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ORIGINAL ARTICLE

A randomised controlled trial testing the rebound-preventing benefit of four days of prednisolone during the induction of oclacitinib therapy in dogs with atopic dermatitis

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Abstract

Background: A rebound of pruritus occasionally occurs after oclacitinib dose reduction in dogs with atopic dermatitis (AD).

Objectives: To determine whether an initial 4-day course of prednisolone decreases the probability of a pruritus rebound after reducing the frequency of oclacitinib administration.

Animals: Forty dogs with mild-to-moderate AD lesions and moderate-to-severe pruritus.

Materials and Methods: Dogs were randomised to receive oclacitinib at 0.4–0.6 mg/kg twice daily for 14 days then once daily, alone or with prednisolone at 0.5 mg/kg, orally, twice daily for the first 4 days. Clinicians graded the Canine Atopic Dermatitis Extent and Severity Index (CADESI)4 and 2D-investigator global assessment (IGA) before and after 28 days; owners assessed the pruritis Visual Analog Scale (PVAS)10 and Owner Global Assessment of Treatment Efficacy (OGATE) on Day (D)0, D4, D14, D21 and D28. We considered a rebound any increase greater than one PVAS10 grade at D21 compared to D14.

Results: On D21, there were significantly fewer rebounds in the dogs receiving prednisolone (three of 20, 15%) compared to those given oclacitinib alone (nine of 20, 45%; Fisher's test, $p = 0.041$). Compared to oclacitinib monotherapy, the concurrent administration of prednisolone for the first 4 days led to significantly lower PVAS10 on D4 and D28, CADESI4 and 2D-IGA on D28, and OGATE on D21 and D28 (Wilcoxon–Mann–Whitney U-tests). Adverse effects of therapy were minor, intermittent and self-resolving.

Conclusions and Clinical Relevance: The initial addition of 4 days of prednisolone significantly decreased the probability of a rebound of pruritus 1 week after oclacitinib dose reduction. This short concomitant glucocorticoid administration led to a higher skin lesion improvement and improved perception of treatment efficacy with minimal adverse effects.

Thierry Olivry and Viktorija Lokianskiene share first authorship.

INTRODUCTION

Oclacitinib (Apoquel, Zoetis) is a first-in-class, first-generation, nonselective-yet-Janus kinase (JAK)1-predominant, JAK inhibitor (JAKinib) approved for the treatment of canine allergic and atopic dermatitis (AD).[1] Oclacitinib exhibits a remarkably rapid and potent antipruritic and antilesional effect in dogs with AD.[2,3]

In three randomised-controlled trials (RCTs) enrolling dogs with AD or allergic dermatitis, the reduction of frequency of administration of oclacitinib after 2 weeks (i.e. from twice daily to once daily) was associated with an unexpected—yet transient—increase in manifestation of pruritus.[2–4] Such a 'rebound phenomenon', which appeared as a mean rise in Day (D)21 or D28 pruritus scores compared to those on D14, was unique to this clinical sign, as it was not observed with skin lesion assessments. A plausible hypothesis for this rebound is the recently published observation of an increase in the transcription of pruritogenic cytokines in allergic skin lesions—as compared with untreated mice—after the abrupt discontinuation of oclacitinib therapy.[5] Such a theory is logical, as this JAKinib, at first, only blocks the intracellular signalling of JAK-dependent cytokine receptors without inhibiting the production and release of pro-allergic cytokines by resident and inflammatory cells. Then, as a consequence of the short half-life of oclacitinib in dogs (about 4 h),[6] any elevated skin levels of pruritogenic cytokines [e.g. interleukin (IL)-31] could result in the activation of sensory neurons and itch once the oclacitinib's administration is reduced to once a day. However, with the continuous administration of oclacitinib, the secretion of pro-allergic cytokines is expected to wane following the eventual deactivation of inflammatory and resident cells. The cytokine changes occurring in the skin in the first month of oclacitinib administration to dogs with AD have not been reported to confirm or refute the above theory as of yet.

Because one of the numerous anti-allergic effects of glucocorticoids is the inhibition of transcription of cytokine-encoding genes,[7] the addition of steroids during the induction phase of oclacitinib therapy should prevent any increase in cytokine secretion, and thus, might reduce the probability of a rebound in pruritus.

The objective of this RCT was to test the hypothesis that a 4-day course of prednisolone at the onset of oclacitinib therapy reduces the proportion of atopic dogs exhibiting a rebound in pruritus, 1 week after decreasing the frequency of administration of the drug. We also expected this early adjunctive glucocorticoid therapy, albeit short, to lead to a greater improvement in clinical signs and better perception of the benefit of oclacitinib therapy after 1 month.

This trial is reported following the guidelines of the 2010 CONSORT statement (http://www.consort-statement.org; page last accessed 7 February 2022), with slight modifications in the order of sections to facilitate reading. The reporting of outcome measures includes those from the core outcome set proposed in the 2018 Core Outcome Set for Canine AD (COSCAD'18).[8]

MATERIALS AND METHODS

Ethics

The two interventions prescribed herein (oclacitinib or prednisolone) were at dosages recommended in the 2015 Practice Guidelines for the Treatment of Canine AD. Consequently, the protocol was considered to follow the best clinical practice standards. Nevertheless, we obtained consent from the owners to enrol their dogs in the study with the possible prescription of an off-label concurrent administration of the two drugs for 4 days in one of the treatment groups.

Trial design

This trial was a 4-week long, open, parallel, 1:1 randomised trial comparing the efficacy of oclacitinib monotherapy to prednisolone and oclacitinib given together for the first 4 days.

