Small animal *Review*

Summary: Allergic dermatitis in dogs can be managed using a range of medical therapies including glucocorticoids, ciclosporin, oclacitinib, loviketmab and immunotherapy. Oclacitinib inhibits janus-kinases leading to depressed function of proinflammatory cytokines. Some cytokines protect against tumour development. Oclacitinib may hinder cell proliferation, differentiation, migration, apoptosis and survival. Oclacitinib's impact in dogs who have neoplasia is unclear. The study discussed here has assessed the risk of neoplasia in dogs treated over a long period with oclacitinib.

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Oclacitinib's role in canines developing neoplasia

Allergic or hypersensitivity dermatitis is not uncommonly described in dogs, and may be managed using a range of medical therapies including glucocorticoids, ciclosporin, oclacitinib (Apoquel; Zoetis), loviketmab (Cytopoint; Zoetis) and immunotherapy. In humans, long-term treatment with ruxolitinib, a related compound, has been associated with an increased risk of developing epidermal tumours (basal cell tumours and squamous cell carcinomas). In contrast, the use of tofacitinib, another inhibitor of janus-kinases (JAKs), has not been associated with significant adverse effects. The impact of using oclacitinib in dogs who have neoplasia is unclear, so a study assessing the risk of neoplasia in dogs treated over a long period with oclacitinib (Lancellotti et al, 2020) is welcome.

The study, published in *JAVMA*, was a retrospective analysis of data from dogs receiving treatment for allergic dermatitis with or without oclacitinib. The study population of dogs with allergic dermatitis comprised 339 dogs that had received oclacitinib for more than 6 months and 321 dogs that had never been prescribed the drug. In the group exposed to oclacitinib treatment, times ranged from 6–58 months and the sum total follow-up duration was 1105.6 patient years. The unexposed group had been treated for 3–107 months and the sum total follow-up duration was 1106.5 patient years. Overall, the cumulative incidence of skin masses, including all masses irrespective of diagnosis, did not differ significantly between the two groups (56.6% in the exposed and 58.3% in the non-exposed dogs) and the overall incidence rate for mass development did not vary (174 new cases/1000 patient years in the exposed dogs and 169 new cases/1000 patient years in the control dogs).

Malignant processes were in 56/339 (16.5%) dogs in the treatment group comprising mast cell tumour (n=13), non-cutaneous lymphoma (n=6), soft tissue sarcoma (n=6), intracranial tumour (n=5), or unspecified malignancy resulting in euthanasia (n=5). In comparison, for the control population 41/321 dogs developed a malignant process, consisting of mast cell tumour (n=11), hepatic mass (n=4), pulmonary neoplasia (n=3), splenic mass (n=3), squamous cell carcinoma (n=3), or unspecified malignancy resulting in euthanasia (n=3). There was no statistically significant difference in the incidence of any malignancy between the two groups.

A wide variety of benign dermal and subcutaneous tumours were reported with the dogs that received oclacitinib, showing a significantly lower incidence of 23.3% of dogs versus 31.5% of control dogs, although the incidence rate of benign skin masses did not vary significantly between the exposed group: 71 new cases/1000 patient years in the treated dogs versus 91 new cases/1000 patient years in the control group.

The mean ages at death or euthanasia were similar between the two groups, 11.2 years for the treated group and 11.8 years for the control group. The authors showed that the mean duration between onset of treatment and euthanasia or death was significantly longer for dogs in the unexposed group (39 months), in comparison to dogs in the exposed group (30 months), although the authors were unable to assess its importance because of confounding factors such as how often a dog received oclacitinib and whether treatment was ever paused after onset.

The authors have shown that the use of oclacitinib at recommended doses did not increase the incidence of neoplastic processes in dogs over treatment spans of 6 months to nearly 5 years with a mean duration of 24 months. Other similar JAK-receptor inhibitors have been associated with a range of tumours in humans, although their use with other treatment modalities and different lifestyles, such as exposure to tobacco smoke, make attributing cause and effect difficult.

The authors urge caution in interpreting the risks associated with this family of drugs. They comment that oclacitinib is a preferential JAK-1 receptor inhibitor, and it may be that other related drugs that inhibit other JAK receptors may show different adverse effects. The authors stress that a large number of their dogs had skin masses that were considered to be benign when clinically examined, and therefore were not removed or investigated. However, in humans treated with ruxolitinib it has been observed that skin tumours can behave aggressively, and the authors of this paper recommend that skin lesions in dogs receiving oclacitinib should at least be investigated and ideally removed.

The authors discuss the limitations of their study, notably its retrospective nature; small numbers of some malignancies, which although numerically higher in the exposed group could not be shown to be statistically different; and short follow-up times in many cases, compared with those in human studies, which are often several years. Oclacitinib appears to be a relatively safe drug in dogs on the basis of this study, but a long-term prospective study following cases over many years would be interesting.

Reference

Lancellotti BA, Angus JC, Edginton HD, Rosenkrantz WS. Age- and breed-matched retrospective cohort study of malignancies and benign skin masses in 660 dogs with allergic dermatitis treated long-term with versus without oclacitinib. JAVMA. 2020; 257:507–516. https://doi.org/10.2460/javma.257.5.507