every other day and then twice a week. Approximately 50% of cats can be maintained on ciclosporin twice a week without deterioration of the clinical signs. The frequency and the extent of dose tapering is more effective in cats that in dogs.

Adverse reactions in cats receiving ciclosporin include gastrointestinal signs (vomiting, diarrhoea and reduced appetite) which are usually mild and transient. Hepatic lipidosis can occur secondary to persistent weight loss. Strategies to reduce the frequency and severity of gastrointestinal signs include freezing the capsule (if used in lieu of liquid) prior to administration or dividing the liquid dose and giving it twice daily, or beginning at a lower dosage and gradually increasing to a therapeutic dosage.

Gingival hyperplasia has been reported in cats receiving ciclosporin. Drug cessation typically results in improvement. Oral azithromycin and azithromycin toothpaste are of benefit to dogs but have not been used in cats. Plaque control has shown to be of benefit in cats.

An important potential adverse effect of using ciclosporin in cats is the increased risk of developing systemic toxoplasmosis. Fatal toxoplasmosis in cats receiving ciclosporin occurs by reactivation of a latent infection or primary exposure in naïve cats. The risk for fatal toxoplasmosis is higher in cats with trough CsA concentrations >1000ng/ml and in cats receiving concurrent prednisolone administration. Routine measurement of ciclosporin trough concentrations (20 hours after dosing) in cats 1 to 2 weeks following commencement of therapy to detect at risk cats is mandatory. Further recommendations to reduce the risk of this disease include feeding only processed foods (or if meat is fed then cooked or frozen/thawed), avoiding raw meat, poultry, viscera or bones and preventing hunting and scavenging. 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, anti-toxoplasma chemotherapy should be commenced immediately to prevent acute systemic disease.

Ciclosporin administration is not recommended for cats that have a positive FIV or FeLV viral status or a history of neoplasia. Ciclosporin may precipitate relapse of feline herpesvirus infection, but these signs are usually mild and self-limiting. The risk of significant herpes relapse may be greater in cats with trough CsA concentrations > 1000ng/ml.

The long-term concurrent administration of oral ciclosporin and glucocorticoids (especially at higher dosages of either or both drugs) is not recommended because of the theoretical higher risk of immunosuppression predisposing to potentially severe opportunistic infections of the skin or other organs. There is no consensus on the need for laboratory monitoring (e.g. haematology, serum biochemistry and urinalysis) during prolonged ciclosporin or prednisolone administration, however, it is our recommendation that laboratory monitoring is performed on an annual basis. Due to the increased risk of urinary tract infections in dogs treated with oral glucocorticoids and ciclosporin in the long term, it is our recommendation that cats receiving these drugs should be monitored with annual urinalyses and urine cultures.

The concurrent use of allergen-specific immunotherapy, EFAs supplements or enriched diets might allow for a further reduction in the dose and/or frequency of oral glucocorticoids and ciclosporin required to maintain remission of clinical signs of AD. The efficacy and safety of these combined approaches has not yet been published.

iii) Antihistamines: there is limited evidence of proven bioavailability and/or demonstrated reliable efficacy of antihistamines in cats and recommendations are anecdotal and based on open trials; success has been reported anywhere from 20 to 73%. A single, randomised, double-blinded, placebo-controlled, cross over study evaluated cetirizine administration at 1mg/kg q 24hrs in cats with mild to moderate cutaneous allergy and no improvement was noted in the population at the dose evaluated.

For optimal efficacy, this class of drugs are best used as part of a preventative strategy before a flare occurs; not during or after it; and they should preferably be administered on a continuous basis. The relatively mild and infrequent side effects make antihistamines a reasonable option, especially in patients with mild allergic disease. The author's preferred antihistamines for cats include cetirizine 2mg/kg q 12 to 24hrs and hydroxyzine 1 to 2mg/kg q 12hrs.

iv) **Tricyclic antidepressants (TCA) and serotonin uptake reinhibitors (SSRI):** in human patients with AD, psychological factors can contribute to the severity of clinical signs. Insufficient evidence exists regarding the role of these factors in cats with FAS but it is probable that environmental or social stress contributes to the pruritic threshold and the exacerbation of clinical signs in some patients. In cats that are not responding to conventional therapy for FAS, evaluate for psychogenic factors and consider using a fluoxetine 0.5 to 1mg/kg q 24hrs, or paroxetine 0.5 to 1mg/kg q 24hrs or sertraline 0.5 to 1mg/kg q 24hrs. Contraindications include hepatic, renal or cardiac disease and drugs must be administered for 4 to 6 weeks before evaluating clinical response.

v) **Biotherapeutic immunomodulators:** recombinant interferons: recombinant canine interferon-gamma (Interdog ®), given subcutaneously at 5,000–10,000 units/kg three times weekly for 4 weeks, then once weekly, is effective for treatment of canine AD. Recombinant feline interferon-omega (Virbagen omega ®), administered subcutaneously or orally, has been shown to provide some inconsistent reduction of skin lesions and pruritus in dogs with AD. There are no studies published using feline interferon-omega in cats with FAS.