Animals

We aimed to enrol at least 40 dogs of any breed, sex and neuter status, aged 12 months or older, with a minimum weight of 3.0 kg.

For selection, the following six criteria had to be met:

1. a diagnosis of AD made according to current standards (i.e. a clinical diagnosis with the exclusion of resembling dermatoses),[9] and,
2. if a diagnosis of food-induced AD had been made following a standard restriction-provocation dietary trial, the atopic signs had to remain uncontrolled after feeding a diet not containing causative ingredients, and,
3. there was no evidence of active bacterial or yeast skin infections, and,
4. the dogs did not receive any oral glucocorticoid or oclacitinib, or allergy-interfering medications in the preceding 2 weeks before selection, and
5. the atopic skin lesions were of at least mild severity [i.e. a Canine Atopic Dermatitis Extent and Severity Index, 4th iteration (CADESI4) score > 10],[10] and,
6. the pruritus manifestations were of at least a moderate grade (i.e. a 10-grade pruritus Visual Analog Scale [PVAS10] score >3.5) in the preceding 24 h.[11]

Interventions

Dogs were given one of two interventions. In the oclacitinib monotherapy (OM) group, they were treated with oclacitinib at the approved dosage of 0.4–0.6 mg/kg, twice daily for 14 days, then once daily for 14 days. In the prednisolone-oclacitinib group (PO), the dogs received oclacitinib as those in the OM group, and we also added prednisolone at the targeted dosage of 0.5 ± 0.2 mg/kg twice daily for the first 4 days. Such a short duration of prednisolone was

selected arbitrarily to decrease the risk of adverse events.

During this trial, we permitted the use of topical antiseptics, topical ear antimicrobials without glucocorticoids, topical ear cleansers and allergen-specific immunotherapy, and only if the latter had been administered for more than one consecutive year without full control of atopic signs.

By contrast, we prohibited the concurrent use of anti-allergic drugs whose effects could alter the interpretation of the benefit of tested interventions. Forbidden drugs were as follows: topical, otic and oral glucocorticoids; topical and oral calcineurin inhibitors; injectable lokivetmab; topical and oral antihistamines; and any other medications known to have any anti-inflammatory or antipruritic effect. Finally, the dog's diet and oral supplements could not be changed for the 8 weeks preceding and during this trial.

Outcomes

In this study, veterinarian investigators were asked to rate the skin lesions using two validated instruments. The CADESI4 was graded on D0, before starting treatment, and 4 weeks later (D28). As two of the lesions of the CADESI4 (lichenification and alopecia) are insensitive to change during short-duration trials, we also extracted the erythema grade of the CADESI4 to report the CADESI4-E, as described previously.[12] Likewise, clinicians also graded, on D0 and D28, their perception of the overall severity of AD skin lesions using the newly validated 2D-Investigator Global Assessment (IGA) scale.[13]

We also asked one of the owners (the same person at each visit) to assess the dog's manifestation of pruritus during the 24 h preceding D0, D4, D14, D21 and D28 using the validated PVAS10 scale.[11]

Likewise, on D4, D14, D21 and D28, we requested the same owner to rate their perception of the efficacy of treatment using the newly proposed Owner Global Assessment of Treatment Efficacy (OGATE).[8]

The primary outcome measure was the proportion of dogs in each group that had a rebound of pruritus on D21, such a rebound being defined as a PVAS10 on D21 that was at least one grade superior to that on D14, the last day of the twice-daily administration of oclacitinib.

For secondary outcome measures, we compared, between groups:

1. the absolute PVAS10 values on D4, D14, D21 and D28
2. the absolute CADESI4 and CADESI4-E scores on D28
3. the proportion of dogs with a 2D-IGA of clear-to-almost clear (0 or 1) with at least a two-grade improvement from baseline scores on D28.

Finally, in addition to the outcome measures proposed above, we also reported those included in the COSCAD'18.[8]

Safety evaluation

We recorded all adverse events during the study and separated those expected to be seen in dogs with AD (e.g. itch, erythema, skin or ear infections) and those that were unexpected.

Sample size

In an unpublished open pilot study performed by one of the authors (LB), eight of 13 dogs with AD (62%) given oclacitinib per the approved regimen exhibited a pruritus increase 1 week after the frequency of administration of oclacitinib was reduced from twice to once daily. Using these pilot data and an online calculator (http://powerandsamplesize.com, page last accessed 7 February 2022), we determined that if we enrolled 16 dogs per group, this study would have an 80% power to detect a significant two-thirds reduction in the proportion of dogs having a rebound if given prednisolone with oclacitinib (one-sided analysis, $p = 0.05$). To allow for the expected participant attrition during the trial, we planned to enrol 20 dogs per group.

Randomisation and blinding

The dogs were randomised to be allocated in the OM or PO group using an online tool (www.random.org, page last accessed 14 February 2022) in a 1:1 ratio without blocks. While owners were made aware of our wish to compare two oclacitinib protocols, we did not specifically explain the expected effect of the addition of the prednisolone.

Statistical methods

PVAS10 values were analysed within each treatment group with nonparametric repeated-measures ANOVA (Friedman test) with Dunn's post-tests comparing each post-treatment value to its respective at baseline. Likewise, we compared before versus after CADESI4, CADESI4-E and 2D-IGA values using Wilcoxon matched-pairs signed-rank tests. We used Wilcoxon–Mann–Whitney U-tests for continuous variables and Fisher's exact test for categorical data for between-group comparisons. As we had two unidirectional hypotheses (post-treatment < baseline scores and post-treatment PO > OM scores), all statistical calculations were performed as one-tailed analyses with $p < 0.05$, using statistical software (Prism 7, GraphPad Software).

