ALLERGIC SKIN DISEASE:
NEW MODELS, NEW TARGETS, NEW TACTICS
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Canine Atopic Dermatitis: An Overview and Historical Perspective
Richard E.W. Halliwell, MA, VetMB, PhD, DACVD, FMedSci, MRCVS

KEY POINTS

♦ There are striking similarities between atopic dermatitis in humans and in dogs.

♦ Although IgE is still thought to play a major role in the release of mast cell–derived mediators and also in allergen capture, the immunopathogenesis of canine atopic dermatitis (CAD) is now known to be far more complex. In the past, a simplistic view was generally held on the pathogenesis of CAD, with a major role for IgE and mast cells and their mediators.

♦ Evidence has shown that the major route of allergen access in CAD is percutaneous, although administration of allergen via the respiratory and oral routes can also exacerbate pruritus in sensitized dogs, albeit less efficiently.

♦ Overproduction of IgE is typically associated with a Th2 response and thus it is relevant to assess the extent to which the cellular response in CAD is Th1 or Th2 driven. Early lesions are thought to be associated with a predominantly Th2 response which changes, due to the ensuing chronicity and secondary infection, to a Th1 response.

♦ Cytokines derived from keratinocytes, T lymphocytes, and macrophages, many of which are pro-inflammatory, are present in the inflammatory milieu in lesional skin of dogs with CAD. However, there is a paucity of definitive information implicating specific mediators in the dog, and further carefully planned studies are urgently needed.

♦ Dermatologists treating human patients with atopic dermatitis (AD) have long believed that barrier function abnormalities play a crucial role in the pathogenesis. These defects appear to play a role in dogs as well, as assessed by measurement of filaggrin, transepidermal water loss, analysis of surface lipids such as ceramides, and ultrastructural studies showing differences between atopic and normal dogs. The extent to which this contributes to the pathogenesis, or results from inflammation, is unknown.

♦ Atopic dermatitis has recently been redefined by the International Task Force on Canine Atopic Dermatitis as “a genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with IgE antibodies most commonly to environmental allergens.”

♦ In around 10% of classical cases of CAD, no relevant allergen-specific IgE is demonstrable. Such cases are termed atopic-like dermatitis. The optimal therapy for this frustrating condition is not known.

♦ Many experienced clinical veterinary dermatologists still make the diagnosis of CAD by 1) observation of compatible clinical signs and 2) failure to document any explanation for these signs even though three sets of diagnostic criteria have been proposed.
THE ATOPIC DISEASES IN HUMANS

The term atopy, derived from the Greek and literally translated as “strange disease,” was introduced by Coca and Cooke in the 1920s to embrace asthma and hay-fever which are familial hypersensitivity disorders of humans. They noted that the conditions were associated with an unusual antibody which they termed reagin, which was 1) heat labile, and 2) could be transferred to the skin of normal individuals by the so-called Prausnitz-Küstner (or PK) test. Many years later, the painstaking work of the Ishizakas and their colleagues determined that this antibody belonged to a hitherto-undescribed antibody class, which was named immunoglobulin E (IgE). Atopic dermatitis (AD), another familial disease, was added to this group of diseases later by Hill and Sulzberger, and through the ages, affected patients have often exhibited “the atopic march,” where their disease commences with AD and they later develop asthma or hay-fever. Although AD and asthma are usually associated with excessive production of IgE and exacerbated by environmental allergens, a subset exists, namely “intrinsic,” in which allergen-specific IgE does not appear to be involved.

ECZEMA AND ATOPIC DERMATITIS IN DOGS

One of the early classical descriptions of “eczema” in dogs was in a paper by Schnelle working at the Angell Memorial Hospital in Boston. He reported that 15% of all cases seen at his clinic were accorded a diagnosis of “eczema” and that 56.9% of all dogs with skin disease and 26.6% of all cats similarly affected were deemed to be suffering from this condition. Comparable data were reported from the clinics at Cornell University in Ithaca, New York.

Although it was generally believed that “eczema” was a manifestation of allergy, the exact nature of the inciting cause was controversial, with most emphasis being placed upon foods. In addition, flea allergy was recognized as an important cause of “summer eczema.” The first documentation that environmental allergens might also be involved was provided in 1941 by Whittich, a human allergist, who gave an elegant description of a dog with perennial pruritus due to a food allergy that suffered from seasonal hay-fever due to a concomitant pollen allergy. The dog was treated with an appropriate hypoallergenic diet and successfully hyposensitized with injections of allergenic extracts of the pollens to which sensitivity was shown. The association with IgE was further confirmed by demonstrating positive PK tests using both canine and human recipients.

Little progress was made until the 1960s when investigations were undertaken on canine ragweed pollenosis in the United States by Roy Patterson, another human physician. He proposed that dogs suffering from this condition could represent a good model for hay-fever and allergic rhinitis of humans, and he developed a colony of atopic dogs suffering from the condition. The dogs were reported as showing signs of hay-fever, and although they did not suffer from spontaneous asthma, the latter was inducible by insufflation with high concentrations of allergen. Furthermore, asthma was inducible in normal dogs following injection of serum from allergic dogs and subsequent antigenic challenge. Despite the fact that there were obvious dermatologic signs in addition to hay-fever-like signs, it was not thought to be truly analogous to AD of humans. Instead it was termed atopy, atopic disease, or allergic inhalant dermatitis, the latter term in the mistaken belief that inhalation was the major route of access of allergen.

This period saw the first detailed clinical descriptions of the condition as seen in clinical veterinary practice. “Atopy” was described as a familial, pruritic dermatitis with a predominantly facial and ventral distribution, often presenting initially without primary lesions, but with chronic changes developing in association with self-trauma. Some patients presented also with hay-fever like signs and rubbed at their nasal and ocular region with or without accompanying dermatitis. Patients presented with seasonal or perennial signs, with many cases commencing seasonally and progressing to perennial involvement.
THE PATHOGENESIS OF CANINE ATOPIC DERMATITIS

Characterization of Canine IgE

Classically, allergic asthma and hay-fever of humans were believed to be associated with IgE antibody, although its role in AD has always been more controversial. As the initial view of canine “atopy” or “atopic disease” was a condition not truly analogous to AD of humans, the major emphasis of early work was on the characterization of canine IgE as a probable key player in the immunopathogenesis. The identification and description of canine IgE was reported in 1973 only 6 years after that of its human counterpart, with which it was antigenically similar, and it was shown to be localized on mast cells in canine skin. The development of tests for the measurement of canine allergen-specific IgE followed shortly thereafter.

What is the Role of IgE in the Pathogenesis of CAD?

In the 1970s and 1980s a simplistic view was generally held on the pathogenesis of CAD with a major role for IgE and mast cells and their mediators. Although IgE is still thought to play a major role in the release of mast cell–derived mediators and also in allergen capture, the immunopathogenesis is now known to be far more complex.

Allergen Access, Capture, and Processing

The term allergic inhalant dermatitis—which was in common use in the 1980s—implied on the basis of mere supposition that the route of access of allergen was via inhalation. Evidence in favor of the percutaneous route was derived from the work of Olivry, who showed that lesions skin of dogs with CAD showed focal proliferation of Langerhans cells and that these cells were armed with IgE antibody. There was also proliferation of dermal dendritic cells also armed with IgE, which implied that these cells were involved in allergen processing. It was only in 2006, however, that Marsella, employing the high IgE-producing beagle model of AD, provided direct evidence that the major route of allergen access was percutaneous, although administration of allergen via the respiratory and oral routes could also exacerbate pruritus in sensitized dogs albeit less efficiently.

Inflammatory Cells in CAD – Are They Indicative of a Th1 or Th2 Response?

Immunohistochemical studies have shown that the infiltrating cells in skin biopsies of spontaneous cases of CAD comprise mast cells, dendritic antigen-presenting cells, T lymphocytes expressing γδ rather than αβ receptors with low numbers of neutrophils and eosinophils and rare B-lymphocytes. Both CD4+ and CD8+ T cells are found in increased numbers, with a major increase in CD8+ cells in the epidermis along with microaggregates of eosinophils. Classically, T cells can be assigned on the basis of function to Th1, promoting cell-mediated immunity, and Th2 favoring antibody production, including IgE. Thus overproduction of IgE is typically associated with a Th2 response. It is pertinent, therefore, to assess the extent to which the cellular response in CAD is Th1 or Th2 driven.

Studies employing a non-quantitative reverse transcriptase polymerase chain reaction (PCR) on clinical cases suggested that a clear Th2 polarization was evident in some 25%. A later study also employing clinical material using semi-quantitative methods yielded evidence of overexpression of both Th1 (interferon gamma, IFN-γ) and Th2 (interleukin-4, IL-4) cytokines. It was suggested that early lesions might be associated with a predominantly Th2 response which changed due to the ensuing chronicity and secondary infection to a Th1 response, conclusions supported by the most recent publication on this topic.

The Th2 versus Th1 issue was investigated further using atopy patch tests in the high-IgE beagle model in which it should be possible to separate out the acute and chronic phases. Among the Th2 cytokines, IL-6 and IL-13 were significantly increased and peaked at 24 hours. Although IL-4 increased over 6 to 24 hours, the increase was not significant. Among the Th1 cytokines, IFN-γ had a biphasic response with peaks at 6 hours and 96 hours with IL-18 gradually increasing through 96 hours. Thus although there is a pattern which is in general accord with that
in humans, results are not conclusive and further studies are required.

