What can we learn from treating atopic itch in dogs?

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Atopic dermatitis (AD) is a common, chronic skin disorder affecting up to 2.4% of the worldwide population. It negatively affects patients and their caregivers owing to the unrelenting itch, rash, and disturbed sleep. Not only does AD affect humans, but it is also very prevalent in domestic canines. Because of the extensive similarities in the phenotype and pathogenesis between human and canine AD, the latter serves as an excellent model to evaluate the use of novel antipruritic drugs.

In this Paradigms and Perspectives article, we review the use of the Janus kinase (JAK) inhibitor (JAKinib) oclacitinib (Apoquel [Zoetis, Parsippany-Troy Hills, NJ]), and the anti–IL-31 mAb lokivetmab (Cytopoint [Zoetis]), which have been available to treat atopic dogs for years. This short synopsis aims to help physicians become more familiar with what to expect when treating human atopic patients with similar therapeutics.

CANINE AD IS A CLOSE HOMOLOGUE OF ITS HUMAN COUNTERPART

AD spontaneously affects dogs, likely owing to a combination of environmental and genetic factors, the latter supported by a strong breed predisposition to develop this disease. In dogs as in humans, the diagnosis of AD stems from the observation of erythema and self-induced lesions that follow an often severe itch at typical body locations (Fig 1); the phenotype of canine AD—like that of its human counterpart—varies among races (breeds).

In both species, the pathogenesis of AD involves IgE sensitizations to allergens, a complex skin barrier dysfunction due to lipid and protein anomalies, a type 2 (ie, T_H2 cell–predominant) immune cascade, a neuronal sensitization to itch, and a cutaneous microbial dysbiosis (reviewed in Nuttall et al[1]). At this time, the main apparent difference between species is the current lack of reports of pathogenic mutations in filaggrin or other keratinocyte genes in canine AD, thus suggesting that the observed barrier dysfunction seen in dogs likely follows dermal inflammation.

As in humans, the historical mainstay of AD pharmacotherapy in dogs has been topical and oral glucocorticoids, even though the dense coat of dogs limits use of the former. In the event of insufficient benefit of glucocorticoids or unacceptable adverse effects, immunosuppressants such as cyclosporine have historically been prescribed. The past decade saw the emergence of small molecules and biologic treatments specifically targeting the harmful effect of proallergic and pruritogenic cytokines. Among these are the JAKinib oclacitinib and the IL-31–inhibiting mAb lokivetmab, which were approved several years ago to treat canine AD; details on their efficacy and safety could be informative for the treatment of the human homologue.

OCLACITINIB IS A POTENT, SAFE, AND RAPIDLY ACTING ANTIPRURITIC JAK INHIBITOR

Approved by the US Food and Drug Administration in 2013 to treat AD and allergic dermatitis in dogs, oclacitinib is a first-generation, nonselective, yet JAK1-predominant JAKinib.[2] The treatment protocol is 0.4 to 0.6 mg/kg administered orally twice a day for 2 weeks, followed by a once-daily administration for maintenance therapy.

Oclacitinib exhibits a remarkably rapid antipruritic effect in allergic dogs, with an effect noted within hours of administration, as with prednisolone.[3] A caveat of oclacitinib is the transient rebound in pruritus scores that was reported in every trial (eg, in Cosgrove et al[4]) when its frequency of administration was reduced from twice to once daily after 2 weeks. Such a rebound is suspected to be caused by a persistent transcription of pruritogenic cytokines in lesional skin during the induction of JAKinib therapy.[5] The concurrent application of topical glucocorticoids or a 4-day course of prednisolone at the onset of oclacitinib therapy (our submitted data, 2022) prevents or diminishes such a rebound. The benefit of oclacitinib in terms of decreasing skin lesions is generally noted within 1 to 2 weeks, which is slower than for itch; the lesion-reducing effect of oclacitinib is similar to that of cyclosporine.[6]

