Veterinary Dermatology

Vet Dermatol 2016; **27**: 22–e7 DOI: 10.1111/vde.12278

Repeated oral dose tolerance in dogs treated concomitantly with ciclosporin and oclacitinib for three weeks

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Background – Ciclosporin and oclacitinib are immunomodulators approved for the treatment of canine atopic dermatitis. The administration of a short course of prednisolone at the beginning of ciclosporin therapy hastens the efficacy of this drug; oclacitinib has a rapid antipruritic effect similar to that of prednisolone.

Objectives – To evaluate the oral tolerance of oclacitinib and ciclosporin given concurrently for three weeks.

Animals – Two groups of eight beagles.

Methods – Dogs were randomized to receive oclacitinib alone (0.4–0.6 mg/kg twice daily for 14 days then once daily for seven days) or in combination with ciclosporin (5 mg/kg once daily) for three weeks. They were examined every day and adverse events were recorded. Blood samples were collected during the acclimatization phase, weekly during treatment and at the end of the study for haematology, clinical chemistry and coagulation evaluation.

Results – There were no abnormal clinical observations following treatment with oclacitinib given alone or concomitantly with ciclosporin, with the exception of diarrhoea in two dogs receiving both drugs. Three dogs from each group experienced transient inappetence; three dogs treated with oclacitinib had mild weight loss. Clinical pathology parameters remained within the reference range for beagle dogs at that facility.

Conclusions and clinical importance – The concomitant administration of ciclosporin and oclacitinib for three weeks to beagles was well tolerated and was not associated with an increase in the number of adverse events or laboratory abnormalities beyond those associated with oclacitinib given alone.

Introduction

Ciclosporin is a cyclic polypeptide with reversible immunosuppressive properties that targets, via its inhibition of calcineurin, T-lymphocytes and other cells involved in allergic and immunological responses.[1–3] Ciclosporin (Atopica, Novartis Animal Health; Basel, Switzerland) has been used also for treatment of canine atopic dermatitis (AD) and for other canine skin diseases such as perianal fistulae and sebaceous adenitis.[3] A systematic review of clinical trials enrolling dogs with AD reported the relatively slow onset of effect of ciclosporin, with skin lesion and pruritus scores abating by 30–52% and 27–34% after four weeks of treatment, respectively.[4] To provide a faster relief of the clinical signs of AD, the concomitant administration of oral glucocorticoids at the onset of treatment with ciclosporin has been proposed.[5] A randomized controlled trial has validated this concept, establishing that the addition of prednisolone at 1 mg/kg once daily for one week, then every other day for two weeks, markedly increased the magnitude of benefit of ciclosporin in the first month of treatment compared to ciclosporin given alone.[6]

Oclacitinib (Apoquel, Zoetis; Florham Park, NJ, USA) is a novel janus kinase (JAK1)-predominant inhibitor that prevents cell signalling following the binding of proallergic, proinflammatory and pruritogenic cytokines to their respective receptors.[7] Oclacitinib has been reported as being rapidly effective in reducing pruritus and skin lesions in dogs with allergic dermatitis[8] and with AD.[9] The speed of pruritus relief with oclacitinib is parallel to that of prednisolone, with visible improvement in itch manifestations noted within the first day of administration of both drugs.[10] When tested against ciclosporin in a randomized controlled trial, oclacitinib provided a faster reduction in pruritus, with a similar effect in improving skin lesions over time.[11]

Given the comparable anti-allergic effect of prednisolone and oclacitinib,[10] and the clinical benefit of adding prednisolone in the first three weeks of ciclosporin administration,[6] the question arises whether the concomitant administration of oclacitinib during the first

Accepted 12 October 2015
Previous Presentation: Results of the study reported herein were presented at the pre-congress day of the British Small Animal Veterinary Association congress in April 2015 and as a poster at the 2015 ESVD-ECVD congress in Krakow, Poland
Vet Dermatol 2015; **26**: 303 (abstract).
Sources of Funding: This study was funded by Elanco Animal Health, Basel, Switzerland.
Conflict of Interest: At the time of study performance all authors were employees of Elanco Animal Health.

weeks of ciclosporin treatment would be safe. If proven to be well-tolerated, using both drugs concurrently during the first month of ciclosporin therapy may be beneficial to dogs with AD.