The issue has also been investigated using whole blood from clinical cases. The first of these assessed mRNA of IFN-γ, IL-4, IL-5, and IL-10 in freshly isolated peripheral blood mononuclear cells (PBMCs) from clinical cases. The results were inconclusive, with a reduction in IFN-γ and an increase in IL-5, with no change in IL-4 and IL-10. The second study evaluated mRNA expression of IL-4, IL-13, IL-10, and transforming growth factor beta (TGFβ) in the high-IgE beagle model. IL-4 and IL-13 were unchanged, but the levels of expression of the immunosuppressive cytokines IL-10 and TGFβ were reduced, which could imply aberrant regulatory T-cell function.

Interest has also focused on the possible role of CC chemokines in CAD. Thymus and activation regulated chemokine (TARC) is produced mainly from keratinocytes in response to inflammatory cytokines such as IL-1β, IFN-γ, and tumor necrosis factor alpha (TNF-α). It plays an important role in Th2 cell migration since its receptor (CCR4) is expressed selectively on Th2 cells. TARC was found to be expressed exclusively on lesional skin of atopic dogs, and was indeed associated with increased expression levels of IL-1β, IFN-γ, and TNF-α. In this study of chronic clinical CAD, no increase in IL-4 was detectable. A later study by the same workers employing a monoclonal antibody to TARC confirmed keratinocytes in lesional skin of CAD as the major source, and that its receptor (CCR4) was expressed on the infiltrating cells. The importance of TARC was also derived from studies using patch tests on the high IgE-producing beagle model. In another study of seven chemokines, levels of the CCL28 expression in lesional skin was significantly increased, whereas those of CCL27 were significantly reduced.

What Are the Mediators of Inflammation and Pruritus in CAD?

Implication of any specific mediator(s) in the development of inflammation and pruritus in CAD is exceedingly difficult. Ideally, studies should show 1) evidence of increased levels in the skin, 2) development of pruritus and inflammation following intradermal injection in normal animals, and 3) amelioration of signs following specific inhibition.

The role of histamine has long been controversial. Histamine levels have been reported elevated in the skin of dogs with AD and histamine is released from basophils of atopic dogs in response to allergen. The generally poor response to antihistamine therapy, however, and negative results in a study employing the Maltese beagle cross model of CAD precludes a major role for this mediator. Interest has also focused on other mast cell–derived mediators including proteases and leukotrienes (LT). In one study, elevated levels of LT4 were found in a number of inflammatory skin diseases including CAD, but the significance of sulfido-LT was later questioned by equivocal results using the high IgE-producing beagle model. There are, of course, a whole plethora of cytokines derived from keratinocytes, T cells, and macrophages present in the inflammatory milieu in lesional skin of dogs with CAD, many of which are pro-inflammatory. Great interest in the study of human AD is the role of IL-31, with levels in sera of patients with AD correlate closely with the level of pruritus and with total IgE. Interestingly, however, there were no significant differences between patients with extrinsic (allergic) and intrinsic AD. There is interest also in the role of the calcium binding protein A8 (S100A8), and a recent study showed higher levels in CAD patients and a correlation with disease severity. Elevated levels of this protein are not exclusive to CAD, but may be seen on other inflammatory skin diseases. Finally, the possible role of neuro-immune reactions must be mentioned and neuropeptides and neurotropins, although veterinary studies supporting their involvement are lacking.

In summary, there is a paucity of definitive information implicating specific mediators in the dog, and further carefully planned studies are urgently needed.
Is Barrier Function Defective in CAD?

Filaggrin

Dermatologists treating human patients with AD have long believed that barrier function abnormalities play a crucial role in the pathogenesis, and placed great emphasis on restoration of function as a major therapeutic target. Of great importance was the recent discovery of a genetically controlled abnormality in the structural protein filaggrin in many human patients with AD. Immunofluorescent studies in dogs first showed that filaggrin staining differed between atopic and normal dogs with finer granules and less intensity of staining in the former. Of great interest was the observation that atopic dogs showed less staining than did normal dogs, and that the staining of normal skin was reduced after dust mite exposure. Very recently a loss-of-function mutation was identified in 4 of 18 atopic dogs analyzed, once again highlighting the similarities between human and canine AD.

Transepidermal Water Loss

The integrity of barrier function is generally assessed by measurement of transepidermal water loss (TEWL). Although some doubt that this provides an accurate assessment, the relationship between the two in dogs has recently been confirmed using tape stripping and gauging the barrier function by permeation of a fluorescent dye. TEWL measurement gives differing results, however, depending on the precise technique used (open versus closed chamber, site variations, movement and presence or absence of hair) and careful validation is necessary. Despite these reservations, some important data has emerged from the beagle model confirming that TEWL is increased in sites prone to the development of CAD prior to allergen exposure, and this is further increased in diseased skin when compared with age-matched normal beagles.

Analysis of Surface Lipids

Ceramides play a major role in maintaining barrier function, and where they are decreased, a vicious cycle can ensue wherein bacterial colonization that is a feature of AD can lead to further lowering of epidermal ceramide levels through action of bacterial ceraminidases. A recent study has shown that the surface lipids of non-lesional skin of dogs with AD do indeed differ from those of normal dogs. The levels of ceramides 1 and 9 were significantly decreased, whereas that of cholesterol was significantly increased, and ceramide/cholesterol ratio was significantly lower. The changes in ceramide 1 may be of especial significance, as this lipid is believed to be of particular importance in the assembly of the intercellular lipid lamellae. A more recent study has confirmed that ceramides are reduced in both lesional and non-lesional skin of atopic dogs, and that this reduction is inversely correlated with the transepidermal water loss. More recently, 11 clusters of peaks representing free ceramide classes have been demonstrated, similar to those seen in humans, and the same three classes known to be reduced in human AD were found similarly reduced in CAD. Sphingosines, which can be cleaved from ceramides, are also important and have marked protective properties. A recent study demonstrated significantly lower levels of sphingosine-1-phosphate in skin from atopic canines as compared with normals, implying an imbalance in the S1P-S1P-lysase axis.

Ultrastructural Studies

Three ultrastructural studies have reported similar findings in dogs with AD. Instead of being organized into lamellae, the lipid deposits are reduced in both lesional and non-lesional skin and the deposits are heterogeneous, with widened intercellular spaces. In one study, delayed release of lamellar bodies was noted, and there was a sudden release of lamellar lipids upon allergen challenge.

In summary, multiple studies from varying angles all point to abnormalities in barrier function and these are obvious therapeutic targets.
THE CLINICAL FEATURES OF CAD

Definitions

Atopic dermatitis has recently been redefined by the International Task Force on Canine Atopic Dermatitis as:

"A genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with IgE antibodies most commonly to environmental allergens."

In some cases (around 10%) of classical CAD, no relevant allergen-specific IgE is demonstrable. Such cases are termed atopic-like dermatitis. This is exactly parallel to the situation in humans where some patients suffer from "intrinsic AD," where there is no evidence of allergen-specific IgE. The definition of atopic-like dermatitis is thus:

"A genetically predisposed inflammatory and pruritic skin disease with clinical features identical to those of atopic dermatitis in which IgE antibodies to environmental allergens are not demonstrable."

Breed Predilections

Breed predilections have long been recognized, and the mode of inheritance is currently under investigation. Those breeds shown to be significantly predisposed in two recent studies were Labrador retriever, golden retriever, West Highland White terrier, Chinese shar-pei, bull terrier, Bichon Frisé, Tibetan terrier, English springer, Boxer, French bulldog, Dalmatian, Hungarian Vizsla, and Basset hound.

Age of Onset

Canine atopic dermatitis is a disease that commences in the young dog, with 78% showing clinical signs at less than 3 years and 16% at less than 1 year. It is exceedingly rare for signs to commence in dogs older than 7 years of age.

The Primary Disease

The cardinal sign is itching, and in the early stage there may be little evidence of inflammation. Later on, erythematous macules and papules develop. The distribution is predominantly ventral and facial, with pedal involvement almost invariably seen. Typically, the flexural surfaces of the limbs are involved. The distribution of clinical signs is at least in part reflective of the route of access of allergen. Otitis is very common, and probably affects all cases at some point in their course. Occasionally it may be unilateral. The otitis associated with CAD in the early stages is highly characteristic and involves the inner ear flap and the vertical canal. When the horizontal canal is observed, it appears normal in the early case although it becomes secondarily infected in chronic cases, with accompanying secondary pathologic changes. In some cases otitis is the only sign. There is some evidence of breed variability in the presenting signs.

There exists much controversy regarding the possible involvement of other body systems. Although asthma can be induced in susceptible animals using insufflation of high concentrations of allergen, it is rare to non-existent in clinical CAD. This may be a reflection of the variations in regional mast cell density between humans, the cat (where allergic asthma does occur), and dogs. Certainly some animals appear to have concomitant hay-fever-like signs, and a recent publication has highlighted the importance of allergic conjunctivitis, which the authors claim is often overlooked. Although the existence of an allergic tracheobronchitis as a manifestation of atopic disease has been proposed, convincing documentation is lacking.

