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Review

An update on the treatment of canine atopic dermatitis

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ABSTRACT

Canine atopic dermatitis is a common skin disease seen in veterinary clinical practice. Several factors appear to contribute to the cutaneous inflammation and pruritus. The therapeutic strategy should focus on control of those factors that can be identified and for which interventional measures are feasible; these include ectoparasites, bacterial/fungal infection and dietary hypersensitivity. Ectoparasites, particularly fleas, are not the cause of atopic dermatitis, but they are a confounding factor, which can exacerbate pruritus, and preventative measures are therefore indicated. Bacterial and yeast infections are frequently associated with atopic dermatitis and initial systemic and/or topical therapy should be considered, followed by regular topical treatment for preventing relapse. Concurrent dietary hypersensitivity should be investigated by undertaking an elimination/provocation trial, followed by feeding of a hypoallergenic diet where appropriate.

Depending on the severity of the clinical signs of atopic dermatitis and the willingness and expectations of owners, symptomatic treatment and/or specific interventional therapy for environmental allergy (allergen avoidance, allergen-specific immunotherapy) may be implemented. Symptomatic treatment includes use of glucocorticoids (systemically or topically), ciclosporin and oclacitinib. Other treatment modalities of lower or less proven efficacy include antihistamines, dextromethorphan, fatty acids, feline interferon-omega, misoprostol, pentoxifylline, specific serotonin re-uptake inhibitors and tricyclic antidepressant drugs. The therapeutic approach should be reviewed at regular intervals and tailored to the individual's needs. A successful long-term outcome can usually be achieved by combining the various treatment approaches in a way that maximises their benefits and minimises their drawbacks.

Introduction

Canine atopic dermatitis (AD) has been defined as a 'genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features, associated with IgE antibodies most commonly directed against environmental allergens (Halliwell, 2006). AD is one of the most common skin diseases of dogs, with a prevalence of 3–15% in the general dog population and representing between 3% and 58% of dogs affected with skin disease presented to veterinarians (Hillier and Griffin, 2001a; Hill et al., 2006; Nødtvedt et al., 2006). The diagnosis of canine AD is based on the characteristic clinical features, with exclusion of other diseases with a similar clinical presentation. Therefore, a clinical diagnosis can be made without necessarily employing further diagnostic procedures, such as intradermal skin testing or IgE serology, although these can contribute to clinical decision making in terms of targeted therapy. Rational clinical management of canine AD is required, since AD is usually a life-long disease that can be controlled but rarely cured.

The age of onset of canine AD is typically between 6 months and 3 years and the most important clinical features include the presence of pruritus, associated with skin lesions of a characteristic distribution around the mouth, eyes (especially in the presence of conjunctivitis), ears, flexor aspects of elbow, carpal and tarsal joints, digits and interdigital skin, ventral abdomen, perineum and ventral aspect of the proximal tail (see Appendix: Supplementary Figs. S1–S4). Clinical signs are either seasonal or, most commonly, non-seasonal, or non-seasonal with seasonal exacerbation (Lourenço-Martins et al., 2011; Marsella, 2013a).

The pathogenesis of canine AD is complex and not particularly well understood, with genetic and environmental factors involved in determining susceptibility to clinical disease. Sensitisation to environmental allergens and/or allergens from food, microbial or insect sources can lead to infiltration of the skin by inflammatory cells, activation of resident cells and local production of inflammatory mediators. Contributory factors include epidermal barrier dysfunction, cutaneous bacterial (usually by *Staphylococcus pseudintermedius*) and yeast (i.e. *Malassezia pachydermatis*) infections, psychogenic factors, and concurrent skin diseases (Nuttall, 2012; Marsella, 2013a). These factors are inter-related (Fig. 1) and, for most, it is unclear whether they represent a primary cause or a secondary phenomenon. Thus,

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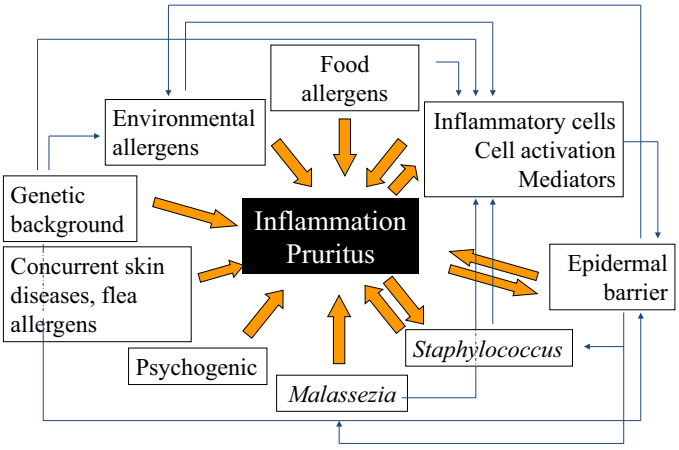

Fig. 1. Pathogenetic factors responsible for cutaneous inflammation and pruritus in dogs with atopic dermatitis and their interrelationships.

a rational approach to treatment is required for each individual dog affected with AD, to manage those factors amenable to specific interventional measures and to institute symptomatic treatment, customised to the needs of each patient and to the expectations and financial circumstances of the owner.

