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IL-31-induced pruritus in dogs: a novel experimental model to evaluate anti-pruritic effects of canine therapeutics

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Background – Pruritus is a characteristic clinical sign of allergic skin conditions including atopic dermatitis (AD) in the dog. IL-31 is a cytokine found in the serum of some dogs with AD and can induce pruritic behaviours in laboratory beagle dogs.

Hypothesis/Objectives – The objectives were to characterize an IL-31-induced pruritus model by evaluating the efficacy of prednisolone, dexamethasone and oclacitinib, and to compare the speed of anti-pruritic effects of oclacitinib against those of prednisolone and dexamethasone.

Animals – Purpose-bred beagle dogs were used in all studies.

Methods – Randomized, blinded, placebo-controlled studies were designed to evaluate and compare the anti-pruritic properties of prednisolone, dexamethasone and oclacitinib following a single intravenous injection of recombinant canine IL-31. Video surveillance was used to monitor and score pruritic behaviours in study animals.

Results – Prednisolone [0.5 mg/kg, per os (p.o.)] reduced IL-31-induced pruritus when given 10 h prior to observation. When the time interval between drug treatment and observation was shortened to 1 h, dexamethasone (0.2 mg/kg, intramuscular) but not prednisolone (0.25 or 0.5 mg/kg, p.o.) reduced IL-31-induced pruritus. Oclacitinib (0.4 mg/kg, p.o.) reduced pruritus when given 1, 6, 11 and 16 h prior to the observation period, and the anti-pruritic activity of oclacitinib was greater when compared to prednisolone and dexamethasone at all time points assessed.

Conclusion and clinical importance – The efficacy of prednisolone, dexamethasone and oclacitinib in the IL-31-induced pruritus model gives confidence that this may be a relevant model for acute pruritus associated with allergic dermatitis including AD and can be used to evaluate novel compounds or formulations.

Introduction

Pruritus is a common complaint in dogs with allergic skin disease and represents a key clinical feature in the diagnostic tree for atopic dermatitis (AD).[1–3] Long term pruritus can significantly affect the quality of life for affected dogs and their owners; therefore, treatments that can significantly and rapidly reduce pruritus are in great demand. To evaluate the efficacy of potential novel therapeutics, a variety of laboratory-based canine models of allergy have been developed such as dogs sensitized to allergens (e.g. house dust mites, fleas), or spontaneous canine models such as Maltese-beagle dogs or basenji-greyhounds that are genetically pre-disposed populations.[4–7] In many of these models pruritus can be assessed and evaluated, but onset of pruritic responses can be delayed or variable within the colony, and sensitization and maintenance of these colonies can be labour intensive and costly.

In order to address some of these concerns, we were interested in developing a canine model of acute pruritus. Findings from murine,[8–10] human[9–19] and canine[20–22] studies suggest that IL-31 cytokine can be produced from T cells in the skin after allergen exposure or exposure to bacterial antigens. This cytokine, in turn, may directly activate peripheral nerves expressing the IL-31 receptor to induce pruritic behaviours and activate additional cells expressing the receptor to drive clinical signs associated with AD.[8–22] Based on these data, we developed a canine model of pruritus which employed canine IL-31 as the pruritogenic agent. The objectives of our studies were to (i) validate the model by evaluating drugs such as prednisolone, dexamethasone and oclacitinib, used in clinical practice and known to rapidly reduce pruritus in naturally occurring canine atopic dermatitis[23–25] and (ii) to compare the speed of anti-pruritic effects of oclacitinib to those of prednisolone and dexamethasone.

Materials and methods

Animals and feeding procedures

Experiments were performed in purpose-bred beagle dogs (neutered males, spayed and intact females, ranging in age from 1 to 8 years old.) Mean weights for males in each study ranged between 12.0 and

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19.9 kg, and mean weights for females in each study ranged between 7.4 and 14.9 kg. Mean body weights among the different treatment groups within a study did not vary beyond 20%. Beagle dogs were obtained from either Marshall BioResources, North Rose, NY, USA, or Ridglan Farms Inc, Mt. Horeb, WI, USA, and were maintained and used as part of an in-house colony whose pruritic behaviours to recombinant canine IL-31 (cIL-31) were extensively characterized. All animal procedures were performed following Institutional Animal Care and Use Committee guidance to assure compliance with the US Animal Welfare Act Regulations, Title 9, Code of Federal Regulations Parts 1, 2 and 3, and with the Guide for the Care and Use of Laboratory Animals, issued by the Institute for Laboratory Animal Research Commission of Life Sciences, National Academy Press (Washington DC, 1996). Water and a limit fed diet of 250 g/day of Purina Lab diet #5007 were available.