Secondary Complications

In time, evidence of self-trauma, hair loss, and seborrheic changes develop. There may be areas of hyperpigmentation, lichenification, and crusting. The otitis often worsens, and progressive pathologic changes lead to hypertrophy of the lining and consequent narrowing of the ear canal. Sometimes a verrucose
proliferation develops which can largely obstruct the canal. Atopic dogs are predisposed to bacterial overgrowth and then to overt pyoderma. This is usually a folliculitis, but occasionally some cases develop a deep pyoderma. The atopic dog is, in fact, “a pyoderma waiting to happen” because:

- Corneocytes from atopic dogs show enhanced adherence to staphylococci.59
- Staphylococci show greater adherence to corneocytes from inflamed skin.60
- Adherence has been shown to correlate with pruritus scores61 although in this study there was no apparent correlation with the propensity to develop pyoderma.
- Atopic dogs have been shown to have a significantly higher level of staphylococci at carrier sites as compared with normals.62
- The propensity to develop anti-staphylococcal IgE has also been shown,63 thus compounding the effects.

Similarly, the ubiquitous yeast Malassezia is found in higher numbers on the skin of dogs with dermatologic diseases,64 although precise data linking Malassezia overgrowth specifically to CAD is lacking. Nonetheless, the fact that sera from atopic dogs have higher levels of Malassezia-specific IgE emphasizes the importance of this organism as a contributor to the total allergenic load65 and to the development of Malassezia dermatitis, manifesting typically as areas of greasy erythema proceeding to lichenification in chronic cases.

**DIAGNOSTIC CRITERIA**

The first paper suggesting that specific criteria would be helpful in the diagnosis of CAD was that of Willemse66 and colleagues, which was followed by some modifications proposed by Prelaud and co-workers.67 More recently, a revised set of criteria based upon a more limited number of observations was developed by Favrot and colleagues.68 Two sets were proposed, namely:

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<th>Set 1</th>
<th>Set 2</th>
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<tr>
<td>Age at onset &lt; 3 years</td>
<td>Age at onset &lt; 3 years</td>
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<tr>
<td>Mostly indoor</td>
<td>Mostly indoor</td>
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<tr>
<td>Corticosteroid responsive pruritus</td>
<td>Pruritus sine materia at onset</td>
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<tr>
<td>Chronic or recurrent yeast infections</td>
<td>Affected front feet</td>
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<td>Affected front feet</td>
<td>Affected ear pinnae</td>
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<tr>
<td>Affected ear pinnae</td>
<td>Non-affected ear margins</td>
</tr>
<tr>
<td>Non-affected ear margins</td>
<td>Non-affected dorso-lumbar area</td>
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<td>Non-affected dorso-lumbar area</td>
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Using the first set of criteria, when five were satisfied, the sensitivity was 0.854 and the specificity was 0.791, and with six satisfied the corresponding data were 0.582 and 0.885. Using Set 2, with five criteria the sensitivity was 0.772 and the specificity 0.83, and with six satisfied the data were 0.42 and 0.937. Obviously, whichever parameters are used, the results are far from perfect. On must also bear in mind that the development of diagnostic criteria is a somewhat circular exercise, in that it employs clinical cases upon which a diagnosis has been made by a wide range of clinicians employing varying techniques. Suffice it to say that a very many experienced clinical veterinary dermatologists make the diagnosis by 1) observation of compatible clinical signs and 2) failure to document any other explanation for these clinical signs.
What Do We Know About "Atopic-like" Dermatitis?

Very little work has been done on this intriguing disease entity. We know nothing about barrier function, and nor do we know about optimal therapy for this frustrating condition.

CONCLUSIONS

This paper has presented a historical overview of CAD and reviewed the current state of knowledge of the pathogenesis. The past 20 years has witnessed an explosion of research in this area, and the recognition of the striking similarities between CAD and the human counterpart will hopefully enable a more ready source of funding to support future endeavors.

REFERENCES


KEY POINTS

- Canine atopic dermatitis (CAD) is a complex genetically programmed disorder with numerous environmental triggers.
- Therapy of CAD should be multimodal and tailored to the needs of each patient.
- The immunopathogenesis of CAD is complex, with abnormalities noted in both the innate and acquired immune responses. Targeting a single cytokine or inflammatory mediator for therapeutic intervention will likely be unsuccessful. By contrast, targeting common pathways should be quite effective.

- Improving allergen immunotherapy outcomes could involve the development of standardized extracts for veterinary use, the development of recombinant allergens and peptides, the use of anti-IgE reagents, and the use of adjuvants designed to modulate the immune response more effectively.

- Improving allergen immunotherapy outcomes could also involve the delivery of allergen by routes other than subcutaneous injection; these could include sublingual, epicutaneous, or intranodal routes.

- Skin barrier defects may occur in at least some patients with CAD; improving the quality of the skin barrier by controlling infections, feeding oral fatty acids and other supplements, and the direct application of lipids to the skin requires further documentation and study.

- The interplay between the immune system, the skin, and the nervous system in CAD requires further study. Receptors and ligands mediating itch should be studied and targeted in order to ameliorate the major sign of CAD: pruritus.

- Stem cell therapy, the use of antisense RNA technology, and gene therapy, while intriguing, remain tools for the future.

Our understanding of canine atopic dermatitis (CAD) has grown by leaps and bounds over the last 15 years. In 2001, the American College of Veterinary Dermatology’s Task Force on Canine Atopic Dermatitis (now an international organization) published a special issue in Veterinary Immunology and Immunopathology on the current understanding of CAD at the time.¹ It became clear that the canine disease had much in common with human atopic dermatitis (AD) including clinical lesions and histopathologic findings as well as progression of the disease and suspected causes. Recently, the International Task Force on Canine Atopic Dermatitis published current recommendations for therapy of both acute and chronic forms.² Aligning CAD with human AD allows veterinary dermatology to take advantage of the basic and translational research so amply available for the human disease and thus we can begin more mechanistic studies into the canine analog. The complexity of the disease suggests monotherapy is rarely effective. Multiple modalities are required to manage dogs with CAD,³ and it is entirely possible that there are differences among individuals in the exact pathogenesis mediating their signs. Therapy often includes allergen-specific immunotherapy to rectify the skewed immune response,
skin barrier repair, control of ectoparasites and infections, and control of itch, the major clinical sign for which treatment is sought.

Most investigators and clinicians have come to understand that AD is a very complex disorder involving multiple genetic abnormalities associated with numerous environmental triggers. Affected genes include those that mediate function of the innate immune response, the adaptive immune response, and the function of the epidermis itself. Furthermore there is a complex interplay between the skin immune system, which includes the keratinocyte, and the nervous system, which enhances itch over time. Future treatments will likely target three major areas: immunologic abnormalities, neurologic abnormalities, and physicochemical abnormalities associated with the dysfunctional skin barrier. Modern technological approaches, to include genomic analysis and such post-genomic analyses as proteomics and metabolomics, are already contributing potential new targets for disease biomarkers and therapeutic targets.

**IMMUNOLOGIC ABNORMALITIES AS TARGETS**

That the immune system is dysfunctional in atopic patients has been known for some time. The immune response is skewed toward the Th2 response, which promotes a pro-inflammatory but nonproductive immune response, in that there is increased susceptibility to cutaneous infections. Cytokines therefore are an attractive target for therapy. It is important to keep in mind some important concepts with regard to cytokine function: these include pleotropy, redundancy, synergism, antagonism, and context. Pleotropy refers to the fact that each cytokine has multiple activities and multiple targets, and redundancy refers to the fact that several cytokines can mediate the same activity. Thus targeting one cytokine is not likely to lead to a therapeutic success, as there will be many others to compensate for it. Furthermore, targeting a cytokine for its allergic activities could lead to undesirable side effects. Cytokines acting within context refers to the fact that the consequences of a cytokine binding to its receptor will be determined by the cell type, the stage of the immune response, and the presence of other cytokines and inflammatory mediators. Furthermore, implicating cytokines in disease requires more than demonstration of simple gene expression. Cytokines are regulated on many levels and ideally one wishes to show protein expression and functionality to invoke a role for any one cytokine.

The hypothesis that atopic dermatitis results from a simple imbalance between T-helper 1 (Th1) and T-helper 2 (Th2) cells has evolved into a much more complex interplay among Th1, Th2, T helper 17/22, and T regulatory cells, each of which has its own subtypes. In fact, rigid separation of T lymphocytes into subsets may be unrealistic. There is more plasticity in these cells than previously thought! Nevertheless, anti-cytokine monoclonal antibodies have been used experimentally in mouse models as well as in clinical trials for human patients with refractory AD with mixed results. Anti-tumor necrosis factor α (TNF-α) reagents (infliximab, adalimumab, and etanercept) have shown promise but the response is not sustained once treatment is stopped; anti-IL-5 monoclonal antibodies have reduced the number of tissue eosinophils very effectively, but with little improvement in clinical signs associated with AD.

