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Evolving Itch Management in Veterinary Dermatology

- Lessons from Human Health

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MSD Animal Health

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Introducing a Second-Generation JAK Inhibitor, Highly Selective for JAK1

Tim Kowalski PhD

Allergic dermatitis, including atopic dermatitis, is a common inflammatory skin condition in dogs that is characterized by pruritus and skin lesions. The pathogenesis involves a complex immunological cascade which is mediated in part by the dysregulation of cytokines that signal via the Janus kinase (JAK)-Signal Transduction and Activator of Transcription (STAT) signaling pathway.[1] The JAK-STAT signaling pathway transduces signals from over 50 cytokines.[2] Several of these cytokines—such as the pruritogenic interleukin (IL) -31, pro-inflammatory IL-2 and IL-6, and pro-allergenic IL-4 and IL-13—play key roles in both human and canine atopic dermatitis.[3,4] The receptors for these cytokines utilize JAK1 in combination with JAK3 (IL-2, IL-4) or JAK2 and TYK2 (IL-6, IL-13 and IL-31) for signal transduction.[1]

In human medicine, first-generation JAK inhibitors (such as tofacitinib and baricitinib) targeting several JAK isoforms have been developed for the treatment of inflammatory diseases, such as rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, and irritable bowel disease.[5] Tofacitinib inhibits JAK3 and to a lesser extent JAK1 and JAK2.[6] Baricitinib inhibits JAK1 and JAK2 and to a lesser extent JAK3 and TYK2.[7,8] In veterinary medicine, two first-generation JAK inhibitors oclacitinib (a derivative of tofacitinib), which inhibits JAK1 and JAK2 and to a lesser extent JAK3 and TYK2,[9] and ilunocitinib (a derivative of baricitinib), which inhibits JAK1, JAK2 and TYK2 and to a lesser extent JAK3,[10] have been approved for the treatment of allergic dermatitis and atopic dermatitis in dogs.

In humans, inhibition of JAK2 and particularly JAK3 may be associated with a higher risk of herpes zoster reactivation,[11] while inhibition of JAK2, the only member of the JAK family that homodimerizes and is responsible for the transduction of erythropoietin (EPO), thrombopoietin (TPO), and granulocyte macrophage-colony stimulating factor (GM-CSF) receptor signaling, is responsible for adverse effects on hematopoiesis.[1] While first-generation JAK inhibitors are effective, it was hypothesized that greater selectivity and sparing other JAK enzymes would provide a wider therapeutic window and a clinically favorable safety profile; specifically, targeting JAK1 in chronic inflammatory skin disease would avoid the negative effects on host defense such as immune response to viruses and hematopoiesis.

Second-generation JAK inhibitors are more selective for specific JAK isoforms with the aim of improving efficacy and reducing adverse effects associated with non-selective JAK inhibition, resulting in a wider therapeutic window.[11] Inhibition of JAK1, with agents such as abrocitinib and upadacitinib, to produce therapeutic effects while sparing unwanted effects due to inhibition of JAK2, JAK3 and TYK2 at recommended doses is used in the treatment of atopic dermatitis.[8] Although head-to-head studies of first- and second-generation JAK inhibitors are not available in humans to directly inform on safety

profiles, clinical studies demonstrating efficacy with reduced herpes zoster reactivation rates and little to no impact on hemoglobin with JAK1 selective agents support a benefit.[12,13]

