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Editorial

Treatment of canine atopic dermatitis: time to revise our strategy?

For decades following the recognition of atopic dermatitis (AD) as a common allergic skin disease of dogs, its treatment relied mainly on the use of oral — and more often than not injectable — glucocorticoids. When the "time was right", allergen immunotherapy (AIT) was used to reduce the need for glucocorticoids because of their ubiquitous adverse effects. It was only in 2004 that the calcineurin inhibitor ciclosporin (Atopica, Elanco; Greenfield, IN, USA) became the first immunomodulator specifically approved for treatment of canine AD. In 2007, the hydrocortisone aceponate-containing spray Cortavance (Virbac; Carros, France) was the second pharmacological intervention approved for allergic skin diseases. More recently, in 2014, oclacitinib (Apoquel, Zoetis; Parsippany, NJ, USA) was the first-in-class Janus kinase (JAK) inhibitor available to treat AD in dogs, years before another JAKinib will be approved to treat the human disease homologue.[1] Finally, 2017 saw the first monoclonal antibody (mAb) fully approved for a canine disease, the anti-interleukin (IL)-31 lokivetmab (Cytopoint, also from Zoetis) for treatment of canine AD.

In 2010, the International Task Force of Canine AD published the first consensus guidelines for treatment of this disease;[2] these were then updated in 2015 under the auspices of the International Committee on Allergic Diseases of Animals (ICADA).[3] Both versions of these guidelines provided a framework placing various interventions in the context of three clinical situations: the treatment of acute flares of cAD, the treatment of chronic stages and, finally, the implementation of strategies to prevent the recurrence of clinical signs. In these papers, the main parameter taken into account for a drug to be proposed for treatment of acute or chronic AD was the time expected for a clinical benefit to occur. Although glucocorticoids and oclacitinib were recommended for both stages of this disease, ciclosporin was suggested only for the treatment of chronic AD.[3]

As shown recently in its human disease counterpart (reviewed in Czarnowicki et al.[4]) and by the variability of clinical presentations between breeds,[5] canine AD is likely not a single entity, but rather a syndrome with different clinical and molecular endotypes/phenotypes. Furthermore, atopic dogs can exhibit, at the same time, both acute (e.g. erythematous macules/patches) and chronic skin lesions (e.g. plaques, lichenification, hyperpigmentation) at different body locations. As the current canine AD treatment guidelines do not recognize such a high degree of clinical heterogeneity, having both acute and chronic AD skin lesions in the same patient would lead to confusion regarding what drug to appropriately select.

Nevertheless, and although it is clear that these guidelines have helped standardize the treatment of cAD, they did not consider a critical parameter in the evaluation and placement of the various pharmacological interventions: their mode of action or, within it, their breadth of inflammation targeting.

The current trend in the development of small molecules or biologicals to treat human or canine AD is that of "targeted therapy", a Holy Grail quest aimed at finding THE single molecule or receptor whose inhibition would eventually control all clinical signs. Unfortunately, this development strategy fails to consider that AD is not a disease due to the release of a single molecule or the activation of a single type of inflammatory cell! It is, in fact, the result of a complex immunological cascade that varies between lesions of different stages and that likely differs between individuals, especially if they come from different genetic origins (for example, dogs from different breeds).

As a result of this complex inflammation involving at least a dozen activated cells and a myriad of mediators, the modern "narrow" targeting of a single molecule or receptor (for example by a monoclonal antibody inhibiting a cytokine) is unlikely to be effective in most patients most of the time. Indeed, the inhibited target might not be pathogenically relevant and the skin lesions or itch might be due to other mediators at the time the drug is administered! By contrast, interventions with a broad inflammation-targeting ability are likely to be beneficial most of the time in most patients, but their wide breadth of action is expected to lead to a higher risk for immunosuppression.

Among the drugs currently available in our arsenal to treat canine AD, glucocorticoids and ciclosporin are those with the largest breadth of action, whereas, at the other end of the spectrum, the IL-31-blocking lokivetmab and the H1R inverse agonist antihistamines are those targeting a single mediator. Whereas oclacitinib initially prevents the signal transduction after the binding of some — but not all — AD-relevant cytokines to their respective receptors, it likely results in secondary waves of anti-inflammatory effects, because the cells downstream in the cascade are no longer activated by the blocked cytokines upstream; we would thus classify such JAKinib, at the recommended anti-allergic dosage, as having a "semi-broad" targeting capacity.