Given the principles of pleotropy and redundancy, a more effective approach would be to look at common signal transduction pathways for cytokines involved in AD and use small molecule inhibitors. This approach is a natural one for pharmaceutical companies, and with high throughput technology to enable the rapid screening of thousands of compounds, one of which is likely to yield encouraging results. In particular, the tyrosine kinase pathways have been very attractive as tyrosine phosphorylation is an upstream event in many signaling pathways for cytokines as well as the high affinity IgE receptor. Masitinib, a preferential c-kit inhibitor with activity against platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor 3 (FGFR3), focal adhesion kinase (FAK) pathways, and lyn kinase, has been used in a pilot study for CAD; out of 11 dogs, one withdrew from the study after developing fever and lethargy 5 days into treatment, 5 dogs had ≥50% improvement, 3 dogs showed no improvement, and 2 dogs were worse. The results are difficult to interpret due to small sample size and the lack of a placebo control. Further studies might be warranted, although the apparent lack of specificity of this inhibitor and the reported potential side effects are of some concern to this author.
More appealing is the targeting of specific Janus kinases (the protein tyrosine kinases JAK1, JAK2, JAK3, and TYK2) and their affiliated transcription agents Signal Transducer and Activator of Transcription (abbreviated JAK/STAT). JAK/STAT are upstream signaling pathways linked to a number of cytokine receptors. The ideal inhibitor would decrease the function of many cytokines partially so that disease is regulated but complete immune suppression is avoided. An example of a successful JAK1,2,3 inhibitor is tofacitinib (Pfizer, Inc.), which has passed its Phase III trials and will be marketed for the treatment of refractory rheumatoid arthritis in human patients.22-24 Tofacitinib seems to be safe with no more side effects than those seen with the injectable anti-TNF biological reagents. In clinical trials it has also been found effective in the treatment of refractory psoriasis. Another JAK inhibitor (JAK1, JAK2 specific) licensed to Eli Lilly by Incyte is also in development for refractory arthritis, and others are coming up.22 Multiple human health and animal health companies, including Pfizer, have ongoing research efforts focusing on new therapeutic targets. Pfizer Animal Health has several reports on the scientific program of this Congress discussing new molecules and possible therapeutic approaches identified in their research labs. A simple model for how these pathways work in allergic disease is found in a paper by Pernis and Rothman.25 By preferentially inhibiting JAKs 1, 2, 3, we can block a Th2 polarized response, allowing the Tyk2-mediated Th1 to predominate. In particular, blocking JAK/STAT pathways would ameliorate the influence of interleukin-4 (IL-4), IL-5, and IL-31; the latter has recently been shown to be critical in the mediation of itch.26-32 Canine IL-31 has recently been cloned, but its expression in canine atopic skin remains to be demonstrated.33

Other targets for attack in treating AD include molecules that mediate cellular activation. Two approaches have shown some promise in the treatment of AD. The first is omalizumab (Xolair, Genentech), a humanized monoclonal antibody that binds to IgE; its affinity for IgE is higher than that of the high affinity Fc-epsilon receptor on mast cells and basophils. Furthermore, it does not bind to cell-bound IgE, thereby avoiding the triggering of allergic mediator release. Because of its expense, it is used primarily to treat people with refractory asthma; however, studies have shown efficacy for a limited number of human patients with refractory AD.34-37 There is some evidence that the use of omalizumab with immunotherapy may in fact enhance the benefits and reduce the risks of allergen-specific immunotherapy in human patients.38

A second point of attack is the B lymphocyte, the cell that produces IgE. Anti-CD20 antibodies reduce B-cell function and have been suggested to ameliorate the clinical signs of AD, suggesting the need for larger scale studies. As a third point of attack, anti-T lymphocyte antibodies have also been used, again in very small uncontrolled studies. Alefacept (Amevive, Astellas) is a fusion protein of IgG1 with LFA3, and works by blocking the activation molecule CD2 on both CD4+ and CD8+ T lymphocytes. Its major indication is for severe and refractory psoriasis, but it is also being used to treat cutaneous T-cell lymphoma and other T-cell lymphomas. Studies in a few human patients with refractory AD have shown some efficacy; however, an equal number of patients became worse.39-41 These studies are small scale and not well-controlled, but results are promising enough.42 Efalizumab (Raptiva, Genentech, Merck Sorono) by contrast is a humanized anti-CD11a monoclonal antibody originally marketed for treatment of severe psoriasis; it works by blocking T-cell activation via LFA-1. Because it was associated with fatal brain infections, it was withdrawn from the market in 2009. A handful of patients with refractory AD did show response.43-45 Unless the anti-T-cell attack can be more focused, though, this approach seems less likely to succeed for a disease like AD.

Allergen-Specific Immunotherapy as a Target

Allergen-specific immunotherapy has been the treatment of choice for veterinary atopic patients and will likely remain so, as it is the only biologic treatment we have with no long-term side effects and a chance at modifying the abnormal immune response in an allergen-specific way. How successful allergen-specific immunotherapy is in veterinary patients can be difficult to determine, but most studies estimate that between 60% and 80% of canine patients will have some positive benefit. It is a difficult therapy that requires a long-term commitment by the dog’s owner with no guarantee of success. Many of the problems associated with immunotherapy, including the potential for side effects and poor efficacy, could be related to the relatively crude allergenic extracts currently in use. What can be done to make immunotherapy more successful?
One of the major problems in both human and veterinary allergology has been the lack of standardized allergenic extracts. In recent years, progress has been made in standardizing extracts to US reference standards maintained and distributed by the US Food and Drug Administration’s (FDA’s) Center for Biologics Evaluation and Research (http://www.fda.gov/BiologicsBloodVaccines/Allergens/StandardizedAllergenicExtracts/default.htm). Several standardized allergenic extracts are now available, although they are not widely used in veterinary medicine. Extracts that are not standardized are likely to vary from lot to lot with respect to the actual concentration of relevant allergen compared with total dry weight or even protein. They are quantified by weight/volume (w/v) or protein nitrogen units (PNU/mL). Standardized extracts are quantified by their ability to induce a specific wheal size and the units are termed bioequivalent allergen units. Even if veterinary allergists were to utilize standardized human extracts, they would have no way of knowing whether they were truly relevant to dogs. Nevertheless, an approach involving standard extracts for diagnosis and therapy would likely improve outcome.

Newer approaches to improving the safety and efficacy of allergen-specific immunotherapy include the use of recombinant allergens, “hypoallergenic” allergens (genetically engineered to reduce side effects while preserving and/or improving efficacy), T cell-directed peptide therapy, adjuvants (immunostimulants directed toward driving a Th1 response), allergens coupled to immunostimulants, anti-IgE reagents, and DNA vaccines. Specific major allergenic proteins contained within pollens, dust mites, and danders have been identified for human allergic patients. These are defined as those allergens that induce reactivity in more than 50% of the allergic population. Recombinant allergens allow for better standardization of allergenic extracts. More importantly, the ability to produce recombinant allergens would allow the expression of minor allergens for those patients not reacting to the same proteins as most patients. Recombinant technology permits the generation of truly patient-specific immunotherapy. Recombinant allergen vaccines have been shown to be efficacious; time will tell whether they will be superior to conventional allergen vaccines. Of interest to veterinary dermatologists is that we do not really know that the major allergens for humans are identical to those for dogs. Determining the identity of the major allergens for dogs would be important if we wish to be sure we get maximum benefit from immunotherapy.

“Hypoallergenic” allergens are those allergens that have been modified to reduce binding to IgE while retaining the ability to induce an immune response. Der p 1 is a protease derived from the bodies and fecal pellets of house dust mites; it is considered a major allergen. Current research suggests that genetic manipulation of this protein may improve its capabilities for immunotherapy while making it less likely to induce anaphylaxis. Specifically, by producing proDer p1 in bacteria and allowing it to aggregate, the protein could be used as effective immunotherapy with reduced incidence of side effects in sensitized mice, by virtue of its decreased ability to bind to IgE. Other modifications have included coupling multiple copies of an allergenic protein, such as that for birch allergen. This seems to promote a Th1 response in recipients and reduces its ability to induce anaphylaxis. Other ways to manipulate proteins include introducing mutations that change folding of the protein. These changes affect IgE binding without affecting the ability to induce tolerance or promote the Th1 response.

T-cell peptide vaccines also offer a novel approach to therapy. Because they are composed of pieces of protein, they are able to stimulate the T cells responsible for inducing tolerance. But because most antibodies, such as IgE, recognize whole proteins and conformations rather than peptides, IgE will not bind. Inability to bind IgE reduces the potential for anaphylactic side effects.

Mycobacterial products and CpG are known to activate a subset of cell surface receptors called Toll-like receptors. These receptors are known to activate the T-helper 1 response, a response that is pro-inflammatory and inhibitory to the T-helper 2 response that mediates the atopic state. These products have been used as adjuvants to make immunotherapy more successful. Perhaps immunotherapy in veterinary patients would be enhanced by such approaches.
Traditionally, immunotherapy has been delivered by subcutaneous injection (subcutaneous immunotherapy or SCIT) for veterinary patients with AD and other atopic diseases. Immunotherapy has not been utilized as frequently for human patients with AD, but recently it has become recognized as a viable treatment option. Certainly, immunotherapy has been used widely for humans with allergic rhinitis and conjunctivitis, as well as for extrinsic asthma. There has been a trend to look for other routes by which to administer the allergens in an effort to reduce side effects and make the therapy more acceptable to patients. Sublingual immunotherapy (SLIT) has been shown to be an effective approach for the treatment of allergic rhinitis and conjunctivitis in humans, although optimized protocols for dosing and frequency of administration have yet to be established. SLIT therapy has been reported as efficacious in veterinary patients only anecdotally. A recent pilot study using research beagles sensitized to house dust mite showed no value after 7 months; however, this modality should be pursued more aggressively in clinical patients. In human patients the oral allergen is often taken two to three times daily. It can be challenging to administer SLIT therapy accurately and effectively in dogs, and a major drawback to this approach in the US is lack of approval by the FDA. A well-designed delivery system and a vehicle that will support retention of the allergen under the tongue for several minutes will be required.

