

A pilot study on the effect of oclacitinib on epicutaneous sensitization and transepidermal water loss in a colony of atopic beagle dogs

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Background – Dogs with atopic dermatitis are prone to sensitization to environmental allergens due to increased skin permeability; the effect of treatments on epicutaneous sensitizations is unknown.

Hypothesis/objectives – To evaluate if oclacitinib (i) prevents new sensitizations and (ii) affects skin barrier function.

Animals – Atopic beagle dogs.

Methods – *Aim 1.* Ten dogs were randomly assigned to placebo or oclacitinib while exposed epicutaneously to a novel allergen. Sensitization was assessed using serum allergen-specific IgE and clinically by development of skin reactions at the site of allergen application. Time to develop dermatitis and allergen-specific IgE were compared between groups. *Aim 2.* Eight dogs were randomly assigned to placebo or oclacitinib for four weeks and challenged with an allergen known to trigger flares. After a four week wash-out, dogs were crossed-over and the protocol repeated. Transepidermal water loss (TEWL) was measured on days 0 and 28 of each arm.

Results – *Aim 1.* Oclacitinib significantly increased ($P = 0.006$) time to develop skin reactions compared to placebo. Four (of five) dogs receiving oclacitinib failed to develop skin reactions, whereas all placebo dogs developed dermatitis. There were no significant differences in allergen-specific IgE between groups. *Aim 2.* TEWL results were difficult to interpret. Significantly higher values were detected from the axilla in placebo compared to oclacitinib-treated dogs ($P = 0.047$). TEWL values were significantly higher from the inguinal area in oclacitinib ($P = 0.039$) treated dogs but not placebo at the end of the study.

Conclusions and clinical importance – Clinically, oclacitinib delayed development of dermatitis at the site of allergen application. TEWL results were difficult to interpret and additional studies are required for clarification.

Introduction

Atopic dermatitis (AD) is a chronic disease resulting from a combination of genetic and environmental factors.¹ Allergic sensitization to environmental allergens is common and exposure to allergens can increase the severity of AD.¹ Impairment of the skin barrier has been described in atopic dogs^{2,3} and increases the risk for epicutaneous sensitization.⁴ It is currently unknown how systemic drug treatment for canine AD affects the rate and frequency of new allergen sensitization. Oclacitinib, a JAK inhibitor, is approved for the treatment of canine allergic dermatitis. JAK inhibitors can affect antigen-presenting cells⁵ and skin barrier function;⁶ oclacitinib could therefore potentially interfere with allergen sensitization. Our primary aim was to investigate if oclacitinib affected epicutaneous sensitization using

a placebo-controlled prospective design. A colony of atopic beagle dogs was used in a controlled environment with standardized allergen exposure.⁷ The second aim was to investigate the effect of oclacitinib on skin permeability by measuring transepidermal water loss (TEWL).

Materials and methods

All procedures were approved by the Institutional Animal Care and Use Committee.

Aim 1

Animals

Ten atopic beagles previously sensitized epicutaneously to both environmental and food allergens and housed in a controlled allergen environment were used.^{7,8} There had been no prior exposure to Bermuda grass allergen. At the time of the study, the dogs were 8 years old. There were four females and six males. The dogs were fed Hill's Science maintenance diet (Topeka, KS, USA). The dogs had functional and ultrastructural impairment of the skin barrier function with increased TEWL compared to age-, gender- and breed-matched control dogs.^{9,10} Skin barrier alterations described were similar to those reported for spontaneous canine AD and predispose the dogs to epicutaneous sensitization.