Sensitisation to environmental allergens and targeted therapy

IgE antibodies, generated against environmental allergens, are demonstrable in ~80% of dogs affected with AD, and there is a temporal association between clinical signs of skin disease and the level of exposure to these allergens (Marsella, 2013a). The current hypothesis is that there is a genetic predisposition in some dogs to become sensitised to such environmental allergens, mainly via cutaneous exposure (Olivry and Hill, 2001; Marsella et al., 2006a, 2006b; Pucheu-Haston et al., 2008). Environmental allergens can be captured by Langerhans cells (immature dendritic cells) that migrate to the lymph nodes and present these, in the context of peptide epitopes bound to major histocompatibility complex (MHC) class II molecules, to CD4+ T lymphocytes. Differentiation of naïve CD4+ T cells to the T-helper type 2 phenotype enhances maturation of allergen-specific B cells and production of allergen-specific IgE. The IgE circulates and will bind specifically to the surface of mast cells, through their expression of the high affinity IgE receptor (FcεRI) (Olivry et al., 1997; Hill and Olivry, 2001; Marsella et al., 2006b; Pucheu-Haston et al., 2008). Upon subsequent exposure, allergens may penetrate the epidermis and cross-link IgE on the surface of the dermal mast cells, leading to degranulation and immediate release of inflammatory mediators including histamine, followed by a late phase reaction that involves de novo synthesis of inflammatory mediators including leukotrienes (LT), prostaglandins (PG) and various cytokines that recruit inflammatory cells into the skin (Hill and Olivry, 2001).

Sensitisation to environmental allergens can be demonstrated, and the specificity of the hypersensitivity reaction elucidated, by performing the intradermal skin test and/or assessing circulating IgE by serology (Table 1). Anti-inflammatory drugs such as corticosteroids and antihistamines can be employed to provide symptomatic treatment of clinical signs (Table 2). Targeted therapy includes allergen avoidance and use of allergen-specific immunotherapy (ASIT).

Depending upon the source of allergen, various strategies have been suggested to reduce exposure to environmental allergens, such as a change in household environment, lifestyle and daily routine of the dog, mechanical and/or thermal removal of allergens, use of impermeable barriers, and, for house-dust mites, use of acaricides, growth regulators or chemicals that denature their allergens (Olivry and Sousa, 2001a; Scott et al., 2001; Swinnen and Vroom, 2004). However, there is limited published evidence in favour of this approach. In an open study, 'excellent' or 'partial' responses were reported in domestic mite-sensitive dogs affected with AD after benzyl benzoate treatment of their households (Swinnen and Vroom, 2004). In another study, there was improvement in clinical signs of house dust mite-associated AD upon a change to a mite-deficient environment (Fujimura, 2011). Since allergen avoidance is often difficult to achieve under most circumstances, it could be argued that there is little benefit in undertaking intradermal skin testing and/or IgE serology for this purpose. However, if a reduction in exposure to offending allergens seems possible, this should be discussed with the owner, since this approach will only benefit and not harm the patient (Scott et al., 2001).

ASIT involves injecting increasing amounts of a bespoke combination of allergens, following identification of those against which they have been sensitised. Although this immunotherapeutic approach has been shown to ameliorate the clinical signs of AD in many cases, its mechanism of action is still unclear (Shida et al., 2004; Hou et al., 2008; Keppel et al., 2008). In the 'traditional' form of ASIT, an aqueous or alum-precipitated mixture of allergens is injected subcutaneously, at increasing doses and time intervals (Griffin and Hillier, 2001). Alternative dosing schedules (e.g. low-dose ASIT, rush ASIT, omission of the induction phase) (Mueller and Bettenay, 2001; Colombo et al., 2005; Mueller et al., 2005), routes of administration (intradermal, oral, sublingual, intra-lymphatic) (Marsella, 2010) and addition of adjuvants (e.g. oligodeoxynucleotides rich in cytosine–

Table 1
Diagnostic investigation for the various factors which are associated with cutaneous inflammation and pruritus in canine atopic dermatitis.

Factor	Tests available
Genetic background	NA
Sensitisation to environmental allergens	Intradermal test, serology for allergen-specific IgE
Sensitisation to food allergens	Restriction–provocation food trial
Inflammatory cells, cell activation, mediators	NA
Epidermal barrier dysfunction	NA
Bacterial infections	Clinical examination, cytology
Malassezia dermatitis	Clinical examination, cytology
Psychogenic factors	History, clinical examination
Concurrent pruritic skin diseases	Dermatologic examination, various tests

NA, non-applicable in the clinical setting.

Table 2
Etiologic and symptomatic treatment modalities for the various factors which are associated with cutaneous inflammation and pruritus in canine atopic dermatitis.

Factor	Treatment
Genetic background	–
Sensitisation to environmental allergens	Etiologic: avoidance, ASIT Symptomatic: antihistamines
Sensitisation to food allergens	Etiologic: avoidance
Inflammatory cells, cell activation, mediators	Symptomatic: glucocorticoids (systemic, topical), ciclosporin, tacrolimus, oclacitinib, misoprostol, pentoxifylline, feline interferon-omega
Epidermal barrier dysfunction	Symptomatic: fatty acids (oral supplements, in the diet, topical), various topical treatments
Bacterial infections	Etiologic: antimicrobials (systemic, topical)
Malassezia dermatitis	Etiologic: antifungals (systemic, topical)
Psychogenic factors	Symptomatic: tricyclic antidepressants, SSRI, NMDA receptor antagonists

ASIT, allergen-specific immunotherapy; SSRI, specific serotonin re-uptake inhibitors; NMDA, N-methyl-D-aspartate.