Test drugs

Oral capsules containing active ingredients were made within five percent of the targeted dose. Oral doses of placebo hydroxypropyl methylcelluose (HPMC) capsules (Capsugel; Peapack, NJ, USA) were filled with microcrystalline cellulose (Acivel PH, FMC Corporation; Philadelphia, PA, USA). Prednisolone, (Prednis Tab® 5 mg tablets, Lloyd Inc.; Shenandoah, IA, USA) or oclacitinib (Zoetis; Kalamazoo, MI, USA) were delivered to the dogs via HPMC capsules back-filled with cellulose. Intramuscular (i.m.) injection of dexamethasone (DexaJext® Dexamethasone Solution 2 mg/mL, Butler Schein Animal Health; Dublin, OH, USA) or placebo injections containing 500 mg/mL polyethylene glycol 400, 9 mg/mL benzyl alcohol, 1.8 mg/mL methaylparaben and 0.2 mg/mL propylparaben, adjusted to pH 4.9 were given.

Video surveillance and pruritus monitoring

On each scheduled day of pruritus measurements, dogs were transferred to video rooms and placed in free-standing, single housed pens (approximately 90 cm × 180 cm), each equipped with ceiling-mounted cameras (Multicam Digital Surveillance System, RMISS Inc.; Wilmington, DE, USA) that digitally recorded the animals for real-time observation and/or viewing of recordings via computer links. Animals were acclimated ≥1 h prior to initiation of any video observation period for pruritus assessment. For each observation period, four dogs were evaluated for 2 h in real time using split-screen monitors by one observer. Video observers were scientists trained to observe and score pruritic behaviours in dogs. There was one observer for every four dogs, and each observer watched and scored their four dogs for the duration of the study. Observers were blinded to treatment. Categorical "yes/no" decisions were made at discrete 1 min intervals with regard to whether at least one pruritic behaviour was displayed by the study animals. Displays of pruritic behaviour such as licking/chewing of paws, flank and/or anal regions, scratching of flanks or neck, floor pawing, head-shaking and scooting of their bottom across the cage flooring were registered with a "yes" response. The cumulative number of "yes" determinations made within each observation period provided the pruritus score.

Induction of pruritus

Recombinant canine IL-31 was produced as described.[20] To induce pruritus, a single intravenous (i.v.) injection of recombinant cIL-31 was given at doses ranging from 1.5 to 1.75 μg/kg approximately 20–40 min before the video observation period began. All IL-31 treatments were prepared in sterile phosphate buffered saline without calcium chloride and magnesium chloride under aseptic conditions within 30 min of scheduled dosing.

Statistical evaluation

Placement of animals to rooms and pens was done according to a statistically generated allotment plan using SAS software v9.2. (SAS; Cary, NC, USA). All hypothesis testing was done at the 10% significance level. Pruritus scores (for 1 min intervals over the 2 h observation period) were analysed using a general linear mixed model. The model included the fixed effect of treatment and random effects of batch, block within batch and error. Least-square means were used as estimates of the treatment means and standard errors; 90% confidence intervals were calculated. Treatment differences were assessed using Fisher's protected least significant difference test.

Study design

Five randomized, blinded, placebo-controlled studies were designed. Treatment groups consisted of eight animals, and pruritic behaviours were observed and quantitated over a 2 h observation window in every study. IL-31 was given 20 min before each observation window to induce pruritus except when noted below.

Repeat dose study with oral prednisolone

Two different treatment groups were included. Dogs were administered either prednisolone (0.5 mg/kg, p.o.) or placebo, p.o., twice daily, every 12 h, for a total of 7 days. Pruritic behaviours were observed and quantified on study Day 0, 10–12 h after dogs were administered their first dose, and again on Day 6, 10–12 h after the last dose was administered (Figure 1a).

Duration of action study after single injection of dexamethasone

Three different treatment groups were included. Dogs were given either a single injection of placebo, i.m., 10 h prior to the observation period or a single injection of dexamethasone (0.2 mg/kg, i.m.) 1 or 10 h prior to the observation window for pruritus (Figure 2a).