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Protocol for allergen exposure

No tape stripping of the skin was permitted. A novel allergen (Bermuda grass) was applied epicutaneously twice a week for up to four months. Bermuda grass allergen extract at a concentration of 40,000 PNU/mL diluted to 50% in glycerin (Greer; Lenoir, NC, USA) and a crude Bermuda grass *Cynodon dactylon* pollen extract at a dilution of 50 mg/mL in PBS/50% glycerin (Nelco Laboratories Inc; Deep Park, NY, USA) were used. A dropper bottle was used to apply 2.6 mL of the grass extract to the left thorax and the same volume of the crude pollen to the right thorax twice a week. When either site developed any positive skin reaction (including macules of erythema, papules), the dog was withdrawn from the study and the allergen exposure ceased. The time to develop positive skin reactions was compared between groups. The investigator evaluating the skin reactions was unaware of group allocation. Dogs that did not react by four months were exposed again twice a week for one week after a two week drug withdrawal to verify that the absence of skin reactions was due to lack of sensitization rather than concurrent drug administration.

Treatment protocol

Dogs were randomly assigned to placebo or oral oclacitinib. Oclacitinib (Apoquel®, Zoetis; Kalamazoo, MI, USA) was administered orally at 0.4–0.6 mg/kg twice daily, 12 h apart, for two weeks and then once every 24 h.

Monitoring of allergic sensitization

Development of allergic sensitization was evaluated clinically and immunologically by monitoring for positive skin reactions at the site of allergen application. The application site was checked at 6 and 24 h after application for signs of erythema, macules and/or papules consistent with a positive response. If a positive result was recorded, then allergen exposure was not repeated.

Serum IgE monitoring

Blood samples to measure Bermuda-specific IgE were collected on Day 0 and every 30 days. Blood samples (4 mL) were sent to Heska (Fort Collins, CO, USA) for measurement of allergen-specific IgE using the Heska Allercept® detection system, results were provided in proprietary units.

Statistical analysis

The sensitization data were analysed by the Kaplan–Meier survival analysis and the IgE data were analysed by independent *t*-test (one-tailed) between groups.

Aim 2

Animals

Eight atopic beagles were used in a cross-over design. Each dog was randomly assigned to either placebo or oclacitinib group (same dose and protocol as for Aim 1) for four weeks and challenged with an allergen to which they had been previously sensitized and were known to respond (house dust mite *Dermatophagoides farinae*). Allergen exposure was done epicutaneously three times a week as described previously.¹¹ After four weeks, a wash-out period of four weeks with no allergen or drug exposure was observed and dogs were crossed over.

TEWL measurements

Measurement of TEWL was conducted on days 0 and 28 of each arm of the study. A closed chamber evaporimeter (VapoMeter, Delfin Technologies Ltd; Kuopio, Finland) was used at an ambient temperature of 20–26°C. Dogs were permitted 30 minutes to acclimatize prior to TEWL measurements. All readings were collected in triplicate and the mean was used for statistical analysis. Three unclipped areas were evaluated: concave surface of pinnae, axilla and inguinal areas. These sites were selected because they are typically affected sites in canine AD and a significant difference in TEWL had been reported in atopic dogs when compared to healthy control dogs.¹⁰

Statistical analysis

For TEWL the Wilcoxon signed rank test, matched two-tailed variant for the between-groups effect at each time point was done. The within-group difference was analysed using paired two-tailed Student's *t*-test. Significant values were at $P < 0.05$.

Results

A significantly increased ($P = 0.006$) time to development of positive skin reactions was observed in the oclacitinib group compared to placebo (mean: 14.5 ± 1.52 versus 7.2 ± 1.5 weeks). Figure 1 demonstrates the response of each dog. Four (of five) dogs receiving oclacitinib failed to develop positive skin reactions by the end of four months. These dogs also did not develop dermatitis after oclacitinib was stopped and with further epicutaneous exposure to Bermuda allergen. ANOVA showed no statistically significant difference in allergen-specific IgE between treatment and placebo groups and over time.

Significantly higher values for TEWL were detected in the axilla region of placebo dogs compared to the oclacitinib-treated group ($P = 0.047$). In the inguinal area, a significant increase of TEWL was detected in the oclacitinib-treated group ($P = 0.039$) but not in the placebo group from days 0 to 28.

Discussion

In this pilot study, treatment with oclacitinib significantly delayed the development of positive skin reactions in a colony of dogs with atopic dermatitis. This colony of dogs readily develops dermatitis after epicutaneous allergen exposure and this has been reproducible with multiple allergens, testing multiple litters and generations of dogs. The mechanisms behind this inhibitory effect are not known at this time.

