Onset and duration of action of lokivetmab in a canine model of IL-31 induced pruritus

Timothy J. Fleck, Lori R. Norris, Sean Mahabir, Rodney R. Walters, Olivier Martinon, Steven A. Dunham and Andrea J. Gonzales

Veterinary Medicine Research & Development, Zoetis Inc., 333 Portage St, Kalamazoo, MI 49007, USA

Correspondence: Andrea J. Gonzales, Veterinary Medicine Research & Development, Zoetis Inc., 333 Portage St, Kalamazoo, MI 49007, USA
E-mail: andrea.gonzales@zoetis.com

Background – Interleukin (IL)-31 is a cytokine involved in allergic inflammation which induces pruritus across species including dogs. Using recombinant canine IL-31 we have developed a model of pruritus in the dog to evaluate onset of action and duration of effect of therapeutic drugs.

Objective – To assess the onset of action and duration of effect of lokivetmab (Cytopoint) in the IL-31-induced pruritus model.

Animals – Twenty-four purpose-bred beagle dogs (neutered males, spayed and intact females) 1.5–4.7 years old and weighing between 6 and 14 kg.

Methods and materials – Randomized, blinded, placebo-controlled studies were designed to evaluate the anti-pruritic properties of lokivetmab. Laboratory beagle dogs were given either placebo, 0.125, 0.5 or 2.0 mg/kg lokivetmab, subcutaneously. IL-31 then was administered to evaluate pruritus 3–5 h post-placebo or -lokivetmab administration as well as one, seven, 14, 28, 42 and 56 days post-dosing. Pruritus was evaluated over a 2 h window in animals by video monitoring and scored using a categorical scoring system.

Results – When animals were given 2.0 mg/kg lokivetmab, a significant reduction in pruritus was observed at 3–4, 4–5 and 3–5 h post-treatment (P ≤ 0.0001). When animals were given either 0.125, 0.5 or 2 mg/kg lokivetmab, the duration of effect was dose-dependent and statistically significant for 14, 28 and 42 days, respectively (P ≤ 0.0288).

Conclusion – These data indicate that a single subcutaneous injection of 2 mg/kg lokivetmab produces a significant suppression of pruritus starting 3 h post-treatment that can be sustained for 42 days.

Introduction

Interleukin (IL)-31 is a cytokine best known for its pruritogenic effects across species. It was discovered back in 2004 by several groups as a cytokine belonging to the glycoprotein 130/IL-6 cytokine family and is believed to be produced by T-helper 2 (Th2) cells after allergen presentation by Langerhans cells.1 It also has been shown to be secreted by activated macrophages, basophils, eosinophils and keratinocytes after allergen exposure or initiation of Type 2 inflammation within tissues.2

Interleukin-31 binds a heterodimeric receptor (IL-31 receptor A and oncostatin M receptor beta) to activate signal transduction pathways within cells. These receptors can be found on immune cell such as macrophages, mast cells, eosinophils and basophils, as well as keratinocytes and dorsal root ganglia of peripheral neurons. When IL-31 binds its heterodimeric receptor, signalling pathways such as Janus kinase (JAK)/signal transducer and activator of transcription (STAT), phosphoinositide 3-kinase (PI3K)/AKT, and different mitogen-activated protein kinase pathways, such as extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal kinase, are activated, leading to biological changes in cells. These changes include immune cell chemotaxis, pro-inflammatory cytokine and chemokine secretion, pruritic responses in the skin, and skin barrier disruption resulting in part from alterations in cell proliferation, differentiation and barrier protein synthesis.3

Concentrations of IL-31 are elevated in pruritic allergic skin conditions and can induce scratching behaviours in a variety of species such as mice, monkeys and dogs.3–6 Studies done in laboratory beagle dogs demonstrated that when IL-31 was given by several routes (intradermally, subcutaneously and intravenously), it induced strong pruritic behaviours within minutes to hours.7 These findings were used to develop a novel experimental model in dogs to evaluate the antipruritic effects of canine therapeutics. This model was able to determine the onset and duration of action of commonly used treatments for atopic dermatitis (AD) or allergic dermatitis such as oclacitinib (Apoquel, Zoetis; Kalamazoo, MI, USA) and glucocorticoids.8

Lokivetmab (Cytopoint, Zoetis) is a caninized monoclonal antibody that binds and neutralizes canine IL-31

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Materials and methods

Animal care and ethics

A group of 24 purpose-bred beagles were used to complete the onset of duration study (eight neutered males, 15 spayed females, one intact female; 2–3 years old weighing 7.2–14.4 kg; originally from Marshall BioResources; North Rose, NY, USA). The duration of effect study was performed in a different set of 24 purpose-bred beagle dogs (10 neutered males, 14 spayed females; 1.5–4.7 years old weighing 8.3–14.8 kg; originally from Marshall BioResources or Ridglan Farms, Inc.; Mt. Horeb, WI, USA). All dogs for both studies were maintained and used as part of an in-house colony whose pruritic behavioural responses to exogenous IL-31 were extensively characterized in previous studies.