RESULTS

Participants

The trial took place between the 24th of January 2019 and the 9th of February 2022. Forty-two dogs were selected and randomised, of which two did not come

back for reevaluation, and 40 completed the 4-week trial. At the time of data curation, one subject (Dog 7; OM group) was noted to have a PVAS10 score inferior to that required *per protocol*, yet we kept its values for intent-to-treat analyses.

Baseline data

Of these 40 dogs, 22 lived in Argentina, 11 in Lithuania, five in Sweden and two in Belgium. There were 14 cross-bred and 26 pure-bred dogs, including six French bulldogs, four West Highland white terriers, and four Labradors or golden retrievers. Signalment and baseline characteristics are summarised in Table 1, while details of all patients, per COSCAD'18 recommendations, are included in Table S1. Altogether, there were no significant differences between the OM and PO groups in sex balance, age or body weight at the time of enrolment.

As shown in Table 1, the two groups of dogs had similar ranges of baseline skin lesion [CADESI4, CADESI4-E (its erythema component) and 2D-IGA] and pruritus scores (PVAS10).

Numbers analysed

All 40 dogs received their originally assigned intervention, and all scores were used for intention-to-treat analyses.

Outcomes

Manifestations of pruritus

Dogs from both OM and PO groups experienced a significant reduction in PVAS10 scores during this 4-week trial (Friedman's repeated-measure ANOVA, $p < 0.0001$ in both groups), with all post-treatment values being significantly lower than those at baseline (Dunn's multiple comparison tests, $p < 0.05$; Figure 1a,b).

In the OM group, nine of 20 dogs (45%) had experienced a rebound in pruritus (i.e. an increase of more than one PVAS10 grade) on D21 compared to D14, the point at which the administration of oclacitinib was reduced in frequency from twice to once daily. In atopic dogs concurrently given 4 days of prednisolone, this proportion was significantly lower (three of 20, 15%; one-tailed Fisher's exact test, $p = 0.041$) at the same time point, than those receiving oclacitinib monotherapy. Consequently, the number-needed-to-treat (NNT), the rounded-up inverse of the difference in proportion between the two groups, was four. In other words, such a NNT means that one would have to treat four dogs with prednisolone to prevent one rebound compared to dogs treated with oclacitinib alone.

When comparing pruritus scores between interventions at each reevaluation visit, the D4 and D28 values in the PO group were significantly lower than those in the OM group (Wilcoxon–Mann–Whitney U-test, $p = 0.003$ and 0.041, respectively; Figure 2), as can be seen with the more homogeneous decline in PVAS10 on D4 in dogs that had received prednisolone (Figure 1a,b); differences in scores between groups were not significant at the other two post-treatment time points.

It is only on D4 that the proportion of dogs with normal-to-mild PVAS10 (PVAS10-N2M; COSCAD'18's outcome measure 2) was significantly—and almost twice—higher in the PO (17 of 20, 85%) than in the OM group (nine of 20, 45%; one-tailed Fisher's exact test, $p = 0.009$; Table 2).

Skin lesions

CADESI4 and CADESI4-E were significantly lower on D28 compared to those at baseline in both treatment groups (Wilcoxon matched-pair signed-rank tests, $p < 0.0001$).

While somewhat similar at baseline between groups (Table 1), CADESI4 and CADESI4-E were significantly lower in the PO than the OM group on D28 (Wilcoxon–Mann–Whitney U-test, $p = 0.045$ and 0.010, respectively; Figure 3a,b).

At the end of the study, the proportion of dogs with CADESI4 values in the range of normal dogs (CADESI4-N; COSCAD'18 outcome measure 1) was nearly twice higher in the PO (nine of 20, 45%) than in the OM group (five of 20, 25%), yet the difference in

TABLE 1 Baseline characteristics of all study participants (given as median with range in parentheses)

	OM	PO	*p*
Female:male (ratio)	10:10 (1.0)	8:12 (0.7)	0.751
Age (years)	4.0 (1.0–10.2)	4.3 (1.2–9.4)	0.253
Body weight (kg)	13.7 (4.8–35.0)	19.7 (6.1–37.0)	0.212
CADESI4	25 (10–103)	29 (11–113)	0.387
CADESI4-E	26 (7–56)	22 (7–50)	0.920
PVAS10	7.1 (2.0–9.0)	7.5 (4.9–9.5)	0.635
2D-IGA	3 (2–4)	3 (2–4)	0.890

Note: Ages and body weights, CADESIs, PVAS10, and 2D-IGA were compared by two-tailed nonparametric Wilcoxon–Mann–Whitney U-tests. The gender ratio was compared by a two-tailed Fisher's exact test.

Abbreviations: 2D-IGA, two-dimensional-Investigator Global Assessment; CADESI4, Canine Atopic Dermatitis Extent and Severity Index, 4th iteration; CADESI4-E, erythema component of CADESI4; OM, oclacitinib monotherapy; PO, prednisolone-oclacitinib; PVAS10, pruritus Visual Analog Score, 10th iteration.