The evaluation of the effects on IgE and TEWL did not detect any significant differences. The relationship between circulating allergen-specific IgE and development of dermatitis is controversial but it is widely accepted that IgE may not predict the development of disease nor correlate with disease severity. A lack of an effect on allergen-specific IgE in dogs that develop dermatitis is not surprising.

Transepidermal water loss has been linked to the integrity of the stratum corneum and measurements of TEWL

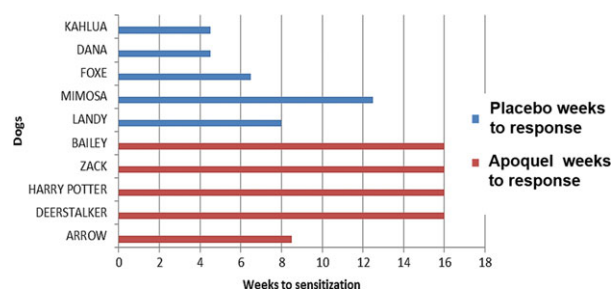


Figure 1. Atopic beagle dogs exposed epicutaneously to a novel allergen and receiving placebo or oclacitinib.

Weeks to positive skin test reactivity (sensitization) for each dog. Although all dogs in the placebo group became sensitized, only one dog in the oclacitinib group developed a positive reaction.

are commonly used to assess skin barrier function in dogs,¹² a method that has significant limitations due to substantial variability of results. In the present study, a closed chamber device was used and dogs were acclimated for 30 min prior to collecting measurements to minimize variability due to technical or environmental reasons. Other factors including blood flow also may affect TEWL. Studies with small numbers of subjects can have results that are difficult to interpret due to variability. The increase of TEWL from the inguinal region in the oclacitinib-treated group is of interest. It could be speculated that oclacitinib actually worsens the skin barrier, although the results in the axilla region contradict this finding. Further studies are indicated to effectively address the question of barrier function in this context.

In conclusion, a delay in sensitization in the oclacitinib-treated group was found. The reasons for the delay are unknown. Additional studies to evaluate skin barrier function using a larger number of dogs and the effects on antigen presenting cells are indicated.

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Résumé

Contexte – Les chiens atopiques sont sujets à la sensibilisation aux allergènes environnementaux en raison d'une augmentation de la perméabilité cutanée; l'effet des traitements sur la sensibilisation épicutanée n'est pas connue.

Hypothèses/Objectifs – Déterminer si l'oclacitinib (i) prévient les nouvelles sensibilisations et (ii) affecte la fonction barrière cutanée.

Sujets – Des chiens beagles atopiques.

Méthodes – *Objectif 1.* Dix chiens ont été répartis au hasard entre placebo et oclacitinib et soumis à une exposition épicutanée d'un nouvel allergène. La sensibilisation a été évaluée par sérologie spécifique d'allergène et cliniquement par le développement de réactions cutanées au site de l'application de l'allergène. Le temps de développement de la dermatite et des IgE spécifiques d'allergène ont été comparés entre les groupes. *Objectif 2.* Huit chiens ont été répartis au hasard entre placebo et oclacitinib pendant quatre semaines et provoqués avec un allergène connu pour déclencher des crises. Après quatre semaines de blanc thérapeutique, les chiens ont été changés de groupe et le protocole répété. La TEWL (transepidermal water loss) a été mesurée à jours 0 et 28 pour chaque membre.

Résultats – *Objectif 1.* L'oclacitinib a significativement augmenté ($P = 0.006$) le temps de développement des réactions cutanées comparé au placebo. Quatre (sur cinq) des chiens recevant de l'oclacitinib n'ont pas développé de réactions cutanées tandis que tous les placebo ont développé une dermatite. Il n'y avait pas de différence significative dans les IgE spécifiques d'allergène entre les groupes. *Objectif 2.* Les résultats de TEWL étaient difficiles à interpréter. Des valeurs significativement plus élevées étaient détectées des plis axillaires des placebo comparé aux chiens recevant de l'oclacitinib ($P = 0.039$) mais pas des placebo à la fin de l'étude.