The objective of this study was to evaluate the oral tolerance and safety of oclacitinib and ciclosporin given simultaneously once daily for three weeks to beagle dogs.

Materials and methods

Study design

This study was designed as a non-Good Laboratory Practice, nonterminal, randomized, open, parallel experiment involving two groups of eight dogs. In the first group (OC group), dogs were treated with oclacitinib (Apoquel, Zoetis) concomitantly with ciclosporin (Atopica, Novartis), whereas the second group of dogs received oclacitinib alone (O group). Swiss national animal welfare legislation was followed and local ethical approval was obtained prior to starting the study.

Animals and management

All study dogs were beagles (eight males, eight females; all intact), aged between 11 months and 4 years and weighing between 9 and 13 kg at enrolment. After acclimatization, dogs were housed in the same group and gender pairs except during the time of drug administration when they were housed individually for up to 5 h per day to facilitate the recording of individual daily feed consumption and to conduct post-treatment clinical assessments. The dogs were fed commercial dog food once daily in relation to their daily body weight whereas water was provided *ad libitum*. On completion of the study, all dogs were returned to their normal housing facilities. Dogs were considered suitable for inclusion in the study if, following a physical examination and clinical pathology assessment (haematology, clinical chemistry and coagulation panels), they were considered healthy. They had not received any anti-inflammatory product in the preceding 2 months.

Treatment administration

Dogs were randomly allocated by computer to the OC or O groups according to their gender and body weight to maintain an effective pairing of four males and four females of comparable weight range in each group.

Day 0 was defined as the first day of dosing. Treatment was administered orally (after feeding for the morning dose) at dosages approved for each drug using the most recently recorded body weight. In the OC and O groups, dogs received oclacitinib, between 0.4 and 0.6 mg/kg twice daily for 14 days, then every morning for 7 d. Ciclosporin was given to dogs from the OC group at 5 mg/kg once in the morning. Following oral dosing, each dog was administered 5–10 mL of water orally by syringe and the oropharynx was examined to confirm that the tablet or capsule had been swallowed.

Observations

A complete physical examination was performed by a veterinarian during the acclimatization and at the end of the treatment period (Day 21). Physical examination included the general appearance (behaviour, body weight and hydration), integument and mucous membranes (colour and vascular filling time), heart and lung auscultation (sounds and rhythm), body temperature, oral cavity, eyes, nares, ears, central nervous system (equilibrium, coordination, muscular use and reflexes), glands and lymph nodes.

During the treatment period, each dog was examined approximately 3 h after each morning dosing. These clinical observations included a subjective monitoring of the dog's general health status, integument, nervous, musculoskeletal, ocular, gastrointestinal and cardiovascular systems, as well as an assessment of the animal's behaviour. Dogs were weighed, pre-feeding, twice weekly throughout the treatment phase of the study.

Adverse events

Adverse events (AE), were considered to be any observations that were unfavourable or unintended, and which occurred after the use of test medications, whether or not they were considered related to the tested drugs. The investigators recorded the AE duration, type (i.e. clinical sign), severity (serious or not serious), outcome (complete recovery, recovery with sequelae, death or other), action taken (concomitant medication, withdrawal or continuation of the dog on the study or test medicine administration) and causality assessment (probable, possible, unlikely, unclassifiable/not assessable).

Clinical pathology

Blood samples were collected from every dog during the acclimatization phase (Day −6 to Day 0), weekly during treatment (days 3, 10 and 17) and at the end of the study (Day 21). Overnight fasting blood samples were collected into ethylenediaminetetraacetic acid (EDTA) for haematology, serum gel tubes for clinical chemistry and sodium citrate for coagulation parameters. Blood samples were analysed in the clinical pathology laboratory of the test facility for the parameters detailed in Table S1. Reference ranges for clinical pathology parameters had been established recently from this colony of beagle dogs.

