Canine Atopic Dermatitis

Man’s best friend shares hope for new therapies.

BY CHRISTOPHER LOGAS AND PETER A. LIO, MD

Atopic dermatitis (AD) is an increasingly common chronic and relapsing disease characterized by pruritus, xerosis, scaling, and lichenification in adults and children. AD is a complex disease that is still not fully understood. There is a genetic component with an increased risk seen among those with a positive family history. There is also strong evidence that environmental triggers are important in the development and severity of the disease. AD may precede or present concurrently with other allergic conditions including allergic rhinitis, food allergies, and asthma. The progression from AD to allergic rhinitis and asthma is referred to as the “atopic march” and may occur in up to 80 percent of children with severe AD.

Canine atopic dermatitis (CAD) is very similar to human AD. It is characterized by similar clinical signs, such as dry skin, pruritus, excoriations, and when chronic, lichenification. Of great interest is that several of the therapies currently being used to successfully manage CAD may also be useful in the management of human AD.

This article will compare the pathogenesis of and treatments used for CAD and human AD, and discuss how therapies used for CAD might be useful for humans.

Canine Atopic Dermatitis vs Human Atopic Dermatitis

There are many important similarities between human AD and CAD (see Table 1). In both humans and canines, symptoms usually develop early in life. In dogs, clinical signs typically begin in the first three years of life with chronic pruritus as the primary clinical sign. Forty percent of children with AD develop symptoms within their first six months, 60 percent by the first year, and 85 percent before the age of five. Forty to sixty percent of children with AD will outgrow their disease by puberty or young adulthood while very few canine AD patients spontaneously clear. Both children and dogs also have a clear genetic component to the development of AD, along with triggers such as environmental allergens that initiate clinical signs.

Studies have shown that both dogs and humans with AD have higher than normal IgE levels. Due to the high correlation seen with IgE and allergic disease, both physicians and veterinarians advise their patients to avoid known allergic triggers.

In human medicine, and more recently in veterinary medicine, emphasis has been placed on the role of barrier function impairment in the pathogenesis of AD. This impairment is directly related to excessive transepidermal water loss, increased staphylococcal colonization, and epidermal inflammation that characterizes AD and CAD patients. Similar epidermal defects have been found in both human AD and CAD skin. Ceramide concentrations in the stratum corneum are significantly lower in human and canine patients with AD compared to normal controls.

Other defects being investigated in both fields of medicine are filaggrin mutations. Studies in humans and dogs have shown a higher rate of faulty expression of epidermal differentiation markers such as the C-terminal filaggrin protein in patients with AD. Humans with filaggrin mutations are three times more likely to develop symptoms of AD.

Finally, defects in cutaneous fatty acid metabolism have been associated with the development of AD in both humans and canines. Patients lacking the enzymes responsible for the synthesis of highly unsaturated n-3 or n-6 fatty acids were more likely to have AD.

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**TABLE 1. COMPARATIVE FEATURES OF AD AND CAD**

<table>
<thead>
<tr>
<th>AD features</th>
<th>Humans</th>
<th>Canines</th>
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<tbody>
<tr>
<td>Symptoms of pruritus, xerosis, scaling, and lichenification</td>
<td>Yes¹</td>
<td>Yes⁵</td>
</tr>
<tr>
<td>Age of onset</td>
<td>1-5 years³</td>
<td>1-3 years⁶</td>
</tr>
<tr>
<td>High IgE levels and correlation of allergies</td>
<td>Yes⁸</td>
<td>Yes⁹</td>
</tr>
<tr>
<td>Structural defect in stratum corneum</td>
<td>Yes¹¹</td>
<td>Yes⁶</td>
</tr>
<tr>
<td>Filaggrin mutations</td>
<td>Yes⁹</td>
<td>Yes¹⁴</td>
</tr>
<tr>
<td>Cutaneous Fatty Acid Metabolism</td>
<td>Yes¹³</td>
<td>Yes¹⁵</td>
</tr>
<tr>
<td>Increased Staphylococcal Colonization</td>
<td>Yes¹⁰</td>
<td>Yes¹⁰</td>
</tr>
</tbody>
</table>
Treating Human Atopic Dermatitis

Human medicine—particularly within dermatology—has more recently been focused on treating the external symptoms of AD by restoring skin barrier function and decreasing the resulting inflammatory response of the patient. This is sometimes referred to as the “outside-in” hypothesis. Topical corticosteroids remain the most common treatment for acute flares. However, the adverse effects of long-term use of these drugs means they are best used to “break the cycle” of acute flare ups, and are not appropriate for long-term continuous use. For patients who have become overly dependent upon steroids or are uncomfortable using them, other treatments with fewer adverse effects may provide benefit.

