

Complementary effect of oral administration of *Lactobacillus paracasei* K71 on canine atopic dermatitis

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Background – Atopic dermatitis is a common skin disease encountered in dogs. Glucocorticoids are commonly recommended for symptomatic therapy and well-tolerated adjunctive therapies may help to reduce the necessary dose and associated risks of chronic glucocorticoid use.

Hypothesis/Objectives – The purpose of this study was to evaluate the complementary efficacy of oral administration of *Lactobacillus paracasei* K71 in canine atopic dermatitis (cAD).

Animals – Forty one dogs with mild to moderate cAD were recruited by 19 animal hospitals.

Methods – Dogs were assigned to receive either the investigational agent (K71 group; $n = 20$) or cetirizine hydrochloride (control group; $n = 21$). Previously prescribed medications were allowed to be continued during the 12 week trial. Dogs were assessed by the investigators using the cAD Extent and Severity Index (CADESI) and a medication scoring system. Pet owners assessed their dogs using a visual analog scale (VAS) and pruritus scores.

Results – The CADESI scores, VAS and pruritus scores in both groups at 12 weeks were improved compared with their baselines. The CADESI and pruritus scores in the K71 group were slightly lower than those in the control group and the reduction of medication scores in the K71 group was significantly lower compared with the control group ($P < 0.05$; Student's t -test).

Conclusions and clinical importance – Oral administration of K71 can be useful in dogs with cAD as a complementary therapy, by providing a steroid-sparing effect.

Introduction

Atopic dermatitis (AD) is one of the most prevalent skin diseases in both humans and dogs. The primary clinical sign is pruritic dermatitis which occurs in a characteristic distribution pattern across the body and with a persistently relapsing course.¹ Guidelines for effective treatment of canine atopic dermatitis (cAD) have been established by the International Task Force on Canine Atopic Dermatitis (ITFCAD).¹ The strength of recommendation for each agent is determined by the category of evidence. According to the guidelines, oral (p.o.) and topical glucocorticoids are recommended in both acute and chronic phases. However, long-term use of glucocorticoids may be associated with significant risk for adverse events.² Well-tolerated adjunctive therapies that act through different pharmacological mechanisms may help

to reduce the required dose of glucocorticoids and may therefore mitigate their associated risks.

There is some evidence that antihistamines can be used safely in combination with glucocorticoids p.o., and these agents may have steroid-sparing effects. One report described the effectiveness of cetirizine hydrochloride, which decreased the pruritus scores in four of 22 dogs (18%) with cAD.³ In the ITFCAD guidelines,¹ supplemental agents, including essential fatty acids and a plant-derived extract (Chinese herbal), are also suggested for use in combination with glucocorticoids p.o. for steroid-sparing effects.^{4,5} The effect of lactic acid-producing bacteria on AD has also been described. In a study of human patients, the skin symptoms, pruritus scores and medication scores were improved in children by the administration of *Lactobacillus acidophilus* L-92 p.o.⁶ Another lactic acid bacterium, *Lactobacillus paracasei* K71 (K71), significantly decreased total and specific serum IgE levels in ovalbumin-sensitized Balb/c mice.⁷ In a double-blinded placebo-controlled study of adult patients with mild to moderate AD it decreased skin symptom scores.⁸ In an open clinical trial of five dogs, which compared K71 with cetirizine hydrochloride (each used in combination with a maintenance dose of prednisolone at 0.5 mg/kg every other day), higher efficacy was demonstrated for K71.⁹

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The purpose of this study was to evaluate the efficacy of K71 in the management of cAD using a multicentre, double-blinded clinical trial, in which cetirizine hydrochloride was used as the active control drug for comparison purposes.

Materials and methods

Sample size estimation

In a preliminary trial K71 and cetirizine hydrochloride were administered to 12 dogs each. The difference in the total level of reduction in cAD Extent and Severity Index (CADESI) scores, visual analog scale (VAS) scores and pruritus scores between the K71 group (60%) and the cetirizine group (17%) was 43%. Therefore, to detect a statistically significant difference between these groups in a prospective clinical trial, using a 5% margin of error for α and a power designation of 80%, we estimated a sample size of 38 dogs (19 per group).

Animals

Forty one dogs with mild to moderate cAD were recruited by 19 animal hospitals. Dogs were selected using the provisional diagnostic criteria of the Japanese Dermatological Association,¹⁰ and conformed to previously defined criteria.¹¹ Written informed consent was obtained from dog owners prior to enrolment and dogs were randomly assigned to a study group by an independent consultant. Dogs with ectoparasite infestation, cutaneous bacterial or fungal infection or a known adverse food reaction were excluded using standard diagnostic procedures, as were pregnant females and any other dogs intended for breeding activity during the trial period. All previously prescribed medications were continued during the trial. However, dogs were excluded from participation if they had either initiated or discontinued antimicrobials within 7 days, antihistamines within 14 days, p.o. or topical glucocorticoids or p.o. ciclosporin within 28 days or essential fatty acids within 56 days of potential enrolment.