Statistical analyses

The daily observed food consumption values were transformed as weekly averages for each individual. Body weight, food consumption and clinical pathology (haematology, clinical chemistry and coagulation) parameters were reported as descriptive statistics (mean, median and standard deviation) and analysed using repeated-measures analysis of covariance (RMANCOVA) using statistics software (SAS v9.2.2, SAS; Cary, NC, USA). The average of two or more pretreatment values was included in the models as a covariate. The fixed factors in the models were treatment group and sex, whereas the repeated factor was time (i.e. study day). The two factor interactions (treatment × sex, treatment × time and sex × time) and the three factor interaction (treatment × sex × time) were also included. The following SAS procedures were used: "MIXED" for analysis with the covariance structures "AR(1)" and "ARH(1)" for data collected on equal intervals, spatial power covariance structure "SP(POW)" for data collected on unequal intervals, and "CS" and "CSH" for data collected at both equal and unequal intervals. We chose to report results from the model with the smallest Akaike's information criterion (i.e. those of best quality for a given set of data); for all pairwise comparisons, the chosen threshold for significance was $P = 0.05$.

Results

Animals and treatments

All treatments were successfully administered, with dogs in both groups receiving one or both drugs according to the study design except for one deviation: one dog from the OC group received a 3% higher dosage of oclacitinib (0.62 mg/kg) for nine consecutive doses (days 4–8) due to weight loss.

Observations

There were no deaths, withdrawals or abnormal clinical observations made following treatment with oclacitinib given alone or concomitantly with ciclosporin, with the exception of diarrhoea observed in two dogs in the OC group. One dog exhibited diarrhoea within 3 h after both morning and evening doses on Day 2; the other had a single episode of diarrhoea within 3 h of the morning dose on Day 17.

Food consumption and body weight

Food consumption was not significantly different between groups. Three dogs in each treatment group demonstrated a moderate transient inappetence (Figure S1). Their appetite fluctuated throughout the study with dogs eating at least 64% (Group OC) or 75% (Group O) of the food offered each day. Altogether there were no significant differences between treatment groups in regards to body weight. Mild weight loss was observed during the acclimatization and dosing phases in one dog from the OC group and in three dogs from the O group; two of these three dogs concurrently showed inappetence whereas the others entirely consumed their daily food.

Clinical pathology

Haematology

There were no significant differences in haematological parameters between groups. Any changes in values observed were considered not clinically relevant (Table S2).

Clinical chemistry

During the pre-treatment acclimatization period (Day −6 to Day 0), one male dog had increased creatine kinase (851 U/L; reference range: 85–450 U/L) and lactate dehydrogenase activity levels (315 U/L; reference range: 30–253 U/L). These were not associated with abnormal clinical signs and were not considered relevant; this dog was subsequently randomized to the O group.

Only two parameters were significantly different when compared between the dogs of both treatment groups:

1. Alanine aminotransferase activity levels were significantly lower in males from the OC (mean: 24 U/L, reference range: 15–50 U/L) than those from the O group (mean: 36 U/L) ($P = 0.05$).
2. Blood urea nitrogen was significantly higher in dogs from the OC (mean: 4.8 mmol/L; reference range: 3.1–7.0 mmol/L) than those from the O group (mean: 4.3 mmol/L) ($P = 0.03$).

In spite of these significant differences, individual values from all parameters always remained within the reference range for beagle dogs held at this facility (Table S3).

Otherwise, and apart from the minor changes reported above, there were no significant differences in clinical chemistry values between the OC and O treatment groups.

Coagulation

There were no statistically significant differences for either prothrombin time, activated partial thromboplastin times or fibrinogen between dogs from the OC and O groups. All values always remained within the reference range for beagle dogs from this facility (Table S4).

Discussion

In this study, we established that the concomitant administration of ciclosporin and oclacitinib, when given according to their manufacturer's instructions for three consecutive weeks, was very well tolerated in beagle dogs. This study was not blinded and whilst observations were made by staff unaware of treatment allocation, we cannot exclude that bias might have occurred. Furthermore, this study involved small numbers (eight per treatment group) of a single breed of dogs (beagle); it will only be when this combination of drugs is used widely in the field, under a variety of conditions and in a range of dog breeds and ages, that the full safety of concomitant treatment with oclacitinib and ciclosporin will be known.