Based upon this hypothesis, our goal was to develop a second-generation JAK1 selective inhibitor to treat canine allergic dermatitis and atopic dermatitis. Atinvicitinib is a selective Janus kinase (JAK) 1 inhibitor that has recently been granted approval for use in animal health. It was discovered by MSD from a novel chemical class of JAK inhibitors and is not derived from a JAK inhibitor for use in humans. Biochemical and cell-based assays demonstrate that atinvicitinib has over 10-fold selectivity for JAK1 compared to JAK2, JAK3 and TYK2. Based on these assays, the selectivity profile of atinvicitinib is highly favorable compared to first-generation JAK inhibitors, such as oclacitinib,[9] which shows ~2-fold selectivity between JAK1 and JAK2 and has less than 10-fold selectivity for JAK1 vs. JAK3 and TYK2, and ilunocitinib, which inhibits multiple JAK isoforms.[10] Furthermore, atinvicitinib exhibited >900-fold JAK1 selectivity against a panel of 261 human kinases (excluding JAK2 and TYK2) and did not inhibit or stimulate a panel of 112 rat, guinea pig or human enzymes, receptors and transporters when tested at 10 µM.

These data establish atinvicitinib as a potent and highly selective second-generation JAK1 inhibitor that effectively targets pruritus and inflammation associated with allergic dermatitis and atopic dermatitis in dogs and clinical signs of atopic dermatitis in dogs.

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Clinically Favorable Safety Profile of a Second-Generation JAK Inhibitor in Dogs

Inka Kuhlmann DVM, Dr med vet

Janus kinase (JAK) inhibitors are small molecules used for the treatment of allergic dermatitis and atopic dermatitis in dogs. In human medicine, both first-generation, non-selective (pan-JAK) inhibitors, and second-generation, JAK1 selective inhibitors are used in the management of atopic dermatitis.[1, 2] In humans, inhibition of JAK2 and particularly JAK3 may be associated with a higher risk of herpes zoster reactivation,[3] while inhibition of JAK2, the only member of the JAK family that homodimerizes and is responsible for the transduction of erythropoietin (EPO), thrombopoietin (TPO), and granulocyte macrophage colony stimulating factor (GM-CSF) receptor signaling, is responsible for adverse effects on hematopoiesis.[1]

In veterinary medicine, two first-generation, non-selective Janus kinase inhibitors have been shown to provide relief in dogs with allergic dermatitis and atopic dermatitis.[4-6] These agents reduce pruritus through the inhibition of JAK1, but have been associated with adverse effects like anaemia, papilloma, skin lumps, and serious infections. These adverse effects are attributed to the inhibition of JAK2 (hematopoiesis) and JAK3/TYK2 (host defense), with immunosuppression at overdoses of three-fold and higher than the recommended treatment dose.[4,7-12]

Second-generation JAK inhibitors exhibit increased selectivity for specific JAK isoforms. It has been hypothesized that selective inhibition of JAK1 maintains efficacy while expanding the therapeutic window and increasing the margin of safety thus avoiding negative effects on host defense (e.g. reduced herpes zoster reactivation in humans) and hematological adverse effects (e.g. anaemia).[3,13-15] Based upon this rationale, we aimed to develop a selective JAK1 inhibitor for the treatment of allergic dermatitis, including atopic dermatitis, in dogs.

Atinvicitinib is a highly selective JAK1 inhibitor.[16] It blocks cytokines involved in itch, inflammation, and allergy dependent on JAK1 activity, while sparing other JAK family members (JAK2, JAK3 and TYK2), thereby limiting potential adverse effects. The safety of atinvicitinib (Numelvi® tablets for dogs) has been assessed in both preclinical and clinical studies in dogs.

In preclinical studies, atinvicitinib was well tolerated by dogs aged 6 months and older.[16] Concurrent treatment with atinvicitinib at 3.6 mg/kg (three times the maximum recommended dose) once daily for 84 days did not impair the response to the primary vaccination course and was well-tolerated with no adverse treatment-related effects in 6-month old dogs. All treated dogs mounted protective antibody

titers following vaccination with modified live canine distemper virus (CDV), canine adenovirus type-2 (CAV-2), modified live canine parvovirus (CPV), and inactivated rabies virus (RV) vaccines.[16]
Atinvicitinib was well tolerated when administered orally to healthy 6-month-old puppies treated with overdoses of up to 5 times the maximum recommended dose of 1.2 mg/kg once daily for 6 months.[16] However, significant overdoses may increase susceptibility to bacterial, fungal and/or parasitic skin infections.[16]

Safety has not been established during pregnancy and lactation or in breeding dogs.[16] Therefore, atinvicitinib treatment is not recommended during pregnancy, lactation or in breeding animals. Laboratory studies in rats and rabbits revealed effects on prenatal development, consistent with the JAK inhibitor class. Laboratory studies in male rats showed JAK1-related reductions in sperm counts and motility.