Conclusions et importance clinique – Cliniquement, l'oclacitinib retarde le développement de dermatite au site d'application de l'allergène. Les résultats de TEWL étaient difficiles à interpréter et des études supplémentaires sont nécessaires pour clarification.

Resumen

Introducción – Los perros con dermatitis atópica son propensos a la sensibilización a alérgenos ambientales debido a una mayor permeabilidad de la piel; el efecto de los tratamientos en las sensibilizaciones epicutáneas es desconocido.

Hipótesis/objetivos – Evaluar si oclacitinib (i) previene nuevas sensibilizaciones y (ii) afecta la función de barrera cutánea.

Animales – Perros beagle atópicos.

Métodos – Objetivo 1. Diez perros fueron asignados al azar a tratamiento con placebo u oclacitinib mientras se exponían epicutáneamente a un nuevo alérgeno. La sensibilización se evaluó utilizando IgE sérica específica de alérgeno y clínicamente mediante el desarrollo de reacciones cutáneas en el sitio de aplicación de alérgenos. Se comparó el tiempo para desarrollar dermatitis y producir IgE específica de alérgeno entre los grupos. Objetivo 2. Ocho perros fueron asignados aleatoriamente a tratamiento con placebo u oclacitinib durante cuatro semanas y fueron desafiados con un alérgeno conocido por desencadenar reacciones de hipersensibilidad. Después de un periodo de lavado de cuatro semanas, se cruzaron los perros y se repitió el protocolo. La pérdida transepidérmica de agua (TEWL) se midió en los días 0 y 28 de cada parte experimental.

Resultados – Objetivo 1. Oclacitinib aumentó significativamente ($P = 0.006$) el tiempo para desarrollar reacciones cutáneas en comparación con el placebo. Cuatro (de cinco) perros que recibieron oclacitinib no desarrollaron reacciones cutáneas, mientras que todos los perros con placebo desarrollaron dermatitis. No hubo diferencias significativas en la IgE específica de alérgeno entre los grupos. Objetivo 2. Los resultados de TEWL fueron difíciles de interpretar. Se detectaron valores significativamente más altos de la axila en el placebo en comparación con los perros tratados con oclacitinib ($P = 0.047$). Los valores de TEWL fueron significativamente más altos en el área inguinal en perros tratados con oclacitinib ($P = 0.039$) pero no con placebo al final del estudio.

Conclusiones e importancia clínica – Clínicamente, oclacitinib retrasó el desarrollo de dermatitis en el sitio de la aplicación de alérgenos. Los resultados de TEWL fueron difíciles de interpretar y se requieren estudios adicionales para su aclaración.

Zusammenfassung

Hintergrund – Hunde mit atopischer Dermatitis neigen zu Sensibilisierung durch Umweltallergene aufgrund einer erhöhten Hautpermeabilität; die Auswirkung der Behandlungen auf die epikutane Sensibilisierung ist unbekannt.

Hypothese/Ziele – Eine Evaluierung ob Oclacitinib (i) neue Sensibilisierungen verhindert und (ii) ob es die Funktion der Hautbarriere beeinflusst.

Tiere – Atopische Beagles.

Methoden – *Ziel 1.* Es erhielten zehn Hunde zufällig Placebo oder Oclacitinib, während sie epikutan einem neuen Allergen ausgesetzt waren. Die Sensibilisierung wurde mittels Allergen-spezifischem IgE im Serum und klinisch durch die Entstehung von Hautreaktionen an der Stelle der Allergenapplikation erfasst. Die Zeit, bis sich eine Dermatitis entwickelte sowie das Allergen-spezifische IgE wurden zwischen den Gruppen verglichen. *Ziel 2.* Acht Hunde erhielten zufällig vier Wochen lang Placebo oder Oclacitinib und an ihnen wurde eine Provokation mit einem Allergen, welches dafür bekannt ist Allergenschübe zu verursachen, durchgeführt. Nach einer vier wöchigen Wash-Out Phase, wurden die Gruppen der Hunde gewechselt und das Protokoll wiederholt. Es wurde der transepidermale Wasserverlust (TEWL) an den Tagen 0 und 28 an jeder Vorderextremität gemessen.