With the exception of one dog, all study subjects received both drugs within approved dosage ranges. The last dog, treated with both drugs, had a body weight that decreased below the minimum weight intended for the 5.4 mg oclacitinib tablet. As a result he received 0.62 mg/kg of the drug for nine consecutive doses before being changed to a 3.6 mg oclacitinib tablet (a 3.3% increase on the maximum approved dosage range). In this dog, however, no adverse events or significant changes in clinical pathology were observed at any time during the study.

Both ciclosporin and oclacitinib have been reported to cause minor adverse events when given as monotherapy to dogs with AD.[4,12] The administration of either of these drugs is associated with transient gastrointestinal disturbances including vomiting, diarrhoea or inappetance/anorexia.[4,11,12] In this study, soft stools were observed on Day 2 in one dog and on Day 17 in another dog; both receiving the two drugs concurrently.

Whilst a decrease in food intake was observed in dogs from both groups during this study, it is unclear if the decrease in food ingestion was due to reduced appetite or to a confounding management factor, as this was observed only during weekends when dogs were fed by different personnel. As similar transient reductions in food intake also had been observed before treatment commenced, this phenomenon was felt to be unlikely due to treatment.

Some dogs in both treatment groups showed mild body weight loss during the study, although the differences in body weights between groups were not significant. These small decreases in body weight could, in part or *in toto*, be due to the decreased food intake discussed above. Apart from this transient weight loss, there were no other reports of adverse events in this study.

In a randomized controlled trial comparing the efficacy and safety of ciclosporin and oclacitinib given alone to dogs with AD, occasional dogs treated with either drug exhibited mild changes in haematology or clinical chemistry parameters, even though the mean values for both treatment groups remained in the reference ranges.[11] The lack of consistent changes in clinical pathology parameters after the administration of ciclosporin for treatment of AD has also been documented in a compilation of previously published trials.[13] Similarly, relevant changes in clinical pathology values were not found in dogs treated with oclacitinib in the long term.[12] In the present study, evaluated haematology and coagulation parameters remained in the reference range established for beagles kept at this research facility; significant differences in values between groups were not observed.

Minor changes in two chemistry parameters (alanine aminotransferase and blood urea nitrogen) were found to be significantly different between the two treatment groups, but as values were still in the reference range for beagles and were not associated with any visible adverse events, they were not deemed to be clinically relevant.

This study demonstrated that the concomitant administration of ciclosporin and oclacitinib for three weeks to beagle dogs was very well tolerated and did not increase the frequency or severity of abnormal clinical signs or laboratory abnormalities beyond the rare changes associated with the administration of oclacitinib alone. Whether or not these findings can be extrapolated to dogs of other breeds and/or to dogs with AD is not known, but there are no reasons suggesting the opposite. Furthermore, as drug blood levels were not monitored in this trial, any interaction between the metabolisms of ciclosporin and oclacitinib would not be detected; the eventuality of such interaction should be evaluated in pharmacological studies. Nevertheless, oclacitinib appears to be a suitable alternative to prednisolone for combination therapy during the induction of treatment with ciclosporin in dogs with AD.

Acknowledgements

The authors acknowledge the help of Sophie Gerber, Francois Aleman and Jeanine Perriard-Fasel for the performance of this study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Mean percentage of total food offered that was consumed in both groups over time. Bar represents the standard deviation.

Table S1. Evaluated clinical pathology parameters.

Table S2. Haematology parameters.

Table S3. Clinical chemistry parameters.

Table S4. Coagulation parameters.

Résumé

Contexte – La cyclosporine et l'oclacitinib sont des immunomodulateurs approuvés dans le traitement de la dermatite atopique canine. L'administration de prednisolone sur une courte période en début de traitement à la ciclosporine accélère l'efficacité de ce traitement; l'oclacitinb a un effet antiprurigineux rapide similaire à celui de la prednisolone.

Objectifs – Déterminer la tolérance orale de l'oclacitinib associé à la ciclosporine pendant 3 semaines.

Sujets – Deux groupes de huit beagles.