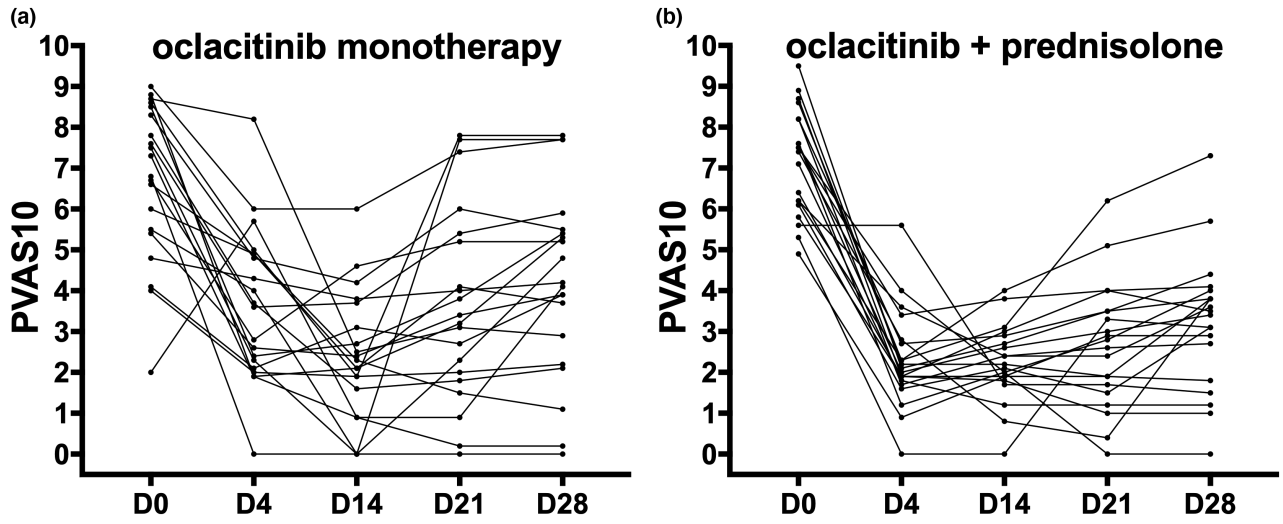

FIGURE 1 Evolution of pruritus visual analog score (PVAS)10 values over time. (a) Oclacitinib monotherapy (OM) group and (b) prednisolone-oclacitinib (PO) group. The reduction of scores was more homogeneous and rapid in dogs from the PO group on Day 4, when prednisolone's administration was stopped.

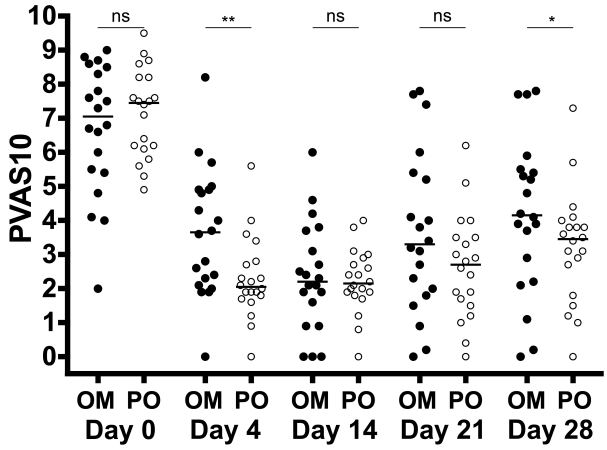

FIGURE 2 Comparison of pruritus visual analog score (PVAS)10 scores between groups. The PVAS10 values were significantly lower on Day (D)4 and D28 in the prednisolone-oclacitinib (PO) compared to the oclacitinib monotherapy (OM) group; bars = medians.

proportion between the two groups was not significant (p = 0.160; Table 2).

While the 2D-IGA extent-and-severity skin lesion scores were identical at baseline (Table 1), on D28 they were significantly lower (Wilcoxon–Mann–Whitney U-test, p = 0.001) in the PO [median (range): 2 (0–3)] than in the OM group [3 (0–3)]. However, at D28 the proportion of dogs with a 2D-IGA of clear-to-almost-clear (i.e. 0 or 1) and at least a two-grade improvement from baseline scores was twice higher (six of 20, 30%) in the PO than in the OM group (three of 20, 15%); this difference was not significant (p = 0.225), however.

Owners' global assessment of treatment efficacy

On D21 and D28, but not earlier, the OGATE scores were higher in the PO than the OM group (Wilcoxon–Mann–Whitney U-test, p = 0.002 and 0.006, respectively). A good-to-excellent treatment response (OGATE-G2E; COSCAD'18 outcome measure 3) was rated by owners of a significantly higher proportion of dogs in the PO than the OM group on both D21 and D28 (p = 0.016 and 0.011, respectively; Table 2).

Finally, as recommended in the COSCAD'18, we added, as an online supplementary material (Table S2), the number and percentage of dogs with CADESI4, CADESI4-E and PVAS10 values in the different categories of disease severity at each time point. Also included therein are the numbers and percentages of dogs with different OGATE scores over time.

TABLE 2 COSCAD'18 outcome measures

	OM	PO	*p*
PVAS10-N2M (Day 4)	9 (45%)	17 (85%)	**0.009**
PVAS10-N2M (Day 14)	15 (75%)	18 (90%)	0.204
PVAS10-N2M (Day 21)	11 (55%)	16 (80%)	0.088
PVAS10-N2M (Day 28)	6 (30%)	11 (55%)	0.100
CADESI4-N (Day 28)	5 (25%)	9 (45%)	0.160
OGATE-G2E (Day 4)	15 (75%)	18 (90%)	0.204
OGATE-G2E (Day 14)	16 (80%)	19 (95%)	0.171
OGATE-G2E (Day 21)	11 (55%)	18 (90%)	**0.016**
OGATE-G2E (Day 28)	8 (40%)	16 (80%)	**0.011**

Note: PVAS10-N2M: percentage of dogs with owner-assessed pruritus manifestation scores in the range of normal dogs or those with mild atopic dermatitis (AD) at study end (i.e. dogs with PVAS10 < 3.6).