Instead of using the "time-to-efficacy" of an intervention to define its place in the treatment of cAD, we propose to use instead a drug's "inflammation-targeting breadth" as the leading factor to consider in a newly

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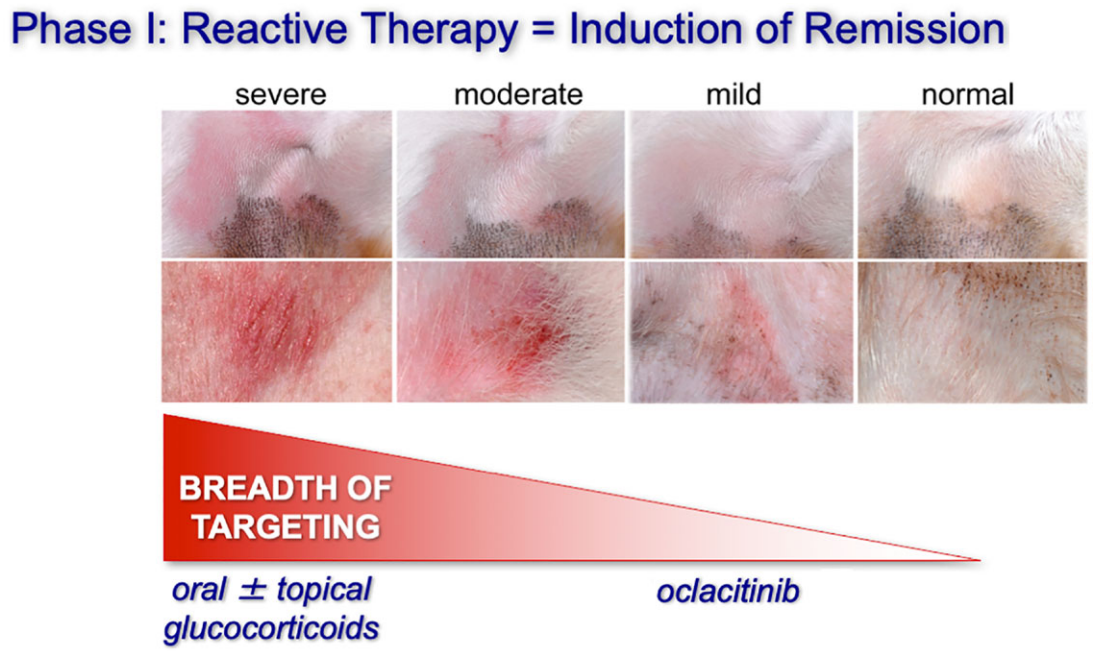

Figure 1. Phase I: reactive therapy = induction of clinical sign remission.

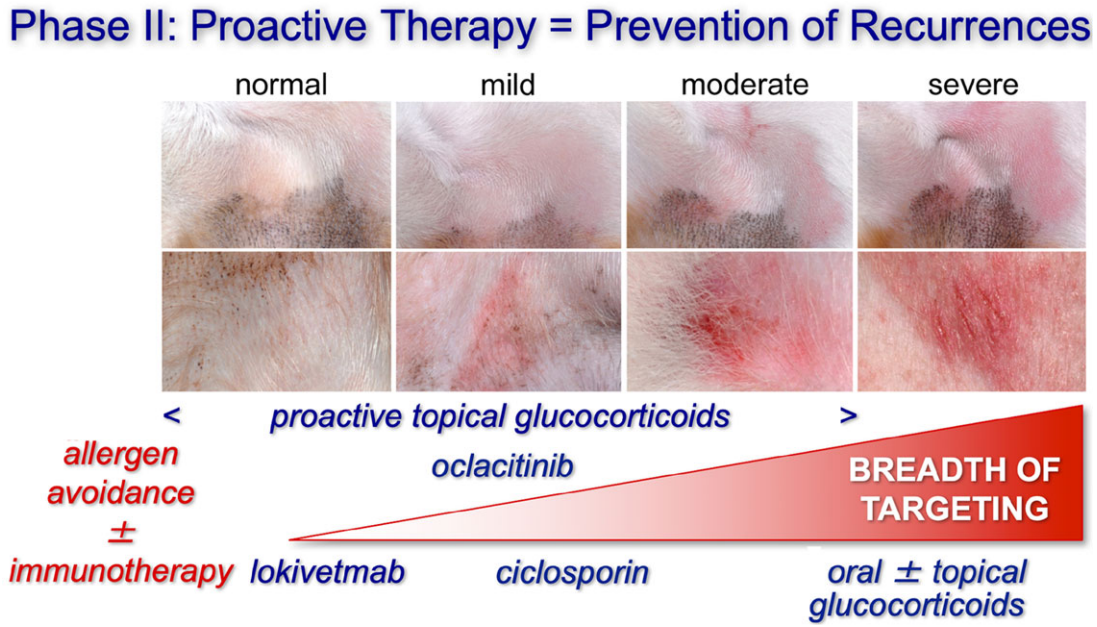

Figure 2. Phase II: proactive therapy = prevention of clinical sign recurrence.

revised treatment strategy that involves two distinct phases.