All animal procedures were performed following site-specific, local and national Animal Health IACUC guidance to assure compliance with the Animal Welfare Act, Regulations 9 CFR parts 1, 2 and 3, and with the Guide for the Care and Use of Laboratory Animals, issued by the ILAR Commission of Life Sciences, National Academy Press (Washington, DC, USA, 1996). Water and a diet (based on calorific needs) of Royal Canin Adult Medium (Royal Canin; Aimargues, France) (onset of action study) or Purina Lab diet #5007 (Purina; St Louis, MI, USA) (duration of effect study) were available. Dogs were not fasted before placebo or IL-31 dosing.

Test article
Refrigerated sterile-filtered stock solutions of vehicle (placebo) and lokivetmab were brought up to room temperature and aliquoted at volumes matched to the D0 body weights of the study animals. Each dog received a single injection of 1 mL per 10 kg body weight of 20, 5 or 1.25 mg/mL of lokivetmab s.c. for doses of 2, 0.5 or 0.125 mg/kg, respectively.

Study design

Onset of action study. This study was run after the approval of lokivetmab to characterize onset of action of lokivetmab, and hypothesis testing was conducted at the two-sided α = 0.05 level of significance. A blinded, randomized, placebo-controlled study was conducted using laboratory beagle dogs. Twenty-four dogs (n = 6 per treatment) were given either placebo or 0.125, 0.5 or 2.0 mg/kg lokivetmab s.c. Dogs were randomized to treatments according to a randomized complete block design, with blocking based on historical pruritus (based on the average of three challenge assessments before study start) and pen location. Blocks then were randomized to two batches (cohorts for pruritus assessment), one containing eight and the second four blocks. They then were challenged with IL-31 (1.75 μg/kg) to induce pruritus before lokivetmab or placebo administration on D–7, and challenged with IL-31 again on D1, D7, D14, D28, D42 and D56 post-lokivetmab or placebo administration to evaluate the duration of antipruritic effect of the monoclonal antibody (mAbs). Pruritus was scored between 0.5 h and 2.5 h post-IL-31 administration on each of those days.

Induction of pruritus and video surveillance and pruritus scoring

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 before initiation of any video observation period for pruritus assessment. For each observation period, four dogs were evaluated for 2 h (recordings started – 15–20 min post-challenge with IL-31-1) in real time by one observer using split-screen monitors. 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.

Statistical methods

Pruritic score data for onset and duration of action studies were analysed using general mixed linear models. In both studies pre-treatment pruritic scores at D–7 were used as a covariate in the statistical models and least squares means (LSM) were used as estimates of the treatment means. If the covariate was not significant (P < 0.05), it was dropped from the final model.

Onset of action. Scores for first hour, second hour and for the total 2 h period were analysed using a model with the fixed effect of treatment, and random effects of batch, block within batch, and interaction between block and treatment within batch (animal term), and error. Treatment comparisons were conducted using the two-sided α = 0.05 significance level. The pre-treatment (D–7) covariate used was time-matched (first hour, second hour or total).

Duration of effect. Scores for the total 2 h period were analysed using a repeated measures model with fixed effects of treatment, time and treatment-by-time, and random effects of batch, block within batch, the interaction between block and treatment within batch (animal term), and error. Treatment comparisons were conducted within time points using the two-sided α = 0.10 significance level.