The administration of oclacitinib to dogs is generally considered to be safe, as the proportion of minor adverse events mirrors that seen in dogs treated with placebo, prednisolone, or cyclosporine.[3,4,6] Occasionally, after weeks of treatment with oclacitinib, dogs develop demodicosis due to *Demodex canis* or papillomavirus infection, which is an unsurprising event inasmuch as these diseases are normally controlled by T cells in immunocompetent dogs (unpublished observation, 2018).[4] Such a potential immunosuppressive effect has restricted the US

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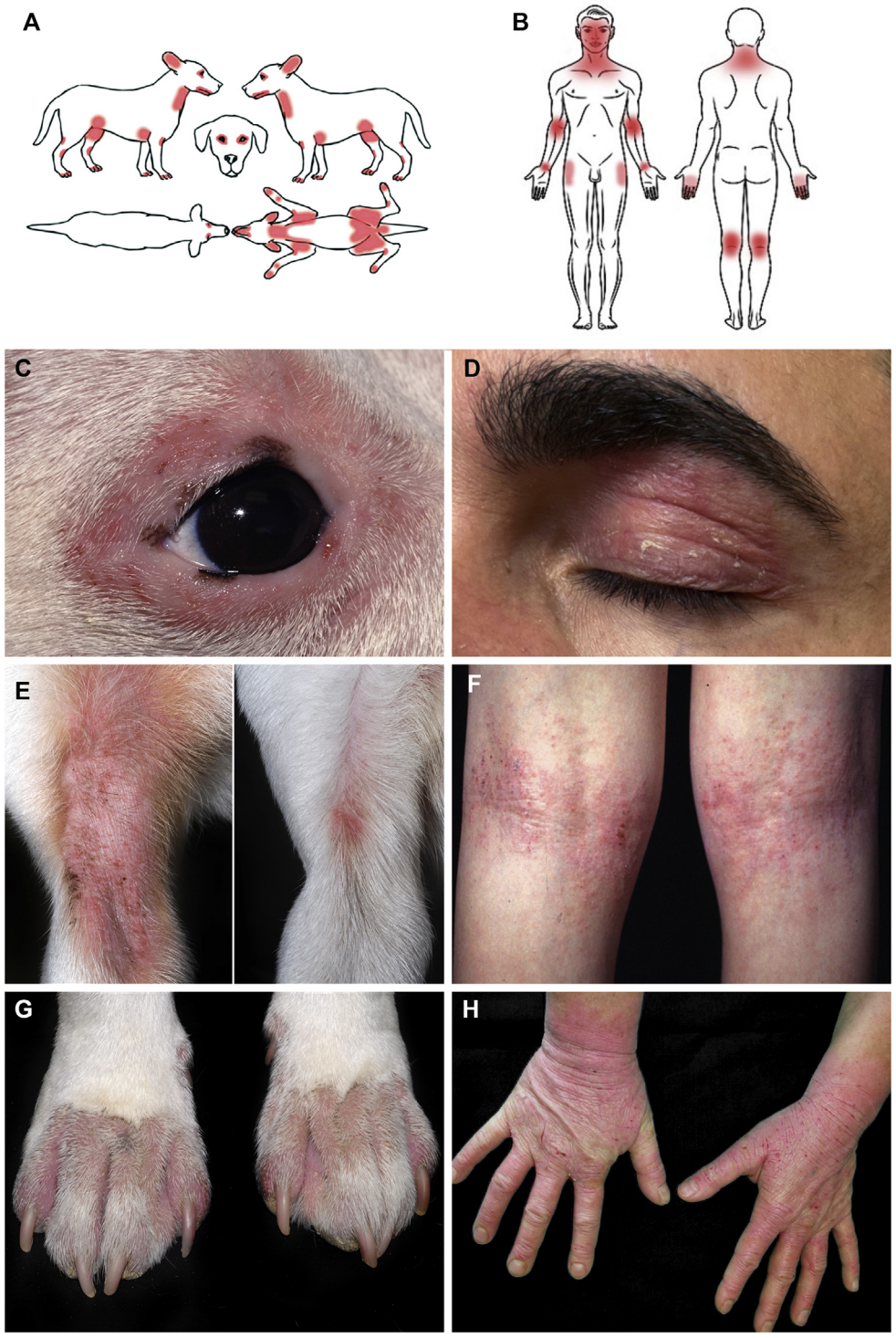