Duration of action study after single dose of oclacitinib

Four different treatment groups were included. Dogs were given either a single dose of placebo, p.o., 6 h prior to the observation

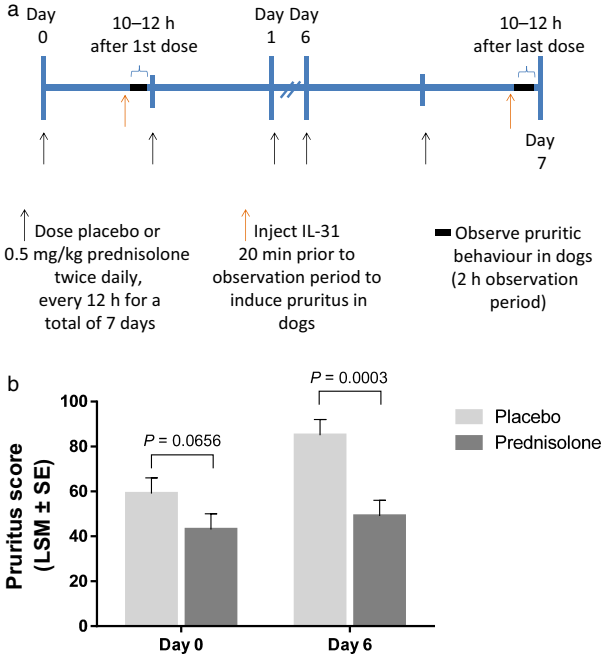

Figure 1. Effect of oral prednisolone on pruritus induced by IL-31 in beagle dogs. (a) Study design. (b) Pruritus scores of placebo and prednisolone (0.5 mg/kg, p.o.) treated animals observed 10–12 h after administration of the first dose and following 7 days of twice daily dosing. Data represent least-square means (LSM) ± SE, $N = 8$ per group.

period or a single dose of oclacitinib (0.4 mg/kg, p.o.) 6, 11 or 16 h prior to the observation window (Figure 3a).

Speed of onset comparison study of oclacitinib and prednisolone

Four treatment groups were included. Dogs were given either a single oral dose of placebo capsule, oclacitinib (0.4 mg/kg, p.o.) or prednisolone (at a dose of either 0.25 mg/kg, p.o., or 0.5 mg/kg, p.o.) 1 h prior to the observation period; IL-31 was given 40 min prior to the observation period to induce pruritus (Figure 4a).

Speed of onset comparison study of oclacitinib and dexamethasone

Three treatment groups were included. Dogs were given either placebo (i.m.), oclacitinib (0.4 mg/kg, p.o.) or dexamethasone (0.2 mg/kg, i.m.) IL-31 was given 40 min prior to the observation period to induce pruritus (Figure 5a).

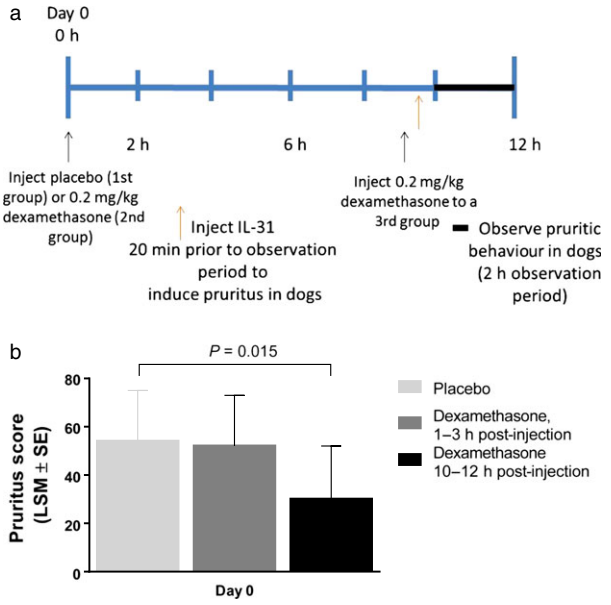

Figure 2. Effect of injectable dexamethasone on pruritus induced by IL-31 in beagle dogs. (a) Study design. (b) Pruritus scores of placebo, and dexamethasone (0.2 mg/kg, i.m.) treated animals observed 1–3 h or 10–12 h post drug injection. Data are graphed as least-square means (LSM) ± SE, $N = 8$ per group.

Results

Repeat dose study with oral prednisolone

Prednisolone reduced pruritic behaviours compared to placebo after a single dose and after repeat dosing (Figure 1). On Day 0, the least-square mean (LSM) pruritus score ± SE for the dogs treated with prednisolone was 43 ± 7 versus 59 ± 7 for placebo ($P = 0.0656$). Following 7 days of twice daily dosing of prednisolone, the LSM pruritus score continued to be reduced compared to the placebo (49 ± 7 versus 85 ± 7 for placebo; $P = 0.0003$).