Moisturizers, oatmeal baths, neutral pH soaps, and wet wraps have become increasingly discussed in the treatment of AD in humans. Recent studies have demonstrated that moisturizers containing ceramides improve the barrier function of skin and have demonstrated compelling results in improving the severity of AD in patients without long-term steroid use. More recently, the veterinary field has begun to investigate the benefits of topical ceramides and essential fatty acids in the treatment of CAD. Initial studies have shown promising results.

In both humans and dogs with AD, colonization of the skin by Staphylococcus is much more common than in healthy patients. More than 90 percent of humans with AD are colonized by Staphylococcus aureus. Topical antibiotics and anti-bacterial soaps are often used to decrease secondary infections and flare ups. Dilute bleach baths and probiotics are also being investigated, with initial studies showing promising results.

Patients with more severe or refractory disease may also be prescribed non-steroidal medications such as topical tacrolimus and pimecrolimus in lieu of or in addition to topical steroids. Twice weekly use of topical calcineurin inhibitors has been shown decrease future flares of AD. This is known as “proactive therapy.” For the most severe cases, systemic immunosuppressive agents such as cyclosporine may be necessary.

Allergen specific immunotherapy in human AD is somewhat controversial. Indeed, the most recent guidelines of the American Academy of Dermatology conclude: “Injection immunotherapy…also cannot be routinely recommended at this time.” However, guidelines by the Joint Task Force, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology are more favorable, concluding: “…[The clinician might consider allergen immunotherapy in selected patients with AD]…”

In addition to the above treatments, research continues on the use of leukotriene inhibitors, the potentially soothing effects of silver-impregnated clothing, a role for mineral water baths, the effects of diet and nutrition, and other areas.

Treating Atopic Dermatitis in Canines

When it comes to treating CAD, veterinary medicine has focused more on the immunologic aspects of the disease, sometimes referred to as the “inside-out” hypothesis. However, many of the same treatments are used including topical corticosteroids and soothing baths for acute flares. (See Table 2)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Humans</th>
<th>Canines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Corticosteroids</td>
<td>Yes&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;23, 24&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rehydration and water loss prevention</td>
<td>Moisturizers, oatmeal baths, neutral pH soaps, and wet wraps&lt;sup&gt;9, 16&lt;/sup&gt;</td>
<td>Oatmeal baths and neutral pH soaps&lt;sup&gt;23, 34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Topical Ceramides</td>
<td>Yes&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Under investigation&lt;sup&gt;11, 18, 19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Immunosuppressants such as Cyclosporine, topical tacrolimus, and pimecrolimus&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Immunosuppressant Cyclosporine&lt;sup&gt;25&lt;/sup&gt;. Allergen specific immunotherapy&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Supplementation of Polyunsaturated fatty acids</td>
<td>Under Investigation&lt;sup&gt;27, 28&lt;/sup&gt;</td>
<td>Yes, mostly high doses of n-3 polyunsaturated fatty acids&lt;sup&gt;15, 26&lt;/sup&gt;</td>
</tr>
<tr>
<td>JAK inhibitors</td>
<td>Under Investigation, working with oral tofacitinib (JAK 1 and 3)&lt;sup&gt;12&lt;/sup&gt; and topical tofacitinib and oclacitinib&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Oral oclacitinib (JAK 1)&lt;sup&gt;34&lt;/sup&gt;</td>
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Janus kinases (JAKs) are transmembrane receptors for cytokines, including interleukin-31 (IL-31), involved in the regulation of hematopoiesis and various other immune system functions. When tyrosine kinases, the first JAKs to be discovered, were found to be potent activators of inflammatory cytokines, it was hypothesized that autoimmune diseases may be the result of an imbalance in the immune system’s control mechanisms mediated by these receptors. This has led to use of JAK inhibitors as treatment for autoimmune diseases such as rheumatoid arthritis (RA) and inflammatory diseases such as AD.