Intervention

The study was designed as a randomized, active drug-controlled, double-blinded clinical trial. A powdered form of K71 (Hifu Sukoyaka Support; Kameda Seika Co. Ltd, Konan, Niigata, Japan) was administered at 5 mg/kg body weight p.o. as the investigational agent (K71 group), and a cetirizine hydrochloride powder (Zyrtec dry syrup 1.25%; GlaxoSmithKline K.K., Shibuya, Tokyo, Japan) was administered at 1 mg/kg p.o. as the active control agent (control group). Both agents, which were similar in appearance, were given once daily for 12 weeks, either dissolved in water or mixed in with solid food. The study was conducted over a 1 year period to reduce seasonal influences. Clinical evaluations were performed at weeks 0 (baseline), 4, 8 and 12. The investigators retrieved empty packages of the agents and any remaining drug and recorded its consumption along with any adverse events. Dog owners recorded logs of health indicators, concurrent use of drugs (including dose and frequency) and ingestion of the trial agents daily.

Medication scores

Consumptive doses of topical and p.o. glucocorticoids and drugs of similar potency (e.g. ciclosporin) were calculated and converted into 'medication scores' (MS) every 4 weeks. A MS of 1.0 was assigned to the following p.o. drug/dose combinations: prednisolone 0.5 mg/kg once daily; methylprednisolone 0.4 mg/kg once daily; and ciclosporin 5 mg/kg once daily, according to prior reports of equipotence.^{1,12} Topical hydrocortisone aceponate 0.0584%, applied at the rate of 0.2 g/100 cm² body surface area (not to exceed one-third of total body surface/day), was also assigned a MS of 1.0 based on its reported equipotence to p.o. ciclosporin for the treatment of cAD.¹³ Other topical glucocorticoids were evaluated based on their comparative potency with hydrocortisone aceponate,¹⁴ mometasone furoate 0.1% (MS = 1.0) and betamethasone valerate 0.12% (MS = 0.7), using the application guidelines outlined above for hydrocortisone aceponate.⁴

Clinical assessments

Clinical signs were evaluated by participating veterinarians using the CADESI score; a score <16 was considered to be consistent with disease remission.¹⁵ Dog owners evaluated their pets using a VAS and a pruritus score. The VAS consisted of a 100 mm scale, where 0 mm indicated no pruritus and 100 mm indicated the worst pruritus imaginable. Pruritus scores were determined by the frequency and severity of pruritus as previously described.¹⁶ Scores were assigned according to the following five-category rule set: 0 = no pruritus, 1 = very mild pruritus with only occasional pruritic episodes, 2 = mild pruritus with more frequent pruritic episodes, 3 = moderate pruritus with regularly noted pruritic episodes, 4 = severe pruritus with prolonged pruritic episodes and 5 = extremely severe pruritus with almost continuous pruritic episodes.

Statistics

Data were expressed as means $\pm$ SD. Efficacy was analysed using CADESI scores and owner-assessed VAS and pruritus scores as the development variables in a three-way ANOVA. Factors included the group (K71 versus cetirizine), medication score (divided into four parts at each 25th percentile) and baseline of the scores for CADESI, VAS and pruritus scores (each divided into four parts at the 25th percentiles). Welch's *t*-test was used to analyse medication scores every 4 weeks in both groups. The level of statistical significance was set at $P < 0.05$.

Evaluation for safety

Safety was evaluated on the basis of the incidence and severity of adverse events throughout the trial in both groups. All adverse events were analysed for their frequency, severity, potential for relatedness to the intervention and outcome.

Results

Animals

The age, breed, sex, body weight and CADESI scores of the 20 dogs in the K71 group and the 21 dogs in the control group at the starting point of the trial are shown in Table S1 in Supporting information; there were no significant differences between the groups. In both groups the majority of dogs were of the shiba inu breed, which is considered to have a high breed prevalence of cAD in Japan. Clinical signs of one dog in the K71 group (A-20) and two dogs in the control group (P-20 and P-21) deteriorated and the dogs were withdrawn from the study at the owners' requests. Two dogs in the control group (P-18 and P-19) dropped out because of seemingly unrelated complications, specifically cholecystopathy and lymphoma, respectively.