Bold characters indicate a significant difference between groups.

CADESI4-N: percentage of dogs with veterinarian-assessed skin lesion scores in the range of normal dogs at study end (i.e. dogs with CADESI4 < 35).

OGATE-G2E: percentage of dogs whose owner rated the overall response to treatment as 'good' or 'excellent' (i.e. OGATE >2).

Per the recommendation of the COSCAD'18, we reported the CADESI4-N and not the CADESI4-N2M, as we enrolled dogs with mild-to-moderate AD skin lesions at baseline. As we had selected dogs with moderate-to-severe pruritus, we then reported the PVAS2-N2M.

Abbreviations: CADESI4, Canine Atopic Dermatitis Extent and Severity Index, 4th iteration; OGATE, Owner Global Assessment of Treatment Efficacy; PVAS10, pruritus Visual Analog Score, 10th iteration.

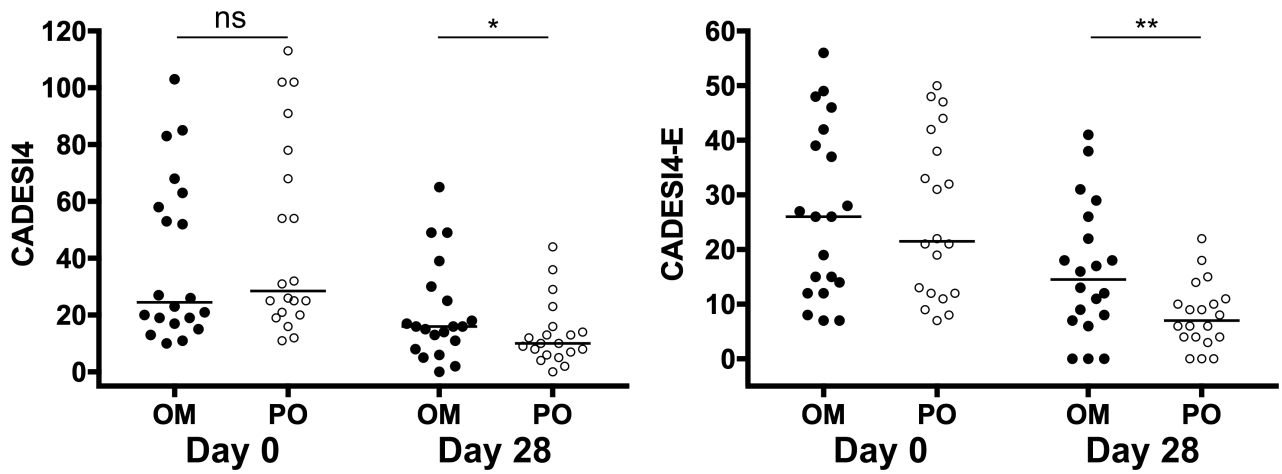

FIGURE 3 Comparison of canine atopic dermatitis extent and severity index, 4th iteration (CADESI4) and its erythema component CADESI4-E between groups. Both CADESI4 and its subset CADESI4-E were significantly lower on Day 28 in the prednisolone-oclacitinib (PO) compared to the oclacitinib monotherapy (OM) group; bars = medians.

Adverse events

Owners reported adverse events in one dog in the OM (vomiting) and five from the PO group [vomiting (two dog), diarrhoea (2), sleepiness (1) and polyuria-polydipsia (1)]. All adverse effects were minor, intermittent and spontaneously resolving; none necessitated symptomatic therapy or the interruption administration of oclacitinib or prednisolone. All adverse events are provided in Table S1.

DISCUSSION

Interpretation

In this 4-week trial, the concomitant administration of 4 days of prednisolone at the initiation of treatment with oclacitinib led to a significant reduction in the frequency of rebounds of pruritus by two-thirds. Furthermore, we observed that, compared to monotherapy with this JAKinib, the initial addition of glucocorticoids resulted in a greater reduction of owner-rated pruritus on D4 and D28, veterinarian-evaluated skin lesion scores on D28, and owner's global evaluation of treatment efficacy on D21 and D28.

For this trial, we had defined, as rebound, an increase of at least one PVAS10 grade, 1 week (i.e. D21) after reducing the frequency of administration of oclacitinib from twice to once daily (i.e. D14), per the approved use of this drug. Such a rebound threshold had been extrapolated from the average increase in PVAS10 values after dose reduction in three RCTs reporting the efficacy of oclacitinib in allergic dogs.[2–4]

Given the mechanism of action of both drug classes, it is not surprising that a short course of glucocorticoids can contribute to the improvement with JAKinib therapy for canine pruritus. On the one hand, JAKinibs can have a rapid effect on itch reduction due to their immediate inhibition of intracellular signalling following the binding of pruritogenic cytokines to their cognate receptors on sensory neurons.[14] On the other, in humans, chronic atopic skin lesions result from the complex interplay of resident and infiltrating cells that intercommunicate via countless mediators, cytokines and others, few of them using JAKinib-targetable JAK-associated receptors.[15–17] In this situation, however, glucocorticoids inhibit the production of most of the pro-inflammatory mediators present in AD skin, thus resulting in a broad and rapid cellular deactivation and anti-allergic clinical benefit.[7]

As mentioned above, the cessation of oclacitinib administration has been shown to increase the secretion of all measured cytokines [IL-31, TSLP and TNF-alpha] in the skin of mice challenged with a T-helper 2 (Th2)-inducing contactant.[5] In theory, in these mice, and probably in atopic dogs treated with oclacitinib, the temporary, concomitant administration of glucocorticoids at the time of JAKinib treatment induction should lead to an inhibition of cytokine gene transcription. As seen in our trial, the benefit of such an adjunctive therapy supports this hypothesis.