Duration of action study after single injection of dexamethasone

Dexamethasone reduced pruritic behaviours in beagle dogs after a single injection when given 10 h prior to the assessment window ($P = 0.0150$). However, dexamethasone did not reduce pruritic behaviours when injected 1 h prior to the assessment window ($P > 0.1$) (Figure 2). LSM pruritus scores ± SE for the treatment groups were 54 ± 21 (placebo), 52 ± 21 (dexamethasone given 1 h prior) and 30 ± 22 (dexamethasone given 10 h prior).

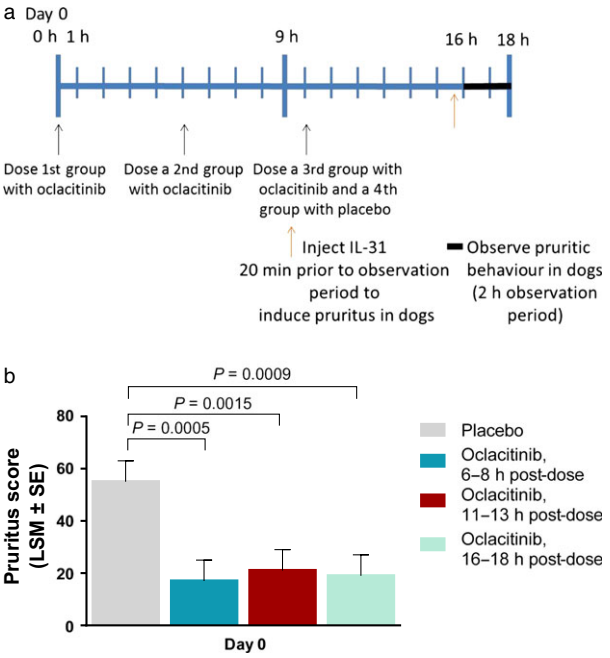

Figure 3. Effect of oclacitinib in beagle dogs over 18 h in IL-31 induced pruritus model. (a) Study design. (b) Pruritus scores of placebo or oclacitinib (0.4 mg/kg, p.o.) treated animals observed 6–8, 11–13 or 16–18 h after dosing. Data represent least-square means (LSM) ± SE, $N = 8$ per group.

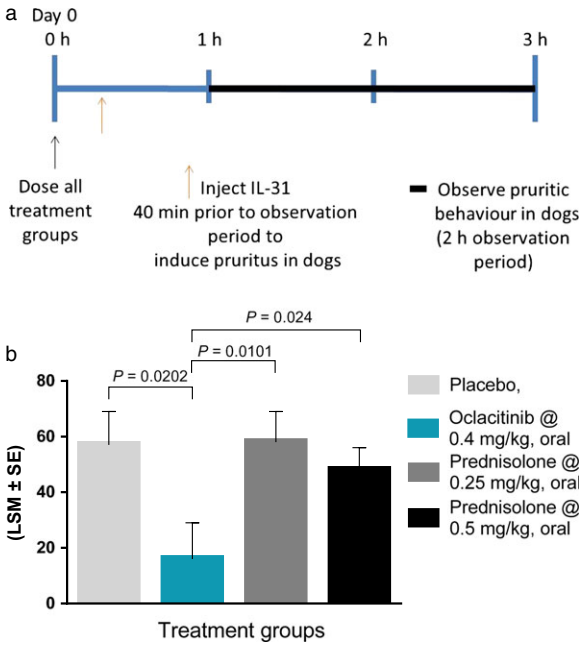

Figure 4. Effect of oclacitinib and oral prednisolone in the IL-31 induced pruritus model. (a) Study design. (b) Pruritus scores of placebo, oclacitinib (0.4 mg/kg, per os), or prednisolone (0.25 mg/kg or 0.5 mg/kg, p.o.) treated animals observed 1–3 h post-dosing. Data represent least-square means (LSM) ±), $N = 8$ per group.