Results

Evaluation of the onset of action of lokivetmab demonstrated that a single dose (2 mg/kg s.c.) significantly reduced pruritic activity in a canine model of IL-31-induced pruritus 3–4 h post-dosing (P < 0.0001). The LSM pruritic scores (± standard error of measurement (SEM))
shown to elicit pruritic responses in multiple species.3 Lokivetmab in this model of pruritus in beagle dogs. us to characterize the onset and dose/duration of action. Results from the duration of effect study showed that a significant reduction in pruritus was observed to D14 for a dose of 0.125 mg/kg (LSM pruritic scores ± SEM of 91 ± 5.1 for placebo versus 51 ± 5.1 for 0.125 mg/kg lokivetmab, P < 0.0001), to D28 for a dose of 0.5 mg/kg (81 ± 8 for placebo versus 55 ± 8 for 0.5 mg/kg lokivetmab, P = 0.0288) and to D42 for a dose of 2.0 mg/kg (90 ± 8 for placebo versus 61 ± 8.7 for 2 mg/kg lokivetmab, P = 0.0245). No significant differences were seen on D56 for any of the doses tested. See Figure 2 for results.

Discussion
Lokivetmab (Cytopoint) is a caninized monoclonal antibody that binds and neutralizes canine IL-31. Its ability to control/treat clinical signs associated with AD confirms that IL-31 is a key mediator in canine AD.9 IL-31 has been shown to elicit pruritic responses in multiple species and induce several pro-inflammatory cytokines from a variety of immune cells implicated in allergic skin disease.10,11 Intravenous administration of canine IL-31 to beagle dogs results in a rapid, transient induction of a variety of pruritic phenotypes including itching, scratching and headshaking.8 This phenotypic response to IL-31 was used to establish a canine model of IL-31-induced pruritus and allowed us to characterize the onset and dose/duration of action of lokivetmab in this model of pruritus in beagle dogs.

By comparing the results of laboratory model studies to clinical field studies it is possible to determine the translatability of model studies to the clinical setting. Lokivetmab is an approved therapy to control clinical signs of itch and inflammation due to allergic dermatitis or AD in the United States, and as such, was tested in a dose-determination, randomized, blinded, placebo-controlled field study.9 That field study demonstrated that administration of lokivetmab at doses of 0.125, 0.5 or 2.0 mg/kg s.c. resulted in a statistically significant (P < 0.05) reduction in LSM values for owner-assessed pruritus relative to placebo for as long as 21, 35 or 49 days, respectively. Those results are in general correlation with the efficacy observed in the present study where statistically significant (P < 0.05) reduction in pruritic behaviour relative to placebo in the laboratory model was observed for 14, 28 or 42 days for 0.125, 0.5 or 2.0 mg/kg doses, respectively. These results, taken together, bring relevance of the efficacy observed in the model to the efficacy observed in the field and suggest that this laboratory beagle dog IL-31-mediated pruritic model may be an attractive translational model for evaluation of IL-31 inhibitors. One critical component in applying this model for the development of inhibitors is the assurance that the binding kinetics and specificity of the test article for the canine homologue is similar to that of target species protein. Another important consideration is the pharmacokinetic properties of the test article in canine species relative to the target species.

There are multiple challenges associated with evaluating the onset of activity in the clinical setting that primarily are consequences of the difficulty in monitoring client-owned animals on an hourly basis for rapid onset molecules and behavioural changes associated with a visit to the veterinarian. To help establish what the predicted onset of action may be in the clinical setting, we evaluated multiple time points shortly post-administration of 2 mg/kg lokivetmab s.c. in the model. This experiment demonstrated a rapid onset of activity (within 3 h) of subcutaneous lokivetmab administration. In accordance with
the model efficacy data observed in this study, clinical field trials demonstrated statistically significant reduction in client-observed pruritus at the first time point evaluated, one day following a single 2 mg/kg s.c. administration. Results from the duration of effect laboratory study support the translationality of effects seen in the IL-31-induced pruritus model to effects seen in a clinical setting. These data further indicate that a single subcutaneous injection of lokivetmab (2 mg/kg) produces a significant suppression of pruritus starting 3 h post-treatment with lokivetmab and is sustained for 42 days.

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Résumé
Contexte – L’interleukine (IL)-31 est une cytokine impliquée dans l’inflammation allergique qui induit le prurit pour toutes les espèces dont le chien. En utilisant un IL-31 recombinant nous avons développé un modèle de prurit chez le chien pour évaluer le début de l’action et la durée des effets des traitements.
Objectifs – Déterminer le début d’action et la durée de l’effet du lokivetmab (Cytopoint) dans le modèle de prurit induit par IL-31.
Sujets – Vingt quatre chiens beagle de reproduction (males castrés, femelles stérilisées et entières) 1,5 - 4,7 ans et pesant de 6 à 14 kg.
Méthodes – Les études contrôlées contre placebo, en aveugle, randomisées ont été étudiées pour évaluer les propriétés antiprurigineuses du lokivetmab. Les chiens beagle de laboratoire ont été attribués aux groupes placebo, 0,125, 0,5 ou 2,0 mg/kg de lokivetmab en sous-cutané. L’IL-31 a ensuite été administrée pour
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évaluer le prurit 3-5h après administration de lokivetmab ou de placebo ainsi que un, sept, 14, 38, 42 et 56 jours après dosage. Le prurit était évalué sur une fenêtre de 2h chez les animaux par monitoring vidéo et scoring utilisant un système d’évaluation catégorielle.