While our study was underway, another small RCT compared the efficacy of oclacitinib with or without the concurrent application of a topical glucocorticoid spray (hydrocortisone aceponate, Cortavance, Virbac).[18] In that trial, the PVAS10 increased significantly on D21 only in the group treated with oclacitinib and the placebo spray, and not in the group also receiving the topical hydrocortisone aceponate. Moreover, the simultaneous application of the topical glucocorticoid also led, as in our trial, to a significant reduction in skin lesion scores during the second half of that study as compared with the placebo control.[18] Altogether, the results of both trials, albeit involving a small number of dogs, support the benefit of concurrent short-term glucocorticoid therapy while initiating treatment with oclacitinib. We alluded to such a possible benefit in a recent editorial in this journal.[19]

Adverse effects

In this trial, we documented intermittent adverse events, which were more commonly seen in the PO than in the OM group. Outside the obvious polyuria-polydipsia (seen in one dog only) that can be attributed to the prednisolone, it is difficult to directly link

the development of gastro-intestinal signs to either of the two drugs administered. Indeed, as shown in the first placebo-controlled trial of oclacitinib monotherapy in dogs with AD, vomiting and diarrhoea were seen equally in both treatment groups.[2] In any case, all of these adverse events were mild, intermittent and spontaneously resolving, thus highlighting the minimal harm caused by oclacitinib or the dual therapy.

Limitations

In this trial, the short duration and small number of dogs were a limitation. However, the significant difference between groups in the primary outcome measure supported the validity of the original power calculation. Another limitation was the lack of blinding and masking of the intervention. However, the pet owner who graded the PVAS10 used for the primary outcome measure had not been made aware beforehand of the possible reductive effect of prednisolone on itch rebound.

Generalisability

We believe that the results of this trial are generalisable to most dogs with AD, as we had a nearly equal representation of both genders, the ages at enrolment mirror those of dogs with AD needing treatment, their skin lesion scores reflected mild-to-severe lesions, and their PVAS10 moderate-to-severe itch.

Implications for practice and research

Altogether, the results of this trial suggest the likely superior benefit of adding a short course of glucocorticoids when starting oclacitinib therapy. This will result in a lower risk of itch rebound when reducing the frequency of administration of this JAKinib, an improvement in skin lesions, and a higher perception of treatment efficacy by the owner in the second half of the first month of treatment. We recommend the performance of additional trials to evaluate the benefit of sequential (glucocorticoids-then-oclacitinib) or possibly longer concomitant glucocorticoid regimens in dogs with moderate-to-severe skin lesions.

AUTHOR CONTRIBUTIONS

Thierry Olivry: Conceptualisation; methodology; validation; formal analysis; visualisation; supervision; project administration; writing – original draft. **Viktorija Lokianskiene:** Investigation; methodology; writing – review and editing. **Alejandro Blanco:** Investigation; writing – review and editing. **Pablo Del Mestre:** Investigation; writing – review and editing. **Kerstin Bergvall:** Investigation; writing – review and editing. **Luc Beco:** Investigation; methodology; writing – review and editing.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Résumé

Contexte: Un rebond du prurit se produit occasionnellement après une réduction de la dose d'oclacitinib chez les chiens atteints de dermatite atopique (DA).

Objectifs: Déterminer si une cure initiale de quatre jours de prednisolone diminue la probabilité d'un rebond de prurit après réduction de la fréquence d'administration d'oclacitinib.

Animaux: Quarante chiens présentant des lésions de DA légères à modérées et un prurit modéré à sévère.

Matériels et méthodes: Des chiens ont été randomisés pour recevoir de l'oclacitinib à raison de 0,4 à 0,6 mg/kg deux fois par jour pendant 14 jours puis une fois par jour, seul ou avec de la prednisolone à 0,5 mg/kg, par voie orale, deux fois par jour pendant les quatre premiers jours. Les cliniciens ont évalué l'indice d'étendue et de gravité de la dermatite atopique canine (CADESI)4 et l'évaluation globale de l'investigateur 2D (IGA) avant et après 28 jours ; les propriétaires ont évalué l'échelle visuelle analogique du prurit (PVAS)10 et l'évaluation globale de l'efficacité du traitement par le propriétaire (OGATE) aux jours (J)0, J4, J14, J21 et J28. Nous avons considéré comme un rebond toute augmentation supérieure à un grade PVAS10 à J21 par rapport à J14.

Résultats: A J21, il y a eu significativement moins de rebonds chez les chiens ayant reçu de la prednisolone (trois sur 20, 15%) par rapport à ceux ayant reçu de l'oclacitinib seul (neuf sur 20, 45%) (test de Fisher, $p = 0,041$). Par rapport à l'oclacitinib en monothérapie, l'administration concomitante de prednisolone pendant les quatre premiers jours a entraîné une baisse significative de PVAS10 à J4 et J28, CADESI4 et 2D-IGA à J28, et OGATE à J21 et J28 (tests U de Wilcoxon-Mann-Whitney). Les effets indésirables du traitement étaient mineurs, intermittents et résolutifs.

Conclusions et pertinence clinique: L'ajout initial de quatre jours de prednisolone a significativement diminué la probabilité d'un rebond du prurit une semaine après la réduction de la dose d'oclacitinib. Cette courte administration concomitante de glucocorticoïdes a entraîné une amélioration plus importante des lésions cutanées et une meilleure perception de l'efficacité du traitement avec un minimum d'effets indésirables.