In masked, placebo-controlled clinical trials in dogs with allergic dermatitis and atopic dermatitis, once daily treatment with atinvicitinib at 0.8-1.2 mg/kg (the recommended treatment dose) was well tolerated by client-owned dogs aged at least 6 months and weighing at least 2 kg. There were no notable changes from baseline or trends in red blood cell count, hematocrit, and hemoglobin concentration, serum chemistry and urinalysis.[16] Treatment led to reductions in mean total white blood cell, neutrophil, eosinophil and monocyte counts compared to baseline, reflecting decreased allergy-mediated inflammation, which is dependent on JAK1 enzyme activity. Similar decreases in neutrophil and eosinophil counts have been reported with the second-generation JAK1 selective inhibitor upadacitinib in human atopic dermatitis patients.[17] Importantly, these white blood cell counts remained within reference ranges, supporting the absence of immunosuppression in treated dogs due to the high JAK1 selectivity of atinvicitinib.

In clinical trials the most common adverse effects (<3% of the treated dogs) were gastrointestinal signs (diarrhea, vomiting) and systemic signs (anorexia, lethargy).[16] These signs were typically mild and transient and did not require veterinary intervention or symptomatic treatment.
Atinvicitinib has a favorable drug interaction profile without known drug interactions.[16] In clinical trials in client-owned dogs, it was safely administered concomitantly with other treatments, such as antimicrobials (including topicals), ecto- and endoparasiticides (isoxazolines, milbemycins, avermectins, pyrethrins and pyrethroids), nutritional supplements, topical skin and ear cleansers that did not contain

glucocorticoids, as well as medicated shampoos. No adverse effects were associated with concurrent treatments.[16]

Atinvicitinib at the recommended treatment dose of 0.8-1.2 mg/kg once daily is safe and well tolerated in dogs treated under field conditions. A comprehensive preclinical and clinical program confirmed both the lack of immunosuppression and the absence of JAK2-mediated effects on hematopoiesis. Atinvicitinib offers a broad margin of safety and is suitable for use in the treatment of allergic dermatitis, including atopic dermatitis, in dogs aged 6 months and older.

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Experience from human medicine: The advantages of JAK1 selectivity in atopic dermatitis

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Janus kinase inhibitors are a class of small molecule drugs that target the JAK family of enzymes—JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). These intracellular tyrosine kinases mediate cytokine signaling through the JAK-STAT (Signal Transduction and Activator of Transcription) signaling pathway.[1] This pathway is involved in the intracellular signal transduction of more than 50 cytokines and growth factors involved in immune regulation and inflammation.[2] By inhibiting these enzymes, JAK inhibitors modulate immune responses and reduce inflammation.

Chronic inflammatory skin conditions, such as atopic dermatitis, are characterized by immune dysregulation and elevated levels of pro-inflammatory (e.g. IL-2, IL-6, IL-12, IL-17, IL-23), pro-allergenic (e.g. IL-4, IL-5, IL-13, IL-22) and pruritogenic (IL-31) cytokines.[1,2] These cytokines signal primarily via JAK1 in combination with JAK3 (IL-2, IL-4) or JAK2 (IL-5, IL-6, IL-13 and IL-31) and TYK2 (IL-22).[1]

First-generation JAK inhibitors, which target several JAK isoforms, were developed for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, atopic dermatitis and ulcerative colitis in humans.[3] Examples include tofacitinib, which inhibits JAK3 and to a lesser extent JAK1 and JAK2,[4] and baricitinib, which inhibits JAK1 and JAK2 and to a lesser extent JAK3 and TYK2.[5,6] However, safety concerns associated with pan-JAK inhibition—such as increased risk of herpes zoster reactivation linked to JAK3 inhibition[7] and hematopoietic adverse effects linked to JAK2 inhibition[1] - prompted the hypothesis that selective inhibition of JAK1 alone could provide effective treatment of atopic dermatitis with a clinically favorable safety profile.