**Résultats** – Quand les sujets ont reçu 2.0 mg/kg de lokivetmab, une diminution significative du prurit était observée à 3-4, 4-5 et 3-5h post traitement ($P \leq 0.0001$). Quand les animaux recevaient soit 0.125 soit 0.5 ou 2 mg/kg de lokivetmab, la durée de l’effet était dépendant de la dose et statistiquement significatif, respectivement, pour 14, 28 et 42 jours ($P \leq 0.0288$).

**Conclusion** – Ces données indiquent qu’une unique injection sous-cutanée de 2 mg/kg de lokivetmab produit une suppression significative du prurit dès 3h après traitement et persiste pendant 42 jours.

**RESUMEN**

**Introducción** – La interleuquina (IL)-31 es una citoquina involucrada en la inflamación alérgica que induce prurito en todas las especies, incluidos los perros. Utilizando IL-31 canina recombinante, hemos desarrollado un modelo de prurito en el perro para evaluar el inicio de la acción y la duración del efecto de los fármacos terapéuticos.

**Objetivo** – evaluar el inicio de la acción y la duración del efecto de lokivetmab (Cytopoint) en el modelo de prurito inducido por IL-31.

**Animales** – Veinticuatro perros Beagle de laboratorio (machos castrados, hembras esterilizadas e intactas) de 1,5 a 4,7 años y con un peso de entre 6 y 14 kg.

**Métodos** – se diseñaron estudios aleatorios, ciegos y controlados con placebo para evaluar las propiedades antipruriginosas del lokivetmab. A los perros Beagle de laboratorio se les administró placebo, 0,125; 0,5 o 2,0 mg/kg de lokivetmab por vía subcutánea. Luego se administró IL-31 para evaluar el prurito 3-5h después de la administración de placebo o lokivetmab, así como a uno, siete, 14, 28, 42 y 56 días después de la dosificación. El prurito se evaluó durante una ventana de 2 h en animales mediante monitorización por vídeo y se puntuó utilizando un sistema de puntuación categórico.

**Resultados** – cuando se administró a los animales 2,0 mg/kg de lokivetmab, se observó una reducción significativa del prurito a las 3-4, 4-5 y 3-5h después del tratamiento ($P \leq 0.0001$). Cuando se administró a los animales 0,125; 0,5 o 2 mg/kg de lokivetmab la duración del efecto fue dependiente de la dosis y estadísticamente significativa durante 14, 28 y 42 días, respectivamente ($P \leq 0.0288$).

**Conclusión** – estos datos indican que una sola inyección subcutánea de 2 mg/kg de lokivetmab produce una supresión significativa del prurito a partir de las 3 h posteriores al tratamiento que se mantiene durante 42 días.

**Zusammenfassung**

**Hintergrund** – Interleukin (IL)-31 ist ein Zytokin, welches bei der allergischen Entzündung involviert ist und Juckreiz bei allen Spezies auch beim Hund auslöst. Wir haben beim Hund ein Juckreiz Modell entwickelt, wobei wir eine rekombinante Form von caninem IL-31 verwendet haben, um den Wirkungseintritt und die Dauer der Wirkung dieser therapeutischen Medikamente zu evaluieren.

**Ziel** – Die Beurteilung des Wirkungseintritts und der Wirkdauer von Lokivetmab (Cytopoint) beim durch IL-31 induzierten Juckreizmodell.

**Tiere** – Vierundzwanzig zu diesem Zweck gezüchtete Beagles (kastrierte Rüden, kastrierte und intakte Hündinnen), im Alter von 1,5 – 4,7 Jahren, mit einem Gewicht zwischen 6 und 14 kg.