Other novel pathways of allergen delivery have also been explored. Epicutaneous administration of allergen has been studied and shows some promising results. Human patients allergic to grasses were treated with the grass allergens applied in petroleum jelly to the upper arm with positive therapeutic benefits when compared with placebo. Epicutaneous administration of immunotherapy may be worth studying in veterinary patients. Immunotherapy delivered directly into the lymph node has also been surprisingly effective, requiring very few injections compared with traditional SCIT.

**PHYSICOCHEMICAL ABNORMALITIES ASSOCIATED WITH THE DYSFUNCTIONAL SKIN BARRIER AS TARGETS**

The notion that a defective stratum corneum barrier contributes significantly to the pathogenesis of AD is becoming well accepted in human and veterinary medicine, and provides new ideas for treatment of CAD. The two major components of the defect include inadequate production of lipids and genetic mutations that result in abnormal proteins (e.g., filaggrin loss of function mutations). The role of filaggrin and other structural or functional barrier genes in CAD remains to be determined, as reports are few and results conflicting. For the most part, these studies have relied on gene expression, which tells us little about protein expression or function. In addition, there may be significant variation among breeds. By contrast, there is reasonable data to suggest that dogs with AD, like humans, have lipid abnormalities in their stratum corneum, particularly decreased ceramides. There are two ways in which barrier repair can be achieved in dogs. It has been shown that feeding omega-6 and omega-3 fatty acids for 2 months can improve the ultrastructural appearance of the canine stratum corneum. Topical therapy with a mix of epidermal lipids containing ceramide, cholesterol, and fatty acids (Allerderm, Virbac) was found helpful in restoring the ultrastructural appearance of the stratum corneum. Barrier repair products are relatively new in veterinary dermatology. Anecdotal reports of improved coat and skin quality abound, but critical assessment of the efficacy of these products in the treatment of CAD is needed. Currently, three product lines are available; these include the phytosphingosine-containing shampoos, sprays, gels, and spot-on products made by Sogeval, the essential oil spot-ons and sprays made by Dermoscent, and the ceramide and fatty acid spot-on product made by Virbac. Each of these products has been used to treat dogs with CAD with some benefit, but as time goes on, we may find that each product has specific indications.

**NEUROLOGIC ABNORMALITIES AS TARGETS**

Recent research has suggested a close interaction between immune and inflammatory cells and the nervous system. Neurons bear receptors for cytokines such as IL-31 on their cell membranes, and many inflammatory cells have receptors for neurotransmitters. It is fair to say that itching is the major complaint from owners of dogs with AD, and that itch impacts significantly on the quality of life of both dog and owner. Itch has
been identified as a sensation distinct from pain, with its own peripheral and spinal neurons, its own mediators, and specific areas within the cerebral cortex (reviewed in Reference 83). This knowledge has led to some new ideas about controlling itch that may enable us to avoid drugs with more global effects such as glucocorticoids or cyclosporine. Substance P, which binds to neurokinin-1 (NK-1) receptors in the skin and brain, is a major mediator of pruritus. In 2009, a number of short commentaries and letters were published reporting success with the anti-nausea drug aprepitant (Emend, Merck) in the treatment of itch associated with Sézary syndrome, drugs, prurigo nodularis, and atopic dermatitis. According to some anecdotal reports, maropitant combined with cyclosporine A and/or antihistamines has been used to treat CAD; published evidence, however, is lacking. Gabapentin has also been used to treat dogs with refractory pruritus; it is believed to block the ability of glutamate to activate the N-methyl-D-aspartate receptor (NMDA-R) at the level of the synapse between the presynaptic and postsynaptic neurons.

In general, the efficacy of traditional antihistamines, which block H1 and H2 receptors, is fair to poor in dogs with CAD. Within the last 10 years H4 receptors have been cloned, and agonists for these receptors have been shown to reduce pruritus in mouse models of AD in a manner independent of mast cells or other hematopoietic cells. H4 receptors are found on nerve cells and likely the effect of antagonists on itch is directly on the nerves themselves. Other nervous system drugs have also been used in the treatment of refractory pruritus in humans with AD, including mu opioid receptor antagonists, kappa opioid receptor agonists, as well as protease inhibitors and protease-activated receptor-2 antagonists and antibodies which act on cutaneous nerves. Also of interest is the transient potential receptor vanilloid (TRPV), the target for capsaicin and one of the targets for tacrolimus. New drugs that inhibit the function of this molecule are currently being studied in mouse models.

**STEM CELL, ANTISENSE, AND GENE THERAPY AS TARGETS**

Truly futuristic treatments could include the use of stem cell therapy, antisense therapy, and even gene therapy. Stem cell therapy is quite appealing, particularly those stem cells derived from mesenchymal tissue such as fat. The mechanism of action for treating allergic disease is hypothesized to be the enhancement of T-regulatory cells, and repression of immune activation. These cells have both regenerative and anti-inflammatory activity; hence the anecdotal success in dogs with severe arthritis. Mesenchymal stem cells have been shown to inhibit the allergic response in ragweed-induced asthma models in mice, and the response of peripheral blood mononuclear cells from human patients with allergic asthma to house dust mite in vitro. One trial has been published on the use of adipose-derived stem cells in CAD. This study utilized one injection of 1.3 million cells per kg. One problem was the system used, which required mailing the harvested fat back to the company, which then prepared the cells then shipped them back. Shipping is likely to result in massive reduction of viable cells. It is possible that this type of therapy might work using the in-hospital systems now available and higher numbers of cells. It is unlikely, however, that one treatment will be effective for such a chronic disease; repeated injections would be needed. Cells can be banked, but prior to the use of such technology in pets, it would be wonderful to study this in mouse and canine models of AD. One study has also been published on the use of adipose-derived stem cells in human atopic patients; these patients were given cells expanded in culture and multiple injections were given. The number of patients was low and the follow-up short, but the study shows that the procedure was safe and relatively easy, using fat from liposuction.

Antisense therapy involves the use of oligonucleotides to inhibit the expression of specific mRNAs. A number of molecules, including cytokines, cell surface receptors, ion channels, and tyrosine kinases, are being targeted in mouse and rat models of asthma with some success. IL-13 antisense RNA has been complexed with cationic elastic liposomes to allow delivery topically. In a mouse model of AD, the application of antisense IL-13 was shown to reduce cellular infiltrates and skin thickening. Short interfering RNAs (siRNA) have been used topically to reduce transcription factor RelA in a mouse model of AD; by using a combination of a cell penetrating peptide TAT and a compound that increases permeability, the investigators were able to deliver the siRNA successfully through the skin barrier.
Gene therapy is appealing but is still a long way off! Currently it has been difficult to deliver the genes of interest to the target organ. Most approaches utilize modified viruses (adenovirus, lentivirus) vectors, which may induce some surprising side effects of their own. Recently, however, Ando and colleagues were able to construct a plasmid vector that allowed for the slow and steady release of interferon-gamma (IFN-γ) in mice and thus avoided the adverse effects associated with previous constructs.

The future is bright for the treatment of AD in general and CAD in particular. While some of the approaches described above may not be developed for clinical use in our lifetimes, they may be available to future veterinarians!

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KEY POINTS

- Itch is a key component of canine atopic dermatitis (CAD) that can have a significant impact on the quality of life for the pet as well as for the owner, but the mechanisms involved in triggering itch are not clearly understood.

- Increasing evidence suggests a synergistic interaction between the nervous system and the immune system within the skin, and these interactions likely participate in the pathobiology of pruritic skin diseases.

- T-cell cytokine imbalance exists in the skin of atopic dogs.

- Several T-helper 2 (Th2) cytokines have been associated with pruritus based on phenotypes observed with transgenic mouse models, e.g., interleukin (IL) 4, IL-13, and IL-31.

- IL-31 is a recently discovered cytokine secreted from Th2 lymphocytes and skin homing T cells that has been implicated in pruritic skin conditions in humans such as atopic dermatitis.

- Our lab has evaluated the role of IL-31 in canine pruritus and has observed the following under experimental conditions:
  - IL-31 can be secreted by Th2-polarized peripheral blood mononuclear cells (PBMCs) isolated from allergen-sensitized dogs.
  - Injection of canine IL-31 can induce pruritus in purpose-bred beagles.

- The investigational compound oclacitinib (Pfizer Animal Health), a selective Janus kinase inhibitor, can inhibit the pruritogenic effects of IL-31 in dogs, suggesting that this agent could be an effective treatment for pruritic allergic skin diseases.