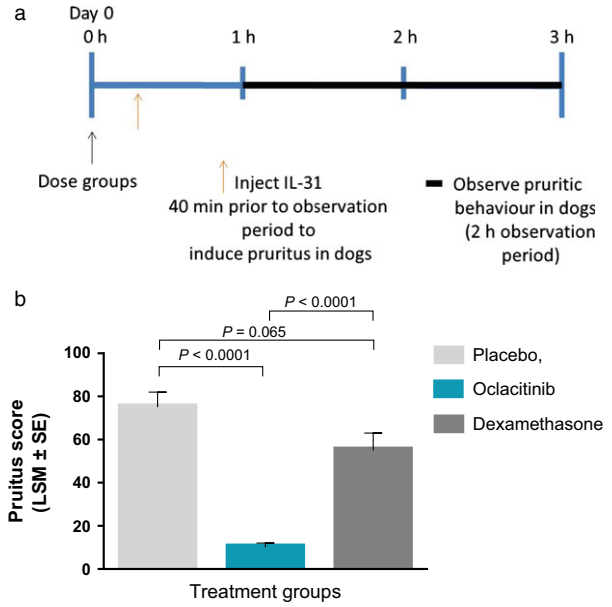

Figure 5. Comparison of effect of oclacitinib and dexamethasone in the IL-31-induced pruritus model. (a) Study design. (b) Pruritus scores of placebo, oclacitinib (0.4 mg/kg, p.o.), and dexamethasone (0.2 mg/kg, i.m.) treated animals observed 1–3 h post-dosing. Data represent least-square means (LSM) ± SE, $N = 8$ per group.

Duration of action study after single dose of oclacitinib

After a single oral dose of oclacitinib, pruritus was reduced regardless of whether oclacitinib was given 6, 11 or 16 h prior to the observation period for pruritus as compared to placebo (Figure 3; $P = 0.0005$–0.0015). LSM pruritus scores ± SE for the treatment groups were 55 ± 8 (placebo), 17 ± 8 (oclacitinib given 6 h prior), 21 ± 8 (oclacitinib given 11 h prior) and 19 ± 8 (oclacitinib given 16 h prior).

Speed of onset comparison study of oclacitinib and prednisolone

Oclacitinib reduced pruritus compared to placebo during the 1–3 h post-dosing window ($P = 0.0202$), whereas oral prednisolone evaluated at either dose did not (Figure 4). Additionally, the reduction in pruritus was greater in the oclacitinib-treated animals than in those treated with 0.25 mg/kg prednisolone ($P = 0.0101$) or 0.5 mg/kg prednisolone ($P = 0.0240$; Figure 4). LSM pruritus scores ± SE for the different treatment groups were 57 ± 12 (placebo), 16 ± 13 (oclacitinib 0.4 mg/kg, p.o.), 58 ± 11 (prednisolone 0.25, mg/kg p.o.) and 48 ± 8 (prednisolone 0.5 mg/kg, p.o.).

Speed of onset comparison study of oclacitinib and dexamethasone

Oclacitinib reduced pruritus compared to the placebo group ($P < 0.0001$). Dexamethasone also reduced pruritus compared to placebo ($P = 0.0650$). However, the reduction in pruritus was greater with oclacitinib when compared to dexamethasone ($P < 0.0001$). LSM pruritus scores ± SE among the different treatment groups were 75 ± 7 (placebo), 10 ± 2 (oclacitinib) and 55 ± 8 (dexamethasone), and illustrated in Figure 5.

Discussion

An IL-31-induced canine model of pruritus was developed to (i) recapitulate key pathways involved in pruritus due to allergy, (ii) assess acute anti-pruritic responses of novel therapeutics and (iii) benchmark novel agents or formulations against current therapies used by veterinarians in clinical practice. Canine IL-31 was chosen as the pruritogenic agent because of its demonstrated ability to induce pruritus in dogs and due to its presence in dogs with allergic skin conditions including AD.[20] Administration of cIL-31 routinely produced a robust but acute pruritic response in normal beagle dogs 20–40 min after infusion, allowing for pruritus to be assessed over an observation window as short as 2 h. Dogs usually returned to baseline levels by 24 h (data not shown), allowing for dogs to be re-used in subsequent studies. Effects of repeat exposure to cIL-31 were not studied extensively, but an increase in pruritus scores were seen after the second exposure to cIL-31 in the *Repeat dose study with oral prednisolone* (Figure 1), in which cIL-31 was given to dogs twice within 1 week. It is unclear whether this increase represented a real biological change or whether it was variation in the model; however, cIL-31 evaluations in mice have demonstrated that IL-31 can induce the expression of IL-31 receptor A and oncostatin M receptor beta in dorsal root ganglia after repeated administration and increase long-lasting scratching.[26] The ability to rapidly and reproducibly induce pruritus in normal animals after a single cIL-31 injection allows for any laboratory beagle dog to potentially be used in studies. The downside to an acute pruritus model is that other endpoints such as skin lesions, erythema, or biomarker analyses such as leukocyte, cytokine or mRNA changes do not make sense to monitor, as skin lesions do not develop. Therefore, this model may be best used as an initial assessment of agents for acute pruritus before evaluation in more complex models where changes associated with allergen sensitization occur naturally, and chronic changes such as immune dysregulation and skin barrier changes can be evaluated clinically or at the cellular and molecular level.