Within the last several years, oclacitinib, a JAK inhibitor, has been approved as an oral tablet for the management of CAD. Although its complete mechanism of action is still being elucidated, oclacitinib’s primary target appears to be JAK-1 dependent cytokines including IL-2, 4, 6, 13, and 31. IL-31 is a fairly recently discovered cytokine important in the propagation of neuronal itch. It is present in higher concentrations in canine and human atopic skin compared to controls.

Initial studies with oclacitinib have shown very positive results. One study of 299 dogs with a history of chronic AD found that 65 percent of the dogs had decreased pruritus scores as well as a 64 percent reduction in clinical severity scores through 28 days.

What makes this drug special compared to the other currently available immunosuppressive drugs used for CAD is its rapid onset of action, efficacy, and lack of short-term side effects. The adverse effects of long term use of oclacitinib are not currently known.

The success of oclacitinib in CAD as well as other JAK inhibitors for treatment of RA has led to evaluation of JAK inhibitors for treatment of AD in humans. In a preliminary study of six AD patients taking tofacitinib (a JAK-1 and 3 inhibitor) orally, all participants showed decreased body surface area of dermatitis, erythema, and pruritus severity. The average SCORAD also decreased by 54 percent during the initial four to 14 weeks of treatment. Enthusiasm is slightly hindered due to the high cost of tofacitinib and the black box warning that details risk for serious infections, lymphoma, and other malignancies.

Initial results of ongoing research evaluating the effectiveness of topical tofacitinib in humans with AD are also promising. Preliminary studies show a very significant reduction in itching behavior in the mouse model for human AD, and have demonstrated that topical application of tofacitinib and oclacitinib may produce dual antipruritic and anti-inflammatory effects. While early, it looks promising that JAK inhibitors may enjoy similar success in treating AD in humans as in dogs, although safety in human AD requires further study.

Immunosuppressive drugs such as cyclosporine and systemic corticosteroids are often used to treat severe CAD. However, long-term steroid use in dogs has many adverse effects, just as it does in humans. Still, as recently as 2013 a systematic review of CAD concluded: “topical or oral glucocorticoids and oral cyclosporine remain the interventions with highest evidence for efficacy and relative safety for treatment of canine AD.”

In contrast to the dissenting views in human AD, allergen specific immunotherapy based on results of intradermal skin testing is the recommended long-term therapy for CAD. Decreasing the patient’s sensitivity to allergens seems to decrease inflammation and pruritus and thereby skin damage. The overall success rate of immunotherapy in CAD is reported to be 50 percent to 80 percent.

Another treatment veterinarians have utilized is supplementation with high doses of n-3 fatty acids. Well-executed studies have shown decreases in pruritus and other clinical signs of CAD with n-3 fatty acid supplementation as well as a decrease in the amount of immunosuppressive drug therapy needed. While the mechanism of action is not completely understood, addition of high doses of polyunsaturated fatty acids to the diet is thought to help repair the skin barrier by providing the deficient structural components of the stratum corneum. Supplementation with n-3 fatty acids is also associated with the production of more anti-inflammatory eicosanoids than those produced from n-6 fatty acids. While earlier literature has concluded that n-6 fatty acids are probably not helpful in human AD, preliminary studies have demonstrated decreased pruritus and other symptoms with n-3 fatty acid supplementation. Additionally, studies have shown fatty acid supplementation during pregnancy can decrease the incidence and intensity of AD in children. There are several new drugs currently in development for human AD that are based on fatty acid supplementation, and perhaps this will emerge as an important therapy for some patients.
CONCLUSION

AD is an increasingly common chronic inflammatory skin disease in humans and canines. Until recently AD has been approached in slightly different ways by human medicine and veterinary medicine. The “outside-in” hypothesis has recently been the focus in humans, given the significant leaps in understanding skin barrier function, while veterinary medicine has focused more on the immunologic aspects of the disease. However, as research continues, both fields are getting closer to a common middle ground by treating both the skin barrier as well as immunologic factors. AD is a prime example of the benefit of collaboration between physicians and veterinarians to treat diseases that are common to our best friends and us.

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