3. Implement strategies to prevent recurrence of signs

A. Implement proactive topical pharmacotherapy: in humans with AD, there is evidence for the high benefit, cost effectiveness and low risk of proactive intermittent applications of topical glucocorticoids and tacrolimus to previously affected skin areas to delay or prevent the appearance of such flares. There is currently no evidence for the effectiveness of a similar approach in cats with FAS, but the possible benefit, low risk and low cost suggest that such strategy is worth considering in suitable cases. In dogs, the application of a topical 0.0584% hydrocortisone aceponate spray (Cortavance ®) to areas of previous skin lesions, two consecutive days each week, can delay the recurrence of lesions at these sites without causing visible skin atrophy. A similar strategy could prove useful in cats.

B. Implement allergen-specific immunotherapy: no controlled studies have been performed to determine the value of allergen-specific immunotherapy (ASIT) as a modifying treatment for cats with FAS; much of what has been reported in cats is based on open trials and anecdotal information. Despite this, ASIT is considered to be a safe and effective treatment option for FAS in cats. Reported success rates in uncontrolled studies vary from 50% to 100%. As in dogs, no single or standardised immunotherapy administration protocol exists for cats with FAS. Interval between injections, injection volume, and allergen concentration are all highly variable between dermatologists; the schedule of administration is typically extrapolated from the preferred canine protocol.

Conventional injection ASIT typically includes an induction phase, where gradually increasing amounts of allergen are administered over a period of several weeks and a maintenance phase, where injections are typically administered every 1 to 3 weeks. Side effects are rare and may include localised pruritus or anaphylaxis.

Rush immunotherapy (RIT) is a technique of administering increasing amounts of allergen in a hospital or clinic setting with careful monitoring over several hours until the maintenance dose is reached. This option for immunotherapy administration has been evaluated in dogs and humans, with few adverse reactions reported. A pilot study in a small number of cats suggested that rush immunotherapy was safe and effective. It is uncertain whether improved efficacy is noted with this method as compared to conventional administration protocols, however, the benefits of rush immunotherapy are that it condenses the induction phase into only a few hours. Our dermatology clinic performs all immunotherapy protocols in dogs and cats using RIT and the reduced burden of frequent injections at the beginning of ASIT and improved owner compliance are definite advantages of this approach.

There is some evidence that ASIT administered via the sublingual route (sublingual immunotherapy; SLIT), are safe and effective for treatment of atopic dogs, but there is no published information evaluating sublingual immunotherapy in cats with FAS. Anecdotally, benefits have been observed for some cats where SLIT was used as part of the therapeutic protocol. It appears to be well tolerated by most cats. The formulation is palatable and even fastidious cats seem to tolerate the small volume necessary for administration. Studies are needed to evaluate the relative efficacy and safety profile in a large number of allergic cats to compare sublingual versus conventional immunotherapy.

SLIT can be a useful alternative for cats and owners adverse to the administration of subcutaneous injections.

Most cats that demonstrate a response to ASIT exhibit a good response within 6 to 12 months. Because the onset of clinical benefit might not appear for months, ASIT must be continued for at least one year to properly evaluate its efficacy. For most allergic cats, concurrent medication is necessary especially during the induction and early maintenance phase of immunotherapy administration. There is currently no evidence suggesting that the concurrent administration of such drugs alters the clinical benefit of ASIT. Efficacy can still be assessed based on the ability to lower concurrent medication doses and potentially discontinue certain medications in favour of safer options.

Whether or not ASIT must be continued for the reminder of the life of cats with FAS has not been established. While most patients appear to require many years of ASIT, attempts should be made to decrease the frequency of administration, or even stop this intervention, in cats exhibiting a prolonged complete remission of signs.

Conclusion

In summary, the treatment of FAS must be an individual prescription for each patient and in the majority of cases, a combination approach is required. Treatment can be challenging and should incorporate identification and elimination of flare factors, a reduction of skin lesions and pruritus, protection of the skin barrier and prevention of recurrence of signs after remission. Not all treatments will be suitable for every patient and not all drugs will be equally effective for, or tolerated by, every cat. We should try to abide by evidence-based veterinary principles and at the same time consider the cost and ease of the various treatment options and the quality of life of each patient.

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