Standard therapies used to control pruritus in allergic skin diseases were effective in reducing pruritus in this model, building confidence that IL-31-induced pruritus may be a relevant model for pruritic allergic skin diseases. Specifically, oral prednisolone, injectable dexamethasone and oral oclacitinib were capable of reducing IL-31-induced pruritus. Oral oclacitinib consistently demonstrated rapid anti-pruritic effects 1–3 h post-dosing in all three studies performed. Oral prednisolone reduced pruritus 10–12 h post-dosing, and injectable dexamethasone reduced pruritus as quickly as 1–3 h post-injection in one study, but responses were variable possibly due to variability in drug bioavailability or pruritic responses in the animal model. A third possibility could be that the null hypothesis may have been incorrectly rejected in one of the studies due to the use of less stringent statistical criteria. Hypothesis testing was done at the 10% significance level due to the acceptance of a higher risk of type I errors for nonclinical studies.

By incorporating objective and quantitative scoring of pruritus, differentiation among drugs could be seen in this model. For example, a single oral dose of oclacitinib demonstrated a faster onset of action than oral prednisolone and produced a greater suppression of pruritus compared to prednisolone or injectable dexamethasone. These findings could be due to differences in pharmacokinetic properties of the drugs, as oclacitinib is shown to have rapid absorption as demonstrated by a t_{max} of 0.9–1.2 h.[27] Although the t_{max} has not been reported for prednisolone, drops in eosinophil cell counts in dogs can be detected around 4–6 h after dosing (PrednisTab™ Freedom of Information Summary, Nov 8, 1991). Alternatively, differential responses in the model could reflect differences in how the drugs work, mechanistically. Oclacitinib inhibits the function of the IL-31 cytokine by inhibiting Janus kinase activity directly downstream of the IL-31 receptor,[28] whereas glucocorticoids bind an intracellular glucocorticoid receptor in target tissues that then translocates to the nucleus, where the hormone-receptor complex binds specific DNA sequences to alter gene transcription.[29] Many of these corticosteroid-responsive genes are involved in decreasing inflammatory mediators. The need to induce gene transcription changes before inhibiting IL-31 function could be contributing to the differences in speed of onset or magnitude of response. Additionally, this study only evaluated two different types of glucocorticoids at commonly used dose levels and formulations; however, there are numerous alternative formulations and dose regimens that can be used based on the needs of the dog that may show a different speed of onset of anti-pruritic activity.[30–32] Nevertheless, this model has the potential to detect differential responses between different formulations, doses, regimens or therapies with different mechanisms of action.

In summary, the IL-31 pruritus model was able to detect the efficacy of standard anti-pruritus therapies such as glucocorticoids and oclacitinib and to quantitate differences in efficacy responses between them. These findings indicate that the IL-31-induced itch model in dogs represents a potential *in vivo* assessment that could be used to evaluate novel anti-pruritus compounds or formulations for dogs and to benchmark them against standard therapies used in clinical practice.

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Résumé

Contexte – Le prurit est un signe clinique caractéristique d'allergie cutanée comme la dermatite atopique (AD) chez le chien. L'IL-31 est une cytokine retrouvée dans le sérum de certains chiens atopiques qui peut entrainer du prurit chez les beagles de laboratoire.

Hypothèses/Objectifs – Les objectifs étaient de caractériser un modèle de prurit induit par IL-31 en évaluant l'efficacité de la prednisolone, la déxaméthasone et l'oclacitinib, et de comparer la rapidité des effets antiprurigineux de l'oclacitinib contre ceux de la prednisolone et de la déxaméthasone.

Sujets – Des chiens beagles d'expérimentation ont été utilisés dans toutes les études.

Méthodes – Des études contrôlées contre placebo, en aveugle et randomisées ont été configurées pour évaluer et comparer les propriétés antiprurigineuses de la prednisolone, déxaméthasone et oclacitinib suivant une simple injection intraveineuse d'IL-31 recombinante canine. Une surveillance vidéo a été utilisée pour enregistrer et noter les comportements de prurit des animaux d'étude.

Résultats – La prednisolone [0.5 mg/kg, per os (p.o.)] diminuait le prurit induit par IL-31 lorsqu'administré 10h avant l'observation. Quand l'intervalle de temps entre le traitement et l'observation était réduit à 1h, la déxaméthasone (0.2 mg/kg, intramusculaire) mais pas la prednisolone (0.25 ou 0.5 mg/kg, p.o.) diminuait le prurit induit par IL-31. L'oclacitinib (0.4 mg/kg, p.o.) réduisait le prurit lorsqu'administré à 1, 6, 11 et 16h avant la période d'observation et l'activité antiprurigineuse de l'oclacitinib était meilleure lorsque comparé à la prednisolone et à la déxaméthasone à tous les points évalués.