FIG 1. Comparing canine and human AD. **A**, Characteristic lesional silhouette in a dog with AD. **B**, Typical silhouette of skin lesions of human AD; the lesional pattern is similar to that of canine AD. **C**, Blepharitis in canine AD, often accompanies allergic conjunctivitis. **D**, Upper blepharitis of an adult with AD. **E-F,** Flexural dermatitis, especially of the elbows, is a specific location for lesions in dogs with AD (**E**), as in humans (**F**). **G**, Canine atopic skin lesions often affect the dorsal paws, a location that is similar to the dorsal aspect of the hands (**H**).

Food and Drug Administration's approval of oclacitinib to dogs older than 1 year on account of side effects seen in younger dogs with more immature immune systems (Freedom of Information summary; New Animal Drug Application no. 141-345).

The long-term administration of oclacitinib to dogs might be of concern to some, as its immunosuppressive effect could be predisposing to malignancies. However, in a case-control study lasting longer than 2 years (a period corresponding to far longer

than a decade in humans), there were no notable differences in the cumulative incidence of neoplasia between dogs with allergy treated with oclacitinib and those receiving other standard-of-care anti-allergic medications.[7]

Altogether, oclacitinib is a remarkable advance in treating canine allergic skin diseases thanks to its potent and rapid efficacy—especially against itch—and its favorable safety profile.

LOKIVETMAB'S INHIBITION OF DOG IL-31 IMPROVES ALLERGIC ITCH AND SKIN LESIONS

IL-31 is a T_H2 cytokine that induces profound itch in several species, including humans and dogs; it is the cytokine most highly expressed after an epicutaneous allergen challenge in house dust mite–sensitized dogs. The caninized mAb lokivetmab prevents the binding of dog IL-31 to its receptor; its approved administration protocol is 2 mg/kg every 6 to 8 weeks in the United States and 1 mg/kg every 4 weeks in the European Union.

In an experimental canine model of IL-31–induced itch, the onset of lokivetmab's antipruritic effect was visible within 3 to 4 hours after challenge.[8] In dogs with spontaneous AD, its beneficial effect on itch was noted within the first day after injection, and nearly half of the dogs had itch visual analog scale values within the range of those of normal dogs after 2 months.[9] Although in the first month, the antipruritic effectiveness of lokivetmab was stronger and faster than that of cyclosporine, the 2 medications were equipotent in reducing atopic skin lesion scores.[9]

The monthly administration of lokivetmab monotherapy to dogs with controlled AD prevented the occurrence of flares for up to 1 year in one-fourth of dogs[10]; in that study, however, the median time to flare was 63 days, suggesting that mediators other than IL-31 were driving AD relapses in most of these patients.[10] Although pretreatment with lokivetmab nearly abolished the itch that followed topical application of allergens in experimentally sensitized dogs, it had little effect in the prevention of acute lesional flares, thus indicating the minimal importance of IL-31 in the generation of acute atopic skin lesions.[10]

Overall, lokivetmab injections are occasionally followed by mild and transient side effects that are similar in prevalence to those seen in placebo-receiving dogs. It can be used simultaneously with other treatments, it has a low risk of antidrug antibody development, and it has no major contraindications. Unlike oclacitinib, lokivetmab has no minimum age requirement, likely because it does not interfere with T-cell function but targets a single cytokine with little importance in physiology.

In summary, it is noteworthy that the sole inhibition of IL-31 with lokivetmab can have such an immediate antipruritic effect in atopic dogs; this establishes a unique role of IL-31 in allergic itch.

CONCLUSION

Although this Paradigms and Perspectives article has reviewed the treatment of canine AD with oclacitinib and lokivetmab, there is still much to learn. Nevertheless, the knowledge derived from treating atopic dogs with these drugs might prove of help to allergists and dermatologists in use of the new small molecules and biologics with similar modes of action that have recently been launched or are in the process of entering the market.

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