Second-generation JAK inhibitors are more selective for specific JAK isoforms with the aim of improving efficacy and reducing adverse effects associated with non-selective inhibition, thereby widening the therapeutic window.[7] JAK1 selective agents, such as abrocitinib and upadacitinib, used in the treatment of atopic dermatitis in humans, deliver therapeutic benefits while sparing JAK2, JAK3 and TYK2 at recommended doses.[6] Although head-to-head comparisons of first- and second-generation JAK inhibitors are lacking, clinical data indicate that JAK1 selective inhibitors achieve efficacy with reduced herpes zoster reactivation rates and minimal impact on hemoglobin, supporting their favorable profile.[8,9]

Moreover, second-generation JAK inhibitors may offer superior efficacy. For example, upadacitinib and abrocitinib have demonstrated higher proportions of patients achieving 75% or 90% reduction in the Eczema Area and Severity Index (EASI-75 and EASI-90) at 16 weeks compared to baricitinib - which is

approximately equipotent for JAK1 and JAK2 - and monoclonal antibodies such as dupilumab.[10]
The development of second-generation JAK inhibitors with enhanced selectivity for JAK1 represents a significant evolution in the treatment of chronic inflammatory skin conditions like atopic dermatitis. These agents combine a clinically favorable safety profile by minimizing adverse effects associated with broader JAK inhibition with the potential for superior efficacy, refining targeted treatment strategies in dermatology.

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Clinical experience with a second-generation JAK1 selective inhibitor in dogs with atopic dermatitis and allergic dermatitis

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Allergic dermatitis, including atopic dermatitis, in dogs is seen commonly in companion animal practice worldwide. Its pathogenesis involves a complex immunological cascade, partly mediated by dysregulation of cytokines that signal through the JAK-STAT (Janus kinase-Signal Transduction and Activator of Transcription) signaling pathway.[1] In veterinary medicine, two first-generation, non-selective JAK inhibitors have demonstrated efficacy in resolving pruritus associated with allergic dermatitis and atopic dermatitis and improving clinical signs of atopic dermatitis in dogs, aged at least 12 months and weighing at least 3 kg.[2-5] Atinvicitinib is a novel, second-generation JAK inhibitor with high selectivity for JAK1 that is approved for use in dogs aged 6 months and older. Its safety and efficacy were evaluated in two randomized, masked, placebo-controlled multicenter clinical trials in client-owned dogs.

Atopic dermatitis

Veterinarians enrolled dogs aged at least 12 months and, weighing at least 3 kg, with a clinical diagnosis of atopic dermatitis,[6] and a baseline owner pruritus visual analog scale (PVAS) score[7] of at least 6 out of a maximum score of 10. Other pruritic skin diseases were excluded through standard diagnostic criteria or targeted treatments. Dogs were assigned randomly to one of two atinvicitinib treatment groups; either 0.4-0.6 mg/kg twice daily for 14 days then once daily for 14 days or 0.8-1.2 mg/kg once daily or to a placebo group. PVAS assessments were conducted daily on days 0 to 7, and on days 14 and 28. The Canine Atopic Dermatitis Extent and Severity Index (CADESI-4)[8] was evaluated on days 0 and 28. The primary efficacy endpoint was the proportion of dogs achieving at least a 50% reduction in PVAS or CADESI-4 scores on day 28 compared to baseline. Both groups treated with atinvicitinib showed a significantly greater proportion of responders than placebo. Secondary efficacy measures included reductions in PVAS and CADESI-4 scores at all time points.