Conclusion et importance clinique – L'efficacité de la prednisolone, de la déxaméthasone et de l'oclacitinib dans le modèle de prurit induit par IL-31 permet de croire à la pertinence de ce modèle pour le prurit aigu associé à une dermatite allergique comme l'AD; il peut ainsi être utilisé pour évaluer de nouveaux composants ou formulations.

Resumen

Introducción – es un signo clínico característico de las condiciones alérgicas de la piel incluida la dermatitis atópica (AD) de la piel en perros. La interleuquina 31 (IL-31) es una citoquina encontrada en el suero de algunos perros con dermatitis atópica y puede inducir comportamientos indicativos de prurito en perros de laboratorio de raza Beagle.

Hipótesis/Objetivos – el objetivo fue caracterizar un modelo de prurito inducido por IL-31 mediante la evaluación de la eficacia de prednisolona, dexametasona y oclacitinib, y comparar la velocidad de los efectos anti-pruriginosos de oclacitinib frente a los de la prednisolona y dexametasona

Animales – perros de raza Beagle con este propósito fueron utilizados en todos los estudios.

Métodos – estudios al azar, ciegos y controlados con placebo fueron designados para evaluar y comparar las propiedades anti pruriginosas de la prednisolona, dexametasona y oclacitinib siguiendo una inyección intravenosa de IL-31 recombinante canina. Se utilizó vigilancia con video para monitorizar y valorar los compartimentos pruriginosos en los animales el estudio

Resultados – la prednisolona (0,5 mg/kg, por vía oral (p.o)) redujo el prurito inducido por IL-31 cuando se administró 10 horas antes de la observación. Cuando el intervalo entre el tratamiento y la observación se hizo más corto a una hora, la dexametasona (0,2 mg/kg, intramuscular) pero no la prednisolona (0,25 o 0,5 mg/kg, por vía oral) redujo el prurito inducido por IL-31. Oclacitinib (0,4 mg/kg, por vía oral) redujo el prurito cuando se administró a 1, 6, 11 y 16 horas previas al periodo de observación, y la actividad anti pruriginosa de oclacitinib fue mayor comparada con la de prednisolona y dexametasona en todos los tiempos evaluados.

Conclusión e importancia clínica – la eficacia de prednisolona, dexametasona y oclacitinib en el control del prurito inducido por IL31 en este modelo aporta mayor confianza de que puede ser un modelo relevante del prurito agudo asociado con la dermatitis alérgica, incluida la dermatitis atópica, y puede ser utilizado para evaluar compuestos novedosos o formulaciones

Zusammenfassung
Hintergrund – Juckreiz ist ein charakteristisches Symptom allergischer Erkrankungen, wie der atopischen Dermatitis (AD) des Hundes. IL-31 ist ein Zytokin, welches im Serum von einigen Hunden mit AD gefunden wurde und Kratzverhalten bei Laborbeagles auslösen konnte.
Hypothese/Ziele – Die Ziele dieser Studie waren die Darstellung eines durch IL-31 induzierten Juckreizmodells zur Evaluierung von Prednisolon, Dexamethason und Oclacitinib, und ein Vergleich der Geschwindigkeit der juckreizstillenden Wirkung von Oclacitinib im Vergleich zu Prednisolon und Dexamethason.
Tiere – Für diese Studie wurden für diesen Zweck gezüchtete Beagles verwendet.
Methoden – Die randomisierten, geblindeten und Plazebo-kontrollierten Studien wurde entworfen, um die juckreizstillende Wirkung von Prednisolon, Dexamethason und Oclacitinib nach einer einzigen intravenösen Injektion von rekombinantem caninen IL-31 zu evaluieren und zu vergleichen. Videoüberwachung wurde verwendet, um das Juckreizverhalten bei den Versuchstieren zu beobachten und zu bewerten.
Ergebnisse – Prednisolon [0,5 mg/kg, *per os* (p.o.)] reduzierte den IL-31 induzierten Juckreiz, wenn es 10 h vor der Beobachtung gegeben wurde. Wenn die Zeitspanne zwischen Medikamentengabe und Beginn der Beobachtung auf 1 h verringert wurde, reduzierte Dexamethason (0,2 mg/kg, intramuskulär), aber nicht Prednisolon (0,25 oder 0,5 mg/kg, p.o.) den IL-31 induzierten Juckreiz. Oclacitinib (0,4 mg/kg, p.o.) reduzierte den Juckreiz bei Gabe von 1, 6, 11 und 16 h vor der Beobachtungsperiode und die juckreizstillende Wirkung von Oclacitinib war zu allen verglichenen Zeitpunkten größer als jene von Prednisolon und Dexamethason.
Schlussfolgerungen und klinische Bedeutung – Die Wirkung von Prednisolon, Dexamethason und Oclacitinib im IL-31 induzierten Juckreizmodell bestätigt, dass es sich hier um ein relevantes Modell für akuten Juckreiz, welcher mit allergischer Dermatitis inklusive AD einhergeht, handelt und dass es verwendet werden kann, um neue Wirkstoffe oder Formulierungen zu evaluieren.