Méthodes – Les chiens étaient randomisés pour recevoir l'oclacitinib seule (0.4–0.6 mg/kg deux fois par jour pendant 14 jours puis une fois par jour pendant 7 jours) ou en combinaison avec la ciclosporine (5mg/kg une fois par jour) pendant 3 semaines. Un examen clinique était réalisé chaque jour et les effets indésirables enregistrés. Les échantillons sanguins ont été collectés au cours de la phase d'acclimatation, chaque semaine pendant le traitement et à la fin de l'étude pour une évaluation hématologique, biochimique et de la coagulation.

Résultats – Il n'y avait pas d'observations cliniques anormales à la suite du traitement avec oclacitinib donné seul ou associé à la ciclosporine à l'exception de diarrhée pour deux chiens recevant les deux traitements. Trois chiens de chaque groupe ont montré une inappétence transitoire; trois chiens traités avec de l'oclacitinb avaient une perte de poids modérée. Les paramètres sanguins restaient dans les normes pour des beagles.

Conclusions et importance clinique – L'administration concomitante de ciclosporine et d'oclacitinib pendant 3 semaines à des beagles a été bien tolérée et n'a pas été associée avec une augmentation du nombre d'effets indésirables ou d'anomalies de laboratoire hormis ceux observés chez les chiens recevant la ciclosporine seule.

Resumen

Introducción – la ciclosporina y el oclacitinib son inmunomoduladores aprobados para el tratamiento de la dermatitis atópica canina. La administración de prednisolona por un corto de tiempo al principio de la terapia con ciclosporina aumenta la eficacia de este fármaco; el oclacinitib tiene un efecto antipruriginoso rápido similar al de la prednisolona.
Hipótesis/Objetivos – evaluar la tolerancia oral de oclacitinib y ciclosporina administrados de forma conjunta durante tres semanas
Animales – dos grupos de ocho perros de raza Beagle.
Métodos – los perros se distribuyeron al azar para recibir oclacitinib sólo (0,4-0,6 mg/kg dos veces al día durante 14 días y después una vez al día durante siete días) o en combinación con ciclosporina (5 mg/kg una vez al día) durante tres semanas. Los perros se examinaron cada día y se anotaron los efectos adversos. Se tomaron muestras de sangre durante la fase de aclimatación, semanalmente durante el tratamiento, y al final del estudio para evaluación de hematología, bioquímica clínica y coagulación.
Resultados – no hubo observaciones de anomalías clínicas tras el tratamiento con un oclacitinib administrado por sí solo o conjuntamente con ciclosporina, con la excepción de diarrea en dos perros que recibieron ambos fármacos. Tres perros de cada grupo experimentaron inapetencia transitoria; tres perros tratados con oclacitinib presentaron ligera pérdida de peso. Los parámetros de la bioquímica clínica permanecieron dentro de los rangos de referencia para los perros de raza Beagle en estas instalaciones.
Conclusión e importancia clínica – la administración conjunta de ciclosporina y oclacitinib durante tres semanas a perros de raza Beagle fue bien tolerada y no estuvo asociada con incremento en el número de efectos adversos o de anomalías laboratoriales más allá de las asociadas con la administración de oclacitinib por sí solo.