PATHOBIOLOGY OF CANINE ATOPIC DERMATITIS

Canine atopic dermatitis is defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with immunoglobulin E (IgE) antibodies most commonly directed against environmental allergens. Recently, the definition has been modified to include the concept of extrinsic versus intrinsic causes of atopic dermatitis (AD). Although each cause leads to similar clinical presentations, extrinsic forms of AD are believed to be triggered by external allergens, and IgE antibodies to environmental allergens are readily detected in the animal. Intrinsic forms (atopic-like) are likely caused by internal dysfunction not necessarily related to IgE, and IgE response to environmental allergens cannot be documented in the animal.1,2

A generally well accepted hypothesis for the pathogenesis of extrinsic AD is as follows: Initial penetration of allergens via defective or damaged skin barrier results in the activation of innate immune cells such as resident Langerhans cells. Langherhans cells function as antigen-presenting cells and activate the adaptive immune system, leading to Th2 cytokine production (e.g., IL-4, IL-5, IL-13, and IL-31). Th2 cytokines create a microenvironment that perpetuates skin barrier dysfunction and promotes allergen-specific IgE (ASlgE) production. ASlgEs then bind to cells such as mast cells and basophils via cell surface Fce receptors. During
subsequent exposures to allergens, these IgE-primed cells will release a variety of substances, such as histamine, neuropeptides, cytokines, and chemokines. These agents can activate and polarize T lymphocytes toward a Th2 phenotype, cause vasodilation, and also recruit additional immune cells into the skin, all of which perpetuate the cycle of itch and chronic inflammation. T-helper type 1 (Th1) responses can also be seen within the skin, particularly in the chronic phase where cytokines such as interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α) commonly can be found. These cytokines may be present due to the increased susceptibility to skin infections seen in dogs with CAD or possibly due to the efforts of Th1 cytokines to counteract the effects of Th2 cytokines, as cytokines from one type can negatively regulate the activity of the other type in an attempt to restore proper immune balance. 

The pathogenesis of intrinsic AD is not as well defined, but it is becoming more clear that genetic defects in skin barrier and immune cell function/regulation may play a large part in the production of clinical signs associated with this form of AD (Figure 1).

**Neuroimmune Interactions in Pruritus**

Itch is a key component of CAD that can have a significant impact on the quality of life for the pet as well as for the owner. Unfortunately, the underlying pathways and mechanisms involved in triggering itch or pruritus are less clear, hampering the development of effective treatments with anti-pruritic activity. Work performed in mouse, rat, and non-human primate models suggests that itch and pain sensations are transmitted by distinct neurons. The itch signals are detected through relevant “itch” receptors present on cutaneous itch-selective sensory nerves residing in the epidermis and dermis. The signals then travel along unmyelinated C nerve fibers and are received by the dorsal root ganglia (DRG) and the lamina I region within the dorsal horn of the spinal cord. The itch signal finally reaches the brain through spinothalamic tract neurons.

Increasing evidence suggests a synergistic interaction between the nervous system and the immune system within the skin. Resident immune cells such as mast cell, Langerhans cells, and transient immune cells present during inflammation (e.g., granulocytes, T lymphocytes) intimately associate with nerve fibers. When such immune cells are activated, they can release substances such as neuropeptides (e.g., histamine, substance P), cytokines (e.g., IL-31), and neurotropins (e.g., nerve growth factor, NGF) that can bind directly to receptors on sensory nerves to cause activation, sensitization, and sprouting of nerve cells. Similarly, activated nerves can release neuropeptides (e.g., substance P, calcitonin gene-related protein, CGRP) and neurotropins (e.g., NGF) that can modulate immune cells and their responses during inflammation. As a result of the complex innervations of the skin with sensory nerve fibers, immune cells and sensory nerves clearly communicate with one another, regulate each other's activity, and likely participate synergistically in the pathophysiology of pruritic skin diseases (Figure 2).

**Cytokine Networks in Atopic Dermatitis**

Cytokines represent a class of secreted signaling proteins that play a role in cell-to-cell communication. Numerous Th2 cytokines (e.g., IL-4, IL-13, IL-5, IL-31, IL-10) and Th2-promoting cytokines (IL-25, thymic stromal lymphopoietin, TSLP) have been implicated in the pathogenesis of human AD over the years, which has triggered investigations into their role in CAD.

Work by several groups showed that T-cell cytokine imbalance does exists in atopic dogs. One study clearly observed one fourth of atopic canine skin samples exhibiting a polarized type-2 profile; however, mixed Th1-Th2 cytokine profiles were also seen. Specifically, elevated levels of Th2 cytokines such as IL-4, IL-13, and IL-5 mRNA were seen in non-lesional and lesional atopic dog skin compared with skin from healthy control dogs. In addition, IFN-γ and TNF-α transcripts were elevated in the skin of many atopic dogs, suggesting a mixed Th1-Th2 cytokine profile can be found, similar to what is seen in human AD. In an experimental model using atopy patch testing in house dust mite-sensitized, high-IgE beagles, cytokine transcripts of IL-6, IL-13, IFN-γ, and IL-18 could be observed further supporting a mixed Th1-Th2 cytokine profile in the skin. Observing changes in cytokine transcripts is encouraging; however, continued evaluation of additional cytokines as well as protein
Figure 1. Pathobiology of canine atopic dermatitis. Based on research in dogs and humans with atopic dermatitis, the current pathobiology of the disease starts with percutaneous exposure and absorption of allergens through an epidermis that may have a defective barrier function.

A (left), Sensitization. The naive Langerhans cell (LC) captures and internalizes allergens. Allergens are then processed, packaged in major histocompatibility complex molecules on the LC surface, and presented to naive T helper (Th0) cells in the draining lymph node. Specific cues from the microenvironment enable dendritic cells to activate T-helper cells and polarize them towards a Th2 phenotype where they produce cytokines such as IL-4 and IL-13. These cytokines can stimulate B cells to become plasma cells that begin producing allergen-specific IgE (ASIgE). Activated Th2 cells migrate to the skin with the help of chemokines produced by various cells in the skin, such as thymus and activation regulated chemokine (TARC). ASIgEs also enter into the circulation and other tissues and bind to cells expressing high and low affinity Fc receptors on their cell surface.

B (right), Progression. Upon re-exposure to the same allergen the epidermal LC with cell surface bound ASIgE efficiently binds allergen and migrates to the dermis. Once there the ASIgE+ LC cells “present” the allergen to T-helper lymphocytes and continue to polarize them toward a Th2 phenotype. Additional Th2 cytokines such as IL-31 can be released and activate the sensory neuron to induce pruritus. Allergens can also cross link ASIgE bound on the cell surface of dermal mast cells and stimulate the release of pre-formed inflammatory mediators such as histamine, serotonin, and substance P along with cytokines such as eosinophil chemotactic factor (ECF). Skin injury by scratching, microbial toxins from staphylococci and Malassezia, or environmental allergens activates keratinocytes and other innate immune cells to release proinflammatory cytokines (e.g., IL-12) and chemokines that can polarize T-helper cells toward a Th1 phenotype where they produce cytokines such as IFN-γ. In turn, IFN-γ promotes monocyte/macrophage cell activation. Activated keratinocytes, monocytes, and mast cells produce additional pro-inflammatory cytokines such as TNF-α, upregulating the expression of P-selectin, and E-selectin, on endothelial cells, thus recruiting more leukocytes from the blood. The epidermis thickens as does the stratum corneum, the barrier function continues to deteriorate allowing increased allergen penetration, and the cycle is perpetuated.
Figure 2. Role of cutaneous itch-selective neurons in the skin. During inflammation, a variety of itch mediators such as cytokines, chemokines, and neuropeptides are released into the microenvironment by immune cells in close proximity to primary afferent nerves in the epidermis and dermis. The itch mediators are detected through relevant "itch" receptors present on cutaneous itch-selective sensory nerves. The signals then travel along unmyelinated C nerve fibers and are received by the dorsal root ganglia (DRG) and the lamina I region within the dorsal horn of the spinal cord. The itch signal finally reaches the brain through spinothalamic tract neurons and affects regions of the brain involved in pruritus.

In addition, peripheral nerve endings can stimulate immune cells as well as neighboring afferent nerves, a process known as axon reflex, by releasing neuropeptides (e.g., substance P, calcitonin gene-related protein, CGRP) and neurotropins (e.g., NGF). These mediators can modulate immune cells and their responses during inflammation as well as directly trigger vascular responses in the skin.
levels of biologically active cytokines in CAD is needed to better understand the role of cytokine imbalance in the pathobiology of CAD.

**Th2 Cytokines Implicated in Pruritus**

Elevated Th2 cytokine transcripts can be found in atopic dogs, and their potential to communicate with the peripheral nervous system is an interesting concept to consider. Several Th2 cytokines have been associated with pruritus based on phenotypes observed with transgenic mouse models. When IL-4, IL-13, or IL-31 is overexpressed in transgenic mice, animals develop several of the hallmarks of AD including increased inflammatory cell infiltration into the skin as well as pruritic dermatitis.12,18

IL-4 is a cytokine that has been shown to be produced by T cells, mast cells, basophils, and eosinophils.19 This cytokine exerts its activity via a heterodimeric receptor complex that consists of IL-4Rα and the IL-13 Rα1 subunit or the common γ-chain (γc).20 IL-4 can regulate immunoglobulin class switching in B cells and can induce polarization of T cells toward a Th2 phenotype. IL-4 also plays a central role in allergic inflammation and asthma by enhancing the expression of FcεRI, the high affinity receptor that binds allergen-specific IgE on a variety of immune cells. IL-4 can also induce proliferation, survival and/or chemotaxis in many cell types such as lymphocytes, mast cells, basophils, and eosinophils, key players in allergy.21,22 The mechanism through which it induces itch in mice is unclear but may in part be due to its activity on mast cells, basophils, eosinophils, and/or lymphocytes that can release pruritogenic mediators.