Phase I of treatment of AD, "reactive therapy", is the treatment of an atopic dog with existing acute and/or chronic skin lesions (and itch) with the goal of inducing clinical remission (Figure 1). During reactive therapy, as some of the clinical signs are often due to an allergen-primed self-sustaining and complex inflammation involving numerous mediators and cells, the patient should — at least theoretically — benefit most from rapidly-acting and broad-targeting drugs. For this reason, our first choice is nearly always a glucocorticoid. At the onset of treatment, using an oral short-acting glucocorticoid is more logical than that of a topical, because the normal-appearing skin of an atopic dog has been shown to be microscopically inflamed, and the lack of visible lesions would be unlikely to prompt treatment of such areas. However, topical glucocorticoids are ideal companions along with systemic formulations to treat strongly inflamed or markedly lichenified local or regional skin lesions.

Once cutaneous inflammation subsides to mild levels, and to avoid the long course of oral glucocorticoids needed by dogs with generalized or severe clinical signs, one could consider substituting glucocorticoids with JAKinibs (Figure 1). A likely advantage of such glucocorticoid-to-JAKinib transition would be the prevention of the pruritus rebound that occurs after oclacitinib dose reduction.

Indeed, pro-allergic cytokines continue to be secreted in atopic skin at the onset of oclacitinib therapy,[6] and the transcription of such cytokines would be inhibited if glucocorticoids were given before or concurrently with the JAKinib. Of course, if the dog's lesions were mild when first needing treatment, another valid strategy would be to use oclacitinib, alone or with a topical glucocorticoid to immediately broaden its anti-inflammatory effect.

Although the current treatment concept calls for the rapid tapering of glucocorticoids to reduce the risk of adverse effects, one should – in fact – consider treating "stronger and longer" to achieve the stable and complete remission of signs. This approach would ensure that only minimal residual inflammation remains in visibly-normal skin, inflammation that – if present – would rapidly flare upon treatment reduction.

Once the patient has remained clear of clinical signs for several weeks, it is time to move to the second phase (i.e. Phase II) of AD treatment, "proactive therapy", which is aimed at preventing the development of flares (Figure 2).

Needless to say, the best prevention of any allergic disease will always be to avoid allergens and other factors known to trigger the recurrence of signs. This Phase II also is the time to consider allergen immunotherapy, whenever an association between allergens and AD flares is suspected.

If the need were to arise for pharmacological interventions at the beginning of this second phase of canine AD treatment, proactive topical glucocorticoids and injectable biologicals such as lokivetmab could be considered (Figure 2).

Proactive topical glucocorticoid therapy is defined as the treatment of previously affected areas on two consecutive days each week, whether or not lesions are visible at these sites.[7] The goal of this approach is to prevent disease flares by regularly inhibiting the residual subclinical cutaneous inflammation. A recent trial confirmed the benefit of the proactive use of a topical hydrocortisone aceponate spray (Cortavance) in atopic dogs, with a nearly four-fold increase in the median time-to-flare compared to placebo without adverse events.[8] This proactive topical glucocorticoid therapy, even though it does not appear to be recommended frequently, clearly deserves more attention throughout this preventive treatment phase.

One could argue that the best time to use a single-target intervention, be it a monoclonal antibody or a small molecule, should be the beginning of this proactive second phase when clinical signs are in stable and full control (Figure 2). Indeed, at that time, the cutaneous inflammation is weakest and "simplest", and the single-target intervention then would have the best chance to hit its mark as it is eventually secreted. Furthermore, if the target were upstream in the inflammation cascade, then blocking it early should prevent skin lesion and/or inflammatory itch development.

If the biologicals and proactive topical glucocorticoid therapy were unable to prevent the flare of clinical signs, one should consider first "resetting" the inflammation with a short course of oral glucocorticoids to return to the complete and stable remission of signs. The failure of flare control with biologicals and topicals should then prompt treatment escalation with broader inflammation-targeting pharmacologicals such as oclacitinib or ciclosporin for their long-term use (Figure 2). In case the latter were to fail to fully control signs, or if one wishes to lower the dose or administration frequency of these drugs in fully controlled atopic dogs, then clinicians could consider adding intermittent topical glucocorticoid applications to regularly flaring areas.

As new drugs or biologicals are approved for the treatment of cAD, treatment concepts should be re-evaluated periodically. It is with such periodic introspection that the best strategies will be developed, thereby ensuring that our atopic dogs will have the best quality of life possible.

Now surely is the time for such periodic treatment strategy re-evaluation!

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Conflict of interest

Pursuant to the drug brands mentioned in this editorial, TO wishes to disclose that, in the last decade, he has received research funding from Zoetis and Elanco, has lectured for Zoetis and has consulted for Elanco and Virbac. FB has no conflict of interest to declare for this editorial.

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