Zusammenfassung

Hintergrund – Ciclosporin und Oclacitinib sind Immunmodulatoren, die für die Behandlung der atopischen Dermatitis des Hundes zugelassen sind. Die kurzfristige Verabreichung von Prednisolon am Beginn einer Behandlung mit Ciclosporin beschleunigt die Wirksamkeit des Medikaments; Oclacitinib hat eine rasche juckreizstillende Wirkung, die jener von Prednisolon ähnlich ist.
Ziele – Eine Evaluierung der oralen Toleranz von Oclacitinib und Ciclosporin bei gleichzeitiger Gabe von 3 Wochen.
Tiere – Zwei Gruppen von je acht Beagles.
Methoden – Die Hunde wurden zufällig eingeteilt, um Oclacitinib alleine (0,4-0,6 mg/kg zweimal täglich für 14 Tage, dann einmal täglich für 7 Tage) oder in Kombination mit Ciclosporin (5mg/kg einmal täglich) für 3 Wochen zu erhalten. Die Tiere wurden täglich untersucht und Nebenwirkungen festgehalten. Während dieser Akklimatisierungsphase wurden Blutproben wöchentlich untersucht. Während der Behandlung und am Ende der Studie wurden hämatologische, biochemische und Koagulierungsparameter festgehalten.
Ergebnisse – Es gab keine abnormalen klinischen Beobachtungen wenn Oclacitinib alleine oder gemeinsam mit Ciclosporin gegeben wurde. Eine Ausnahme machten zwei Hunde, die bei Verabreichung beider Medikamente Durchfall bekamen. Drei Hunde aus jeder Gruppe zeigten vorübergehende Inappetenz; drei Hunde, die mit Oclacitinib behandelt wurden, zeigten einen geringen Gewichtsverlust. Die klinisch-pathologischen Parameter blieben innerhalb der Referenzwerte für Beagle der Klinik.
Schlussfolgerungen und klinische Bedeutung – Die 3 Wochen dauernde gleichzeitige Verabreichung von Ciclosporin und Oclacitinib wurde gut vertragen und konnte nicht mit zunehmenden Nebenwirkungen oder Abweichungen der Laborwerte über jene bei alleiniger Oclacitinib Verabreichung hinaus in Zusammenhang gebracht werden.

要約

背景 — シクロスポリンおよびオクラシチニブはイヌアトピー性皮膚炎の治療のために承認された免疫調節剤である。シクロスポリン療法の開始時のプレドニゾロンの短期投与はこの薬剤の効果を早める。オクラシチニブはプレドニゾロンと同様に急速な抗そう痒効果がある。
目的 — オクラシチニブとシクロスポリンを3週間併用した際の経口寛容性を評価することである。
供与動物 — 8頭のビーグルからなる2つのグループ。
方法 — イヌにオクラシチニブ単独(1日2回0.4–0.6 mg/kgを14日、その後1日1回で7日間)あるいは、シクロスポリン(1日1回5 mg/kg)との併用で3週間、ランダムに投与した。イヌを毎日検診し、有害事象を記録した。血液サンプル

を血液学、臨床化学、ならびに血液凝固の評価を行うために順化段階中、治療中に週1回、および試験の最後に採取した。
結果 — オクラシチニブ単独あるいはシクロスポリンとの併用治療による異常な臨床事象は、両方の薬剤を投与していた2頭のイヌで生じた下痢を除いて、認められなかった。それぞれの群で3頭ずつ一過性の食欲不振を示し、オクラシチニブ治療中の3頭では軽度の体重減少がみられた。臨床病理学的なパラメーターはその施設のビーグルの正常範囲内であった。
結論および臨床的な重要性 — 3週間に渡るビーグルへのシクロスポリンおよびオクラシチニブの併用投与はよく寛容され、オクラシチニブ単独で投与した時以上の有害事象や検査上の異常値の数の上昇は認められなかった。

摘要
背景 — 免疫调节剂环孢素和奥拉替尼经审批可用于治疗犬异位性皮炎。在环孢素治疗初期,短时间使用泼尼松龙能够增强药物疗效;奥拉替尼与泼尼松龙一样有快速止痒的作用。
目的 — 同时经口给予环孢素和奥拉替尼三周,评估其耐受性。
动物 — 两组、共八只比格犬。
方法 — 随机选择犬只单独口服奥拉替尼(0.4–0.6 mg/kg,前14天每日两次,后七天每日一次)或同时口服环孢素(5 mg/kg,每日一次)连续三周。每三天检测一次并记录不良反应。在适应期、治疗期间的每周以及研究结束时,分别采集血样进行血液学、临床生化和血凝试验等检测。
结果 — 除了同时服用两种药物有两只犬出现腹泻外,无论单独服用奥拉替尼或与环孢素联合服用,治疗均没有异常临床表现。每组有三只犬有短暂的食欲不振;单独口服奥拉替尼组的3只犬有轻微的体重减轻。比格犬在检测上的临床病理学参数保持在参考范围内。
总结和临床意义 — 比格犬联合使用奥拉替尼和环孢素三周有较好的耐受性,与单独给予奥拉替尼组相比,未出现不良反应增多或实验室异常。