IL-13 is a cytokine secreted by T cells, mast cells, basophils, and eosinophils and can produce many of the effects seen with IL-4 because they both bind and activate cells via the IL-4Rα/IL-13 Rα1 heterodimeric receptor. IL-13, however, is thought to have more potency toward the receptor. One important difference between IL-13 and IL-4 is that IL-13 does not polarize or expand Th2 lymphocytes, likely due to the lack of IL-13 Rα1 chain expression in those cells. In several models of asthma, IL-13 (and IL-4) is thought to affect cells in addition to immune cells, particularly epithelial cells (e.g., keratinocytes and bronchial epithelial cells) and smooth muscle cells.21-23 The mechanism through which IL-13 produces itch is unclear but may be similar to the role of IL-4.

Of greatest interest is IL-31, a recently identified cytokine implicated in pruritic skin conditions in humans such as atopic dermatitis. IL-31 has been found in humans to be produced by activated Th2 lymphocytes and by cutaneous lymphocyte-associated antigen (CLA)-positive skin homing T cells in AD patients and is preferentially elevated in pruritic versus non-pruritic human skin conditions. Furthermore, serum levels of IL-31 are detected in AD patients and correlate with disease severity in adults as well as children with AD.24-30

IL-31 binds to a heterodimeric receptor consisting of the IL-31 receptor A and the oncostatin-M receptor β. These receptors are found on a variety of cells, such as keratinocytes, macrophages, and eosinophils, and participate in regulating immune responses in these cell types.31-33 Interestingly, these receptors have been found on a subset of small-sized nociceptive neurons of adult mouse and human dorsal root ganglia,24,34 suggesting that this cytokine can directly activate pruritogenic signals in peripheral nerves.

**Pfizer Animal Health has been interested in exploring the relationship between Th2 cytokines and pruritus.** Because of the difficulty in recapitulating all mechanisms of interest in one model, we have developed a variety of in vivo and ex vivo model systems to better understand cellular sources of canine Th2 cytokines and the role of such cytokines in canine pruritus. We have been able to demonstrate that canine IL-4 and IL-31 can be produced by peripheral blood mononuclear cells (PBMCs) freshly isolated from allergen-sensitized dogs. Of greatest interest is our finding that IL-31 can induce pruritic behaviors in dogs, suggesting that IL-31 may be an important cytokine that promotes itch in a variety of conditions and/or diseases in dogs. Whether IL-31 exerts its pruritogenic effects via direct activation of the IL-31 receptor on sensory nerves or indirectly via activation of other IL-31R–expressing cells (e.g.,keratinocytes, macrophages, eosinophils) intimately associated with peripheral nerves in the skin still remains to be determined.
**THERAPEUTIC APPROACHES TO Th2 CYTOKINE INHIBITION**

Numerous cytokines implicated in pruritus and CAD are known to activate the Janus activated kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, the mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol 3-kinase (PI3K) pathway, nuclear factor (NF) kappa B pathway (NFkB), or NF of activated T cells (NF-AT) pathways. A variety of small molecules designed to target these pathways are currently under clinical investigation or have recently been approved for use in human diseases.

Most appealing are the Janus kinase inhibitors due to their effectiveness in human pruritic skin diseases. These inhibitors selectively target Janus kinase family members, of which there are four (JAK1, JAK2, JAK3, and Tyk2). These compounds inhibit the enzymatic activity of the Janus kinase, thereby inhibiting the ability of cytokines to transmit signals from the external environment to the nucleus of target cells to initiate biological responses that may be involved in disease (Figure 3).

**Figure 3. The JAK-STAT pathway and JAK inhibition.** The Janus kinases are a family of cytoplasmic tyrosine kinases, of which there are four members (JAK1, JAK2, JAK3, and Tyk2). Upon binding to their receptors, cytokines activate JAK enzymes that are associated with the intracellular portion of the cytokine receptor complex. When JAK enzymes are activated, they phosphorylate intracellular domains of the cytokine receptor, creating docking sites for signaling proteins, notably, members of the signal transducer and activator of transcription (STAT) family. Once at the receptor, STATs are phosphorylated by JAKs on a conserved tyrosine residue. The STATs are then released from the receptor and dimerize with one another. These dimers translocate to the nucleus where they bind to specific DNA sequences and induce targeted gene transcription. Therefore, JAK enzymes play a key role in allowing extracellular proteins such as cytokines to transmit signals to the nucleus of target cells to initiate biological responses that may be dysregulated in disease. Janus kinase inhibitors represent an attractive way to intervene and inhibit cytokine pathways that may be dysregulated in disease.

Pfizer Animal Health has developed its own Janus kinase inhibitor, oclacitinib, which is currently being evaluated for the control/treatment of pruritus associated with allergic dermatitis and the control/treatment of atopic dermatitis in dogs. We have been interested in studying the activity of oclacitinib in some of our newer models of pruritus and have demonstrated that oclacitinib can inhibit the production of IL-31 from canine PBMCs and inhibit IL-31–induced pruritus in dogs. We continue to evaluate the role of cytokines in pruritus in the hopes of expanding our understanding of the pathobiology of canine atopic dermatitis and improving our ability to identify promising new approaches for this disease.
REFERENCES


KEY POINTS

♦ Historically, the approach to treatment of canine atopic dermatitis (CAD) has been reactive—focused on treating the inflammatory process after it had already become well established in the skin.

♦ We now stress a proactive approach to treatment—correcting the underlying pathogenesis of the disease where possible, preventing acute flares where we can, and forestalling the development of chronic inflammatory changes in the skin that become much more difficult to reverse.

♦ The International Task Force on Canine Atopic Dermatitis, an independent group of clinicians and researchers in veterinary allergy, recently published a set of practice guidelines for CAD.

♦ Throughout both acute and chronic treatment, the most common clinical sign and reason for patient and owner distress is itching.

♦ Short-term treatment is necessary while progressing through the diagnostic evaluation scheme, and longer-term treatment may become extremely valuable to decrease the cycle of neuronal stimulation of itch, scratch, and inflammation.

♦ Treatment of acute flares should focus on 1) identification and elimination of “flare factors,” 2) reduction in pruritus and lesions with short-term drug therapy, and 3) improvement of skin and coat hygiene and care.

♦ Treatment of chronic disease includes 1) identification and avoidance of “flare factors,” 2) long-term reduction of pruritus and lesions with drugs, 3) improvement of skin and coat hygiene, and possibly epidermal barrier function, and 4) implementation of strategies to prevent recurrence of signs.

♦ Allergen-specific immunotherapy remains one of the single most valuable and proven long-term treatments for CAD.

♦ CAD is a lifelong disease that is controllable but not curable. Clients need to be told explicitly: there is no cure for allergy!

The many recently uncovered factors involved in the pathogenesis of canine atopic dermatitis continue to add to the evidence that this is a multifactorial disease that probably requires a multifactorial approach to treatment. But how, exactly, do these new facts about pathogenesis translate into treatment protocols? Treatment approaches for CAD must be individualized and flexible, combine several modes of therapy, and be aimed at both the primary disease and at secondary complications to maximize success and client satisfaction. Our goal with each patient is to find just the right combination of therapies to provide lifelong management that is effective, affordable, convenient, and with as few adverse effects as possible.
CHANGING VIEWS OF TREATMENT

Historical View

Historically, management of CAD has been aimed at the end process of the disease—in other words, focused on anti-inflammatory therapies. "Managing inflammation" has been the first goal of therapy. This traditional approach was a rather "blunt instrument," often consisting principally of oral corticosteroids, with antihistamines or fatty acids as possible adjuncts. As our understanding grew, we gained additional tools to manage the inflammation—for example, the oral and topical calcineurin inhibitors such as cyclosporine A—and effective topical steroid products that could manage inflammation with less systemic effect. We also gained a renewed understanding of the importance of treating secondary complications such as bacterial and yeast infections. Even as they evolved, all of these approaches were still completely reactive—reacting to the inflammatory process after it had already become well established in the skin.