The trends in CADESI-4 scores (days 0 and 28), and PVAS scores for all collection days (0-7, 14, and 28) were assessed. The percentage of dogs with at least a 2 cm reduction in PVAS, which is considered clinically relevant, was also assessed.[2] At each assessment, a higher percentage of dogs treated with atinvicitinib met this criterion compared to placebo. Mean CADESI-4 and PVAS scores showed a steeper decrease in the atinvicitinib-treated groups than in the placebo group.

Atinvicitinib at 0.8-1.2 mg/kg once daily was superior to atinvicitinib at 0.4-0.6 mg/kg twice daily for 14 days then once daily for 14 days for all primary and secondary efficacy criteria. A dosing regimen of

atinvicitinib at 0.8-1.2 mg/kg once daily was selected. Atinvicitinib was safe and effective for the treatment of atopic dermatitis in dogs.

Allergic dermatitis

A clinical trial was conducted to evaluate the efficacy and safety of atinvicitinib at the recommended treatment dose of 0.8-1.2 mg/kg once daily in dogs with allergic dermatitis. Veterinarians enrolled dogs aged at least 6 months old and weighing at least 2 kg, with a clinical diagnosis of allergic dermatitis attributed to one or more of the following: atopic dermatitis, flea allergy dermatitis, food responsive dermatitis, contact dermatitis or other. A baseline PVAS score of at least 6 was required for enrollment.[7] On day 0, veterinarians assessed the presumptive cause(s) of each dog's itch. Over 80% of dogs in each group had a presumptive diagnosis that included atopic dermatitis, with 38.4% having a presumptive diagnosis of atopic dermatitis alone.

Efficacy was primarily assessed using daily PVAS scores from day 0 through day 7. The primary efficacy endpoint was the proportion of dogs achieving at least a 50% reduction in PVAS from baseline on at least 5 out of 7 days, compared to placebo. Treatment success with atinvicitinib was significantly different from placebo (p=0.0109). Secondary efficacy measures included PVAS reductions at each assessment relative to baseline, veterinary dermatitis visual analog scale (DVAS) scores at baseline and on days 7 and 28, and the percentage of dogs achieving a PVAS reduction of at least 2 cm at each time point.

The mean PVAS reduction from baseline was significantly greater in the atinvicitinib group than placebo group on days 1 through 7. At least a 2 cm reduction in PVAS (considered clinically relevant)[2] was observed in significantly more dogs treated with atinvicitinib than placebo throughout this period. Additionally, PVAS scores returning to thresholds consistent with normal skin (<2 cm) or mild dermatitis (<3.6 cm) in dogs with atopic dermatitis—parameters that may be more relevant clinically because they are independent of baseline PVAS score—were assessed.[9] The percentage of dogs with PVAS consistent with normal skin (<2 cm) was significantly greater in atinvicitinib-treated dogs than placebo-treated dogs from day 3 onwards and reached 30.5% by day 7. The percentage of dogs with PVAS consistent with mild atopic dermatitis (<3.6 cm, including dogs with normal skin) was significantly greater in atinvicitinib-treated dogs than placebo-treated dogs from day 2 onwards and had reached 51.7% by day 7. By day 7, veterinary-assessed DVAS scores in the atinvicitinib-treated dogs had decreased by an average of 51%

and were significantly lower than those in the placebo-treated dogs.

Clinical studies demonstrate that atinvicitinib at 0.8-1.2 mg/kg once daily was safe and effectively reduces pruritus and clinical signs in dogs with allergic dermatitis including atopic dermatitis aged 6 months and older.

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Notes

NUMELVI (atinvicitinib) tablets for dogs for the treatment of pruritus associated with allergic dermatitis, including atopic dermatitis, and clinical manifestations of atopic dermatitis. For complete information, refer to the Summary of Product Characteristics in the Union Product Database: *https://medicines.health.europa.eu/veterinary/*.

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