要約
背景 — そう痒はイヌにおいてアトピー性皮膚炎を含むアレルギー性皮膚疾患に特徴的な臨床症状である。IL-31は一部のADのイヌの血清中に検出されるサイトカインであり、実験ビーグル犬において痒み行動を誘発することができる。
仮説/目的 — プレドニゾロン、デキサメサゾンおよびオクラシチニブの効果を評価することによって、IL-31誘発そう痒モデルの特徴を示すこと、オクラシチニブの抗そう痒効果の速度をプレドニゾロン、デキサメサゾンと比較することを目的とした。
供与動物 — 目的のため繁殖されたビーグル犬をすべての研究で用いた。
方法 — 組み替えイヌIL-31の単回静脈注射後のプレドニゾロン、デキサメサゾンおよびオクラシチニブの抗そう痒特性を評価、比較することを目的に、ランダム化、盲検化、プラセボ対照試験を作成した。試験動物のモニターおよびそう痒行動のスコア化をするためにビデオ監視を使用した。
結果 — プレドニゾロン[0.5 mg/kg、経口投与 (p.o.)]は観察の10時間前に投与した際、IL-31誘発そう痒を減少させた。薬剤投与と観察の間の時間を1時間に早めた時、プレドニゾロン(0.25あるいは0.5 mg/kg、p.o.)ではなく、デキサメサゾン(0.2 mg/kg、筋肉内投与)はIL-31誘発そう痒を減少させた。オクラシチニブ(0.4 mg/kg、 p.o.)は観察時間の1、6、11、および16時間前に投与した時、そう痒を減少させ、オクラシチニブの抗そう痒活性はすべての評価ポイントでプレドニゾロンとデキサメサゾンと比較し優れていた。
結論および臨床的な重要性 — IL-31誘発そう痒モデルにおけるプレドニゾロン、デキサメサゾンならびにオクラシチニブの効果により、このモデルがADを含むアレルギー性皮膚炎に関連した急性そう痒に対する現実的なモデルとなり、新規の化合物や製剤を評価するために使用できるという信頼性が得られる。

摘要
背景 — 瘙痒是过敏性皮肤病的特点,如犬异位性皮炎(AD)。IL-31这种细胞因子会出现在某些AD患犬血清中,且可导致实验用比格犬的瘙痒行为。
假设/目的 — 通过评估泼尼松龙、地塞米松和奥拉替尼的效果,来描述IL-31诱导的瘙痒模型,并对比奥拉替尼和泼尼松龙、地塞米松抗瘙痒的起效速度。
动物 — 研究使用的均为实验用比格犬。
方法 — 设计随机、双盲、安慰剂-对照实验。一次静脉注射重组犬IL-31,评估和对比泼尼松龙、地塞米松和奥拉替尼的抗瘙痒效果。使用视频监视器监测并给实验动物的瘙痒评分。
结果 — IL-31诱导瘙痒的犬,使用泼尼松龙[0.5 mg/kg,每日一次 (口服)] ,在给药后10h见效。当给药时间和观察时间缩短至1h时,地塞米松(0.2 mg/kg,肌肉注射)组瘙痒有缓解,而泼尼松龙(0.25 或 0.5 mg/kg,口服)组瘙痒无缓解。奥拉替尼(0.4 mg/kg,口服)在1、6、11及16h观察其瘙痒行为,其在所有时间点的抗瘙痒效果都强于泼尼松龙和地塞米松。
结论与临床意义 — 在IL-31诱导的瘙痒模型上,泼尼松龙、地塞米松和奥拉替尼的效果显著,这提示我们可建立其他慢性瘙痒的模型,如AD等过敏性皮肤病,用于评估新型药品或配方。