**Methoden** – Es wurden randomisierte, geblindete, Plazebo-kontrollierte Studien designed, um die juckreizstillenden Eigenschaften von Lokivetmab zu evaluieren. Laborbeagles wurde entweder Plazebo oder 0,125; 0,5 oder 2,0 mg/kg Lokivetmab subkutan verabreicht. IL-31 wurde verabreicht, um den Juckreiz 3-5h Post-Plazebo oder -Lokivetmab Verabreichung zu evaluieren, sowie nach einem, sieben, 14, 28, 42 und 56 Tage post-Administration. Der Juckreiz wurde über ein 2-stündiges Fenster evaluiert, wobei die Tiere mittels Videoüberwachung und mit Hilfe eines kategorischen Systems bewertet wurden.

**Ergebnisse** – Wenn den Tieren 2,0 mg/kg Lokivetmab verabreicht wurde, konnte eine signifikante Reduktion des Pruritus 3-4, 4-5 und 3-5h nach der Behandlung ($P \leq 0.0001$) beobachtet werden. Wenn den Tieren entweder 0,125; 0,5 oder 2 mg/kg Lokivetmab verabreicht wurden, war die Wirkungsdauer Dosis-abhängig und für 14, 28 bzw 42 Tage statistisch signifikant ($P \leq 0.0288$).

**Schlussfolgerung** – Diese Ergebnisse zeigen, dass eine einzige subcutane Injektion von 2 mg/kg Lokivetmab eine signifikante Unterdrückung des Juckreizes bewirkt, welche 3h nach der Administration beginnt und 42 Tage lang anhält.

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実験動物 — 1.5〜4.7歳、体重6〜14kgの24頭の実験ビーグル犬（去勢済みオス、去勢済みメス、未処理メス）。

方法 — ロキベトマブの抗瘙痒特性を評価するため、無作為化盲検プラセボ対照試験を実施した。実験用ビーグル犬にプラセボ、0.125、0.5または2.0mg/kgのロキベトマブを皮下投与した。その後、IL-31を投与し、プラセボまたはロキベトマブ投与3〜5時間後、および投与1日後、7日後、14日後、28日後、42日後、56日後の瘙痒を評価した。瘙痒は、ビデオモニタリングにより動物を2時間評価し、カテゴリーとするシステムを用いて点数化した。

結果 — 被験動物に2.0 mg/kgのロキベトマブを投与した場合、瘙痒の有意な減少が3-4、4-5および3-5時間後に観察された（P≤0.0001）。動物に0.125、0.5または2mg/kgのロキベトマブを投与した場合、効果の持続期間はそれぞれ14日、28日および42日で用量依存的であり、統計的に有意であった（P≤0.0288）。

結論 — これらのデータは、2mg/kgのロキベトマブを単皮下注射することで、治療後3時間後から瘙痒が有意に抑制され、その後の効果は42日間持続することを示している。

Resumo

Contexto — A interleucina (IL) -31 é uma citocina envolvida na inflamação alérgica que induz prurido em várias espécies, incluindo cães. Utilizando IL-31 canina recombinante, desenvolvemos um modelo de prurido em cães para avaliar o início da ação e a duração do efeito de drogas terapêuticas.

Objetivo — Avaliar o início de ação e a duração do efeito do lokivetmab (Cytopoint) no modelo de prurido induzido por IL-31.

Animais — Vinte e quatro cães beagle criados para fins específicos (machos castrados, fêmeas esterilizadas e intactas) com 1.5〜4.7 anos de idade e pesando entre 6 e 14 kg.

Métodos — Estudos randomizados, cegos e placebo-controle foram elaborados para avaliar as propriedades antipruriginosas do lokivetmab. Os cães beagle de laboratório receberam placebo, 0.125, 0.5 ou 2.0 mg/kg de lokivetmab, por via subcutânea. A IL-31 foi então administrada para avaliar o prurido 3〜5 h após a administração de placebo ou lokivetmab, bem como um, sete, 14, 28 e 42 dias após a administração. O prurido dos animais foi avaliado através de monitoramento por vídeo ao longo de uma janela de 2h e pontuado usando um sistema de pontuação categórica.

Resultados — Quando os animais receberam 2.0 mg/kg de lokivetmab, uma redução significativa do prurido foi observada em 3-4, 4-5 e 3-5h após o tratamento (P<0.0001). Quando os animais receberam 0,125, 0,5 ou 2 mg/kg de lokivetmab, a duração do efeito foi dependente da dose e estaticisticamente significativa durante 14, 28 e 42 dias, respectivamente (P<0.0288).

Conclusão — Esses dados indicam que uma única injeção subcutânea de 2 mg/kg de lokivetmab produz uma supressão significativa do prurido começando 3 horas após o tratamento, que é mantida por 42 dias.