

Letter to the Editor

Canine models of allergic skin disease

Dear Editor,

I would like to provide food for thought on a couple of points that may be of interest to the readers of *Veterinary Dermatology* and provide some examples to illustrate such points. The first one is the questionable validity of the concept that injecting drugs or pruritogens can be considered a suitable model for allergic skin disease such as atopic dermatitis (AD). The second one is the assumption that just because a certain mediator when injected is able to cause pruritus, this implies that it is an important mediator for AD and therefore that drugs aimed at decreasing such a mediator could be considered suitable treatments for AD.

Itching is a sensation that can be induced by injection of a variety of substances¹ with important differences among species.² However, just because itching can be induced with such substances, this type of model cannot be interpreted as a model for AD, because this is a very complex clinical syndrome resulting from the interaction of multiple factors. While pruritus is an important sign for this condition, AD also involves skin barrier impairment and a genetic component; thus, injecting substances in otherwise normal individuals does not necessarily make them a suitable model for testing drugs aimed at this condition. Additionally, atopic pruritus has been shown to be different from pruritus of other conditions.³ This is something well demonstrated in humans with AD.

The logic of injecting something in a dog as a suitable model for allergic skin disease and as a way to test efficacy of drugs is dangerously flawed, because it completely ignores other components of AD. One study showed that injection of chloroquine induced pruritus in dogs,⁴ and thus drugs proposed for the treatment of AD could be tested in this model. Should we take it that chloroquine is a mediator of canine AD? In a study published in *Veterinary Dermatology*, similar conclusions were made about the injection of IL-31.⁵ The understanding in this and another study from the same group,⁶ was that if we inject IL-31 and induce pruritus, it means that IL-31 is an important mediator of allergic skin diseases such as AD and that this model can be used to test new therapeutics.

Although IL-31 is certainly an important mediator of pruritus, at this point in time we do not have sufficient published evidence in veterinary medicine to conclude that IL-31 is a critical mediator of canine AD. One published study actually failed to detect IL-31 in the skin of dogs with AD.⁷ Another study was able to detect IL-31 in the serum of only 57% of atopic dogs.¹ Thus, at this point, we do not have the evidence to make this type of conclusion.

Importantly, even blocking a proven mediator, such as one that can induce pruritus after injection and that also has been proven to be increased in spontaneously

occurring AD, is *still* not an accurate way to predict success in the clinical environment. This type of modelling approach fails to acknowledge the redundancy of mediators and can lead to misleading results. The classic example of that lesson comes from human medicine with histamine. Histamine in people is one of the most well known pruritogens. Histamine was found at high concentrations in AD lesions and most of the cells involved in the inflammatory responses express the histamine 1 and 2 receptors.⁸ Despite all of this evidence in AD patients, antihistamines showed only limited clinical efficacy in controlling pruritus,^{9,10} suggesting that histamine is unlikely to be a major peripheral mediator of pruritus in human AD.¹¹

Thus, I encourage dermatology researchers to make conclusions that are consistent with the results of the studies that we have at this point in time. Can we say that IL-31 induces pruritus in dogs? – yes, we can. Can we say that IL-31 is a key mediator in canine AD? No, because we do not have studies in veterinary medicine, as they have been done in human medicine, to prove that IL-31 is a biomarker of *canine* AD. And we have certainly learned over the years that dogs do not always follow the path of what is reported in human medicine when it comes to many diseases including AD. But, more importantly, I encourage differentiating the mere injection of a compound or a cytokine as a suitable model for allergic skin disease in dogs and to make conclusions on clinical efficacy of new therapeutics using a model where itching is triggered by one single mediator.

Thank you for your attention.

Sincerely,

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Conflict of interest

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