Resumen

Introducción: ocasionalmente se produce una recidiva del prurito después de la reducción de la dosis de oclacitinib en perros con dermatitis atópica (AD).

Objetivos: Determinar si un curso inicial de cuatro días de prednisolona disminuye la probabilidad de una recidiva del prurito después de reducir la frecuencia de administración de oclacitinib.

Animales: Cuarenta perros con lesiones de AD de leves a moderadas y prurito de moderado a severo.

Materiales y métodos: los perros se distribuyeron al azar para recibir oclacitinib a 0,4–0,6 mg/kg dos veces al día durante 14 días, luego una vez al día, solo o con prednisolona a 0,5 mg/kg, por vía oral, dos veces al día durante los primeros cuatro días. Los veterinarios calificaron el índice de extensión y severidad de la dermatitis atópica canina (CADESI)4 y la evaluación global 2D del investigador (IGA) antes y después de 28 días; los propietarios evaluaron la escala análoga visual de prurito (PVAS)10 y la evaluación global del propietario de la eficacia del tratamiento (OGATE) en el día (D)0, D4, D14, D21 y D28. Consideramos una recidiva cualquier aumento superior a un grado PVAS10 en D21 en comparación con D14.

Resultados: En el D21, hubo significativamente menos recidivas en los perros que recibieron prednisolona (tres de 20, 15 %) en comparación con los que recibieron oclacitinib solo (nueve de 20, 45 %) (prueba de Fisher, $p = 0{,}041$). En comparación con la monoterapia con oclacitinib, la administración concomitante de prednisolona durante los primeros cuatro días condujo a una PVAS10 significativamente más baja en D4 y D28, CADESI4 y 2D-IGA en D28, y OGATE en D21 y D28 (prueba U de Wilcoxon-Mann-Whitney). Los efectos adversos de la terapia fueron menores, intermitentes y de resolución automática.
Conclusiones y relevancia clínica: La adición inicial de cuatro días de prednisolona disminuyó significativamente la probabilidad de una recidiva de prurito una semana después de la reducción de la dosis de oclacitinib. Esta breve administración concomitante de glucocorticoides condujo a una mejoría de las lesiones cutáneas y también mejoró la percepción de la eficacia del tratamiento con efectos adversos mínimos.

Zusammenfassung
Hintergrund: Gelegentlich kommt es bei Hunden mit atopischer Dermatitis (AD) nach der Reduktion von Oclacitinib zu einem Rebound des Pruritus.
Ziele: Das Ziel war es festzustellen, ob eine vier tägige Initialbehandlung mit Prednisolon die Wahrscheinlichkeit eines Rebounds des Pruritus bei Reduzierung der Frequenz der Oclacitinib Verabreichung vermindern würde.
Tiere: Vierzig Hunde mit mild bis moderaten AD-Läsionen und moderat bis hochgradigem Pruritus.
Materialien und Methoden: Die Hunde wurden zufällig in Gruppen eingeteilt, um Oclacitinib bei einer Dosierung von 0,4-0,6 mg/kg zunächst zweimal täglich 14 Tage lang, dann einmal täglich zu erhalten; allein oder mit Prednisolon bei einer Dosis von 0,5 mg/kg, *per o*s, zweimal täglich für die ersten vier Tage. KlinikerInnen bewerteten mittels Canine Atopic Dermatitis Extent und Severity Index (CADESI)4 und 2D-Investigator Global Assessment (IGA) vor und nach 28 Tagen; die BesitzerInnen beurteilten den Juckreiz mittels Visual Analog Scale (PVAS)10 und Owner Global Assessment of Treatment Efficacy (OGATE) am Tag (D)0, D4, D14, D21 und D28. Als Rebound wurde jede Zunahme bewertet, die größer war als ein PVAS10 Grad am D21 im Vergleich zu D14.
Ergebnisse: Am D21 bestanden signifikant weniger Rebounds bei den Hunden, die Prednisolon (drei von 20; 15%) erhielten im Vergleich zu jenen, die Oclacitinib alleine (neun von 20; 45%) (Fisher´s Test, $p = 0{,}041$) bekamen. Im Vergleich zu Oclacitinib Monotherapie führt die gleichzeitige Verabreichung von Prednisolon für die ersten vier Tage zu signifikant niedrigeren PVAS10 Werten am D4 und D28, CADESI4 und 2D-IGA am D28, und OGATE am D21 und D28 (Wilcoxon-Mann-Whitney U-Tests). Nebenwirkungen waren gering, vorübergehend und verschwanden von selbst.
Schlussfolgerungen und klinische Bedeutung: Die anfängliche Zugabe von Prednisolon für vier Tage reduzierte die Wahrscheinlichkeit eines Pruritus Rebounds eine Woche nach Dosisreduzierung des Oclacitinib signifikant. Diese kurze gleichzeitige Glukokortikoid Verabreichung führte zu einer rascheren Verbesserung der Hautveränderungen und verbesserte die Wahrnehmung der Behandlungseffizienz mit minimalen Nebenwirkungen.