An Emerging, Broader View

Our newer approach to treating CAD encompasses a broader, "whole-patient" approach, stressing a multifaceted approach, based on a multifaceted pathogenesis, and multifaceted clinical signs that are likely different in each patient. In addition, we now stress a proactive approach to treatment—in other words, correcting the underlying pathogenesis of the disease where possible, preventing acute flares where we can, and forestalling the development of chronic inflammatory changes in the skin that become much more difficult to reverse. Important elements of this "new approach" include:

- Controlling the primary factor in patient discomfort—that is, pruritus—and if possible, modifying the neuro-immunologic 'vicious cycles' that contribute to chronicity
- Elimination of allergens where possible (decreasing allergen load) by targeting environmental, parasitic, dietary, and microbial allergens
- Augmenting or repairing the epidermal barrier in an attempt to limit percutaneous penetration of allergens and irritants
- Control of secondary infections when and as they occur
- Augmenting the epidermal antimicrobial barrier—preventing infections where possible, as opposed to recurring cycles of treatment
- Modification of the immunologic response through allergen immunotherapy, including new possibilities for an oral "allergy drop" approach
- Managing inflammation where possible, targeting the therapy to treat specific signs such as itch, or to treat regionally with topical products

PRACTICE GUIDELINES FOR CANINE ATOPIC DERMATITIS: A CLINICAL FRAMEWORK

"Practice guidelines" are a new concept in which principles of evidence-based medicine are applied to specific, common case presentations, providing practical recommendations to assist veterinarians in choosing effective treatment protocols. The International Task Force on Canine Atopic Dermatitis, an independent group of clinicians and researchers in veterinary dermatology, recently published a set of practice guidelines for CAD (Table 1). These guidelines are freely available online (see http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3164.2010.00889.x/pdf) and can be downloaded in many different languages. The guidelines stress that one approach or set of therapies is appropriate for short-term or immediate management of clinical flares, and a second set is used in an attempt to gain longer-term control of the disease.
Indeed, the most common clinical situation faced by a veterinarian in treating CAD is the dog whose clinical signs have gone suddenly and completely out of control. The patient may have erupted with lesions, may be so pruritic as to be causing extensive self-trauma, and may be dramatically affecting the owner’s own quality of life through frustration and lack of sleep! Treating acute flares should focus on three important elements of the clinical situation:

1. **Identify and eliminate flare factors**
   - Bacterial or yeast infections
   - Parasites
   - Food allergens
   - Environmental allergens

2. **Reduce pruritus** and lesions with short-term drug treatment
   - Oral corticosteroids
   - Topical corticosteroids

3. Improve skin and coat hygiene and care
   - Bathing

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**TREATING ACUTE FLARES**

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   - Oral corticosteroids
   - Topical corticosteroids

3. Improve skin and coat hygiene and care
   - Bathing

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**TREATING THE CHRONIC DISEASE**

1. Identify and **avoid** flare factors
   - Preventing bacterial or yeast infections
   - Preventing parasitism
   - Food allergen control
   - Environmental allergen avoidance

2. **Reduce pruritus** and lesions longer-term, with drug treatment as necessary
   - Corticosteroids
   - Cyclosporine A or Tacrolimus
   - Interferons

3. Improve skin and coat hygiene and care
   - Shampooing
   - Epidermal barrier repair strategies

4. Implement strategies to prevent recurrence
   - Allergen-specific immunotherapy – subcutaneous or sublingual

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**Table 1. Summary of Practice Guidelines for Treatment of Canine Atopic Dermatitis, Outlining the Goals of Therapy for Each Typical Clinical Situation (summarized from reference 1).**

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**Treating Acute Flares**

Indeed, the most common clinical situation faced by a veterinarian in treating CAD is the dog whose clinical signs have gone suddenly and completely out of control. The patient may have erupted with lesions, may be so pruritic as to be causing extensive self-trauma, and may be dramatically affecting the owner’s own quality of life through frustration and lack of sleep! Treating acute flares should focus on three important elements of the clinical situation:

1. **Identification and elimination of “flare factors.”** Flare factors are short-term alterations that cause a patient under good control to suddenly worsen and develop substantial clinical signs of CAD (Figure 1). Perhaps the most common factor in an acute flare is the development of a staphylococcal or yeast infection. Identification and
treatment of such infections is paramount, both as a short-term consideration and in a longer term preventive approach. Other factors, such as varying environmental exposure (pollen counts, etc.) may be responsible for the flare, as well as development of flea infestation or dietary indiscretion in a dog with a food-hypersensitivity component to their disease. These factors need to be considered and eliminated where possible.

2. Reduction in pruritus and lesions with short-term drug therapy. In this situation, a short course of oral glucocorticoids is a frequent treatment of choice if the pruritus is widespread. A pet with more regional signs can often be effectively controlled with a topically applied corticosteroid spray; low-concentration triamcinolone (Genesis, Virbac) and hydrocortisone aceponate (Cortavance, Virbac) both have good evidence of effectiveness.

3. Improvement of the skin and coat hygiene and care. Bathing with a non-irritating shampoo may provide temporary relief, remove microbial and environmental allergens, and limit further microbial colonization. There is no good evidence for the superiority of any specific shampoo product, and no evidence for increased efficacy of shampoos containing ingredients such as oatmeal, anesthetics, or antihistamines.

Interventions of little or no benefit in treatment acute flares of AD include antihistamines, fatty acid supplements, and calcineurin inhibitors. From a strictly evidence-based point of view, there is no convincing evidence that conventional antihistamines are beneficial in treating CAD, especially in an acute flare. Fatty acid supplements may be beneficial in the long term, but their slow onset of action, over months of time, makes them inappropriate for acute use. Likewise, although calcineurin inhibitors such as cyclosporine A or tacrolimus can be effective over time, they often take several weeks to have a substantial effect.

Treating Chronic Disease

Once the “forest fires” are extinguished, the clinician and owner must focus on a management plan consisting
of therapies that will provide safe, effective, long-term relief. Clients need to be told explicitly: there is no cure for allergy! CAD is a lifelong, controllable, but not curable disease. Owners should expect that things will not go perfectly; there will be relapses and secondary problems, and they should plan on higher-than-normal medical care costs over the patient’s life. The owner must be made aware of the “integrated approach” concept and accept that maximum clinical benefit occurs only over time. The practice guidelines stress that, for the patient presented with a goal of developing a long-term management plan, the following elements should be considered:

1. **Identification and avoidance of flare factors.** If fleas have been a periodic factor, monthly preventive should be instituted. Because infections are so commonly implicated as flare factors, consideration should be given to reducing skin colonization with topical products containing such ingredients as chlorhexidine, phytosphingosine, or nisin (Wipe-Out Dairy Wipes, ImmuCell).4

2. **Long-term reduction of pruritus and lesions with drugs.** Drugs that have proven effective for long-term control of pruritus and lesions of chronic CAD include oral or topical glucocorticoids, topical tacrolimus (Protopic, Astellas),5 oral cyclosporine A (Atopica, Novartis),6 and in countries where available, injection of various interferon products such as recombinant canine interferon-gamma (Interdog, Toray)7 or interferon-omega (Virbagen, Virbac).8 All of these medications must be individually targeted for patient use, considering not only variation in efficacy but their costs and individual longer term adverse effect profiles.

3. **Improvement of skin and coat hygiene, and possibly epidermal barrier function.** In addition to bathing—perhaps with an antiseptic product if infections have been a problem—therapies aimed at repairing the epidermal barrier should be considered. It should be noted that, at the time of this writing, only limited evidence for effectiveness of such measures is available, but it appears that such evidence may be mounting. Dietary approaches may become useful, such as supplementation with fatty acids9 or barrier-enhancing micronutrients.10 Topical approaches with spray-on or spot-on products are the subject of considerable investigation, and may be useful in certain cases.11,12 Our knowledge of this area of therapy is likely to expand greatly over the coming years.

4. **Implementation of strategies to prevent recurrence of signs.** Allergen-specific immunotherapy remains one of the single most valuable and proven long-term treatments for CAD. It is one of the very few treatments currently available that is aimed at actually reversing an important part of the underlying pathogenesis of the disease, has an excellent safety profile, and is the only treatment that in some cases can effect a virtual cure of the disease. For needle-shy owners, there is initial evidence that a new sublingual “allergy drop” formulation (Allercept Therapy Drops, Heska13 is effective, and may even work via different mechanisms as it may benefit dogs that have failed conventional “allergy shots.”

Interventions that have insufficient evidence for use in controlling chronic CAD include antihistamines, pentoxifylline, misoprostol, nonsteroidal anti-inflammatory drugs (NSAIDs), and leukotriene inhibitors. All of these therapies have received only limited study, and the evidence to date is not convincing that these medications are satisfactory long-term solutions.

Throughout both acute and chronic treatment, the most common clinical sign and reason for patient and owner distress is pruritus. Short-term treatment is necessary while progressing through the diagnostic evaluation scheme, and longer-term treatment may become extremely valuable to decrease the cycle of neuronal stimulation of itch, scratch, and inflammation.14

**FUTURE DIRECTIONS IN THERAPY**

In the same way that new knowledge has led to new approaches to treating CAD, continued research is uncovering new therapeutic targets that are bound to provide more treatment options in the future. Cytokine signaling, cellular regulation, histamine receptors all will be subjected to scrutiny and ‘small molecule’
bombardment by pharmaceutical chemists. New molecular and genetic studies will change our thoughts and may lead to improved ability to identify specific patient groups that will benefit by targeted therapies. We may see new approaches to effective epidermal barrier repair, or to limiting microbial colonization and growth on skin. New biological pathways to immunomodulation via adjuvanted allergen-specific immunotherapy, immunomodulatory bacterins, probiotics, and even vitamin D have already shown promise in mechanistic and clinical studies. We can all look forward to a time when the prednisone tablet will be viewed as an outdated and unnecessary therapeutic relic!

REFERENCES