Ergebnisse – *Ziel 1.* In der Oclacitinib Gruppe dauerte es im Vergleich zur Placebogruppe signifikant länger ($P = 0.006$) bis Hautreaktionen entstanden. Vier (von fünf) Hunden, die Oclacitinib erhielten, entwickelten keine Hautreaktionen während alle Hunde, die Placebo bekamen, eine Dermatitis entwickelten. Es gab zwischen den Gruppen keine signifikanten Unterschiede zwischen den Allergen-spezifischen IgE. *Ziel 2.* Die TEWL Ergebnisse waren schwer zu interpretieren. Es wurden signifikant höhere Werte im Bereich der Axilla bei der Placebogruppe im Vergleich zur Oclacitinib Gruppe der Hunde ($P = 0.047$) gefunden. Die TEWL Werte waren am Ende der Studie in der Inguinalgegend signifikant höher bei den mit Oclacitinib ($P = 0.039$) behandelten im Gegensatz zu den mit Placebo behandelten Hunden.

Schlussfolgerungen und klinische Bedeutung – Klinisch verzögerte Oclacitinib die Entstehung einer Dermatitis an der Stelle der Allergenapplikation. TEWL Ergebnisse waren schwierig zu interpretieren und es bedarf zusätzlicher Studien zur Klarstellung dieser Ergebnisse.

要約

背景 – アトピー性皮膚炎の犬は、皮膚透過性の亢進によって環境アレルゲンに対する感作を受けやすい傾向にある。しかしながら、皮膚感作に対する治療効果は未だ不明である。

仮説/目的 – 本研究の目的は、オクラシニブが(i)新たな感作を予防するかどうか、(ii)皮膚バリア機能に影響するかどうかを評価することである。

被験動物 – アトピーを有するビーグル犬。

方法 – 目的 i. 10頭の犬を無作為にプラセボ群またはオクラシチニブ投与群に割り当て、経皮的に新奇アレルゲンを曝露した。感作は血清アレルゲン特異的IgEを用いて評価し、また曝露部位における皮膚の反応性を臨床症状により評価した。さらに皮膚炎が発症するまでの期間ならびにアレルゲン特異的IgEを2群間で比較した。目的 ii: 8頭の犬を無作為にプラセボ群またはオクラシチニブ投与群に割り当て、炎症を誘発することが確認されているアレルゲンに4週間曝露した。4週間のウォッシュアウト期間後に、同じプロトコールによるクロスオーバー試験を実施した。各治療群における経皮水分蒸散量(TEWL)を、治療開始0日目および28日目に測定した。

結果 – 目的1. オクラシチニブ群では、プラセボ群と比較して皮膚反応を発症するまでの期間が有意に延長した($P = 0.006$)。オクラシチニブを投与された4頭(5頭中)の犬は皮膚反応を示さなかったが、プラセボ群の全ての犬は皮膚炎を発症した。2群間でアレルゲン特異的IgEには有意差が認められなかった。目的2. TEWLの結果は解釈が困難であった。TEWL値は腋窩部においては、オクラシチニブ投与群($P = 0.047$)よりもプラセボ群において有意に高値を示した。鼠径部における試験終了時のTEWL値は、プラセボ群よりもオクラシチニブ投与群において有意に高値を示した($P = 0.039$)。

結論と臨床的重要性 – 臨床的に、オクラシチニブはアレルゲン曝露部位における皮膚炎の発生を遅延させた。しかしながら TEWLの結果については解釈が難しく、追加の研究が必要であると考えられた。