要約
背景: アトピー性皮膚炎(AD)の犬において、オクラシチニブ減量後に掻痒のリバウンドが生じることがある。
目的: 本研究の目的は、オクラシチニブの投与頻度を減らした後、プレドニゾロンの4日間投与により、掻痒のリバウンドが生じる確率が減少するかどうかを検討することであった。
対象動物: 軽度から中等度のAD病変を有し、中等度から重度の掻痒を有する犬40頭。
材料と方法:　対象犬を、オクラシチニブ0.4~0.6mg/kgを1日2回14日間投与後、オクラシチニブ1日1回単独で、またはプレドニゾロン0.5mg/kgを1日2回、最初の4日間経口投与する方法のどちらかに無作為に分けた。臨床医は28日前後に犬アトピー性皮膚炎の程度および重症度指数(CADESI)4および2D-調査者グローバル評価(IGA)を評価し、飼い主は0日(D0)、D4、D14、D21およびD28に痒みの視覚的アナログスケール(PVAS10)および治療効果に関するグローバル評価(OGATE)を評価した。D14と比較してD21でPVAS10が1段階以上上昇した場合、リバウンドとした。
結果:　D21において、プレドニゾロン投与群(20頭中3頭、15%)では、オクラシチニブ単独投与群(20頭中9頭、45%)と比較してリバウンドが有意に少なかった(Fisher's test、p=0.041)。オクラシチニブ単剤療法と比較して、最初の4日間のプレドニゾロン同時投与により、D4およびD28のPVAS10、D28のCADESI4および2D-IGA、D21およびD28のOGATEが有意に低下した(Wilcoxon-Mann-Whitney U-tests)。治療による有害事象は軽微で、断続的であり、自己回復的であった。

結論と臨床的意義: 最初の4日間のプレドニゾロン加療により、オクラシチニブ減量1週間後の痒みのリバウンドの発生率が有意に減少した。この短期間のグルココルチコイド併用投与により、皮膚病変の改善度が高く、有害事象も少なく治療効果の認識も改善された。

摘要

背景: 患有特应性皮炎 (AD) 的犬在降低奥拉替尼剂量后 , 偶尔会出现瘙痒反弹。

目的: 确定泼尼松龙初始4天疗程是否可降低奥拉替尼给药频率后瘙痒反弹的概率。

动物: 40只患有轻度至中度 AD 病变和中度至重度瘙痒的犬。

材料和方法: 犬随机接受奥拉替尼0.4–0.6 mg/kg每日两次给药14天 , 单独给药 , 或者前4天同时泼尼松龙0.5 mg/kg每日两次经口给药。临床医生在28天之前和之后对犬特应性皮炎程度和严重指数 (CADESI)4 和 2D 研究者整体评估 (IGA) 进行分级 ; 犬主人在第 (D)0、D4、D14、D21和 D28 天评估瘙痒视觉模拟量表 (PVAS)10 和犬主人治疗有效性整体评估 (OGATE)。我们认为与 D14 相比 , D21时 PVAS10 等级的任何反弹增加均大于1级。

结果: 在D21 , 接受泼尼松龙的犬反弹 (3/20 , 15%) 显著少于接受奥拉替尼单药的犬 (9/20 , 45%)(Fisher检验 , p = 0.041)。与奥拉替尼单药治疗相比 , 在前4天同时给予泼尼松龙导致 D4 和 D28 时PVAS10、D28时 CADESI4 和 2D-IGA 以及 D21 和 D28 时 OGATE 显著降低(Wilcoxon–Mann–Whitney U检验)。治疗的不良反应为轻微、间歇发生和可自愈。

结论和临床相关性: 初始加用4天泼尼松龙显著降低了奥拉替尼减量后1周瘙痒反弹的概率。这种短期伴随糖皮质激素给药导致更有好的皮肤病变改善 , 以及更显著地感知治疗疗效 , 不良反应极小。

Resumo

Contexto: Após a redução da dose de oclacitinb, ocasionalmente ocorre um efeito rebote de prurido nos cães com dermatite atópica (DA).

Objetivos: Determinar se um curso inicial de quatro dias de prednisolona é capaz de reduzir a probabilidade de um efeito rebote de prurido após reduzir a frequência de administração de oclacitinib.

Animais: Quarenta cães com lesões leves a moderadas de DA e prurido moderado a intenso.

Materiais e Métodos: Os cães foram divididos aleatoriamente para receber oclacitinib na dose de 0,4-0,6 mg/kg duas vezes ao dia por 14 dias e depois uma vez ao dia, isoladamente ou associado à prednisolona na dose de 0,5 mg/kg, por via oral, duas vezes ao dia nos primeiros quatro dias. Os clínicos utilizaram o Índice de Extensão e Gravidade da Dermatite Atópica Canina (CADESI)4 e a avaliação global do investigador 2D (IGA) antes e após 28 dias; os proprietários utilizaram a Escala Visual Analógica de Prurido (PVAS)10 para avaliar o prurido e a Avaliação Global da Eficácia do Tratamento pelo Proprietário (OGATE) no Dia (D)0, D4, D14, D21 e D28. Consideramos um rebote qualquer aumento maior que um grau no PVAS10 no D21 comparado ao D14.

Resultados: No D21, houve significativamente menos rebotes nos cães que receberam prednisolona (três de 20, 15%) em comparação com aqueles que receberam oclacitinib isoladamente (nove de 20, 45%) (teste de Fisher, $p = 0{,}041$). Em comparação à monoterapia com oclacitinib, a administração concomitante de prednisolona nos primeiros quatro dias levou à redução significativa de PVAS10 em D4 e D28, CADESI4 e 2D-IGA em D28 e OGATE em D21 e D28 (testes U de Wilcoxon-Mann-Whitney). Os efeitos adversos da terapia foram mínimos, intermitentes e auto-limitantes.

Conclusões e relevância clínica: A inclusão inicial de quatro dias de prednisolona diminuiu significativamente a probabilidade de rebote do prurido uma semana após a redução da dose de oclacitinib. Esta curta administração concomitante de glicocorticoides levou a uma melhor resposta na redução das lesões cutâneas e melhor percepção da eficácia do tratamento com efeitos adversos mínimos.