摘要

背景 – 由于皮肤通透性增加,异位性皮炎患者易对环境过敏原致敏;对表皮致敏的治疗效果尚不了解。

假设/目的 – 评估奥拉替尼(i)是否能预防新的致敏过程,以及(ii)是否影响皮肤屏障功能。

动物 – 患有异位性皮炎的比格犬。

方法 – 任务1. 将10只病犬随机分配到安慰剂组或奥拉替尼组,同时使动物暴露在新的皮肤过敏原中。使用血清过敏原特异性IgE评估过敏原,并且对皮肤局部涂抹过敏原,观察皮肤的临床反应。比较两组间发生皮肤病变的时间和过敏原特异性IgE。任务2. 将8只病犬随机分配到安慰剂组或奥拉替尼组,治疗4周,并用已知的过敏原刺激动物发病。经过四周的清洗,将2组犬对换,并重复治疗方案。在第0天和第28天,检测每条腿的经表皮水分流失量(TEWL)。

结果 – 任务1. 与安慰剂组相比,奥拉替尼显著延迟了($P = 0.006$)皮肤病变出现的时间。使用奥拉替尼治疗的病犬,5只中有4只并未发生皮肤病变,而安慰剂组的病犬均出现了病变。两组间的过敏原特异性IgE没有显著差异。任务2. TEWL结果难以判读。与使用奥拉替尼治疗的病犬相比,安慰剂中的腋窝检测数值显著增高($P = 0.047$)。在实验结束时,与安慰剂组相比,使用奥拉替尼($P = 0.039$)治疗的病犬,腹股沟区域的TEWL值显著增高。

结论和临床意义 – 临床中,奥拉替尼的使用,延迟了涂抹过敏原的皮肤病变出现的时间。TEWL的结果很难判读,还需要进一步的研究来证实。

Resumo

Contexto – Os cães com dermatite atópica são predispostos à sensibilização a alérgenos ambientais devido a sua maior permeabilidade cutânea; o efeito de tratamentos na sensibilização epicutânea é desconhecido.

Hipótese/objetivos – Avaliar se oclacitinib (i) previne a sensibilização e (ii) afeta a função da barreira cutânea.

Animais – Cães atópicos da raça Beagle.

Métodos – *Objetivo 1.* Dez cães foram aleatoriamente selecionados para receber placebo ou oclacitinib enquanto eram expostos epicutaneamente a um alérgeno novo. A sensibilização foi avaliada utilizando dosagem sérica de IgE alérgenos-específica e clinicamente através da observação do surgimento de reações cutâneas no local de aplicação de alérgenos. O tempo de desenvolvimento de dermatite e IgE alérgeno-específica foram comparados entre os grupos. *Objetivo 2.* Oito cães foram aleatoriamente selecionados para receber placebo ou oclacitinib por quatro semanas e desafiados com um alérgeno conhecido por causar crises. Após quatro semanas de carência, os cães foram alternados e o protocolo foi repetido. Mensurou-se a perda de água transepidermica (*transepidermal water loss*, TEWL) nos dias 0 e 28 de cada ciclo.

Resultados – *Objetivo 1.* Oclacitinib aumentou significativamente ($P = 0.006$) o tempo de desenvolvimento de reações cutâneas, comparado ao placebo. Quatro (em cinco) cães recebendo oclacitinib não desenvolveram reações cutâneas, enquanto todos os cães do grupo placebo desenvolveram dermatite. Não foram observadas diferenças significativas nos níveis séricos de IgE alérgeno-específicas entre os grupos. *Objetivo 2.* Os resultados de TEWL foram difíceis de se interpretar. Valores significativamente mais altos foram obtidos das axilas dos cães do grupo placebo comparado aos cães do grupo oclacitinib ($P = 0.047$). Os valores de TEWL foram significativamente mais altos na região inguinal dos cães tratados com oclacitinib ($P = 0.039$), mas não no grupo placebo no fim do estudo.

Conclusões e importância clínica – Clinicamente, oclacitinib retardou o desenvolvimento de dermatite no local da aplicação de alérgeno. Os resultados de TEWL foram difíceis de se interpretar, desta forma, mais estudos são necessários para elucidação.