Canine Atopic Dermatitis Extent and Severity Index

Table 1 shows CADESI scores during the 12 week intervention period. The CADESI scores decreased with time in both groups. No significant difference was detected between the groups ($P = 0.22$; ANOVA). When the degree of improvement in CADESI from baseline to week 12 was calculated, the value for the K71 group was higher than that of the control group, but was not statistically significant ($P = 0.96$; ANOVA).

Visual analog scale and pruritus scores

Table 1 shows the VAS scores during the 12 week intervention period. The VAS score in the K71 group increased slightly at 4 weeks and decreased at 8 and 12 weeks. The VAS score in the control group decreased over time. It was slightly lower than the K71 group but there was no significant difference between the groups ($P = 0.92$;

Table 1. Canine Atopic Dermatitis Extent and Severity Index, visual analog scale and pruritus scores of the K71 and control groups; summary of the medication scores

	Score (mean ± SD)				Reduction rate (%)
	0 Weeks	4 Weeks	8 Weeks	12 Weeks	
Canine Atopic Dermatitis Extent and Severity Index score					
K71	108.0 ± 20.4	84.8 ± 20.3	71.1 ± 19.3	58.6 ± 14.8	45.8
Control	100.7 ± 31.3	78.8 ± 30.0	68.1 ± 30.7	62.4 ± 30.4	38.1
Visual analog scale score					
K71	48.5 ± 4.5	53.0 ± 4.8	36.9 ± 5.6	35.5 ± 5.2	26.8
Control	55.4 ± 5.6	46.2 ± 5.0	41.8 ± 5.5	36.5 ± 6.1	34.2
Pruritus score					
K71	3.3 ± 0.2	3.2 ± 0.2	2.6 ± 0.3	2.3 ± 0.3	30.3
Control	3.1 ± 0.2	2.8 ± 0.2	2.7 ± 0.3	2.5 ± 0.4	19.4
	0–4 Weeks	4–8 Weeks	8–12 Weeks	Reduction of the score	
Medication score					
K71	0.64 ± 0.10	0.56 ± 0.10	0.44 ± 0.10	0.20 ± 0.07*	
Control	0.48 ± 0.13	0.52 ± 0.13	0.64 ± 0.23	−0.17 ± 0.14	

* $P < 0.05$ (Student's *t*-test).

ANOVA). Table 1 shows the pruritus scores during the 12 weeks. The pruritus score decreased over time in both groups; the value in the K71 group was lower than that of the control group, but this difference was not statistically significant ($P = 0.28$; ANOVA).

Medication scores

No dog had received immunotherapy in either group. Table 1 summarizes the changes in medication scores; Tables S2 and S3 in the Supporting information show the medication scores during the 12 week intervention period. The scores decreased slightly over 12 weeks in the K71 group. This improvement can be attributed to six cases; in particular one dog (A-16) was weaned entirely from p.o. glucocorticoids, and another dog (A-13) was weaned entirely from both p.o. and topical glucocorticoids. Conversely, in the control group the scores between weeks 4–8 and 8–12 were slightly increased compared with those for weeks 0–4. The scores decreased for three control dogs, but increased slightly for three others. Glucocorticoids could not be discontinued in any of the control dogs. When the mean medication scores for weeks 8–12 were compared with those for weeks 0–4, it was noted that they had decreased by 0.20 (31.3%) in the K71 group, but increased to 0.17 (33.3%) in the control group. Significant differences in the mean medication scores were present between both groups ($P < 0.05$; Welch's *t*-test).

Intention-to-treat analysis

An intention-to-treat analysis revealed no significant differences between groups for CADESI, VAS or pruritus scores ($P = 0.056$, $P = 0.71$ and $P = 0.089$, respectively). The mean medication scores were also analysed by intention to treat, and as in the 'per protocol' analysis, significant differences were observed ($P < 0.05$). As the results of the intention-to-treat and per protocol analyses were the same, it is suggested that the conclusions of the study were not influenced by case withdrawals.

Trial extension phase

An extension of the trial period was not originally included in the study design but the investigators recognized that

both positive and negative seasonal variations could have influenced some individual outcomes. Therefore, owners who had favourable opinions of their pets' trial outcomes were offered an extension of K71 therapy for up to 48 weeks; seven owners elected to participate in the extension phase. Clinical signs continued to be evaluated every 4 weeks using the original study assessments. Among these seven dogs, five continued administration of K71 p.o. for a full 48 weeks. The CADESI score for Case A-1 decreased to <16 (assessed as clinical remission) at 12 weeks and this dog's status was maintained up to week 48. Cases A-2 and A-9 did not reach clinical remission by week 12 but had achieved remission by week 48. Cases A-10 and A-18 gradually improved throughout the 48 weeks but did not reach complete remission. The medication scores at 48 weeks decreased by 0.18, 0.1 and 0.71 in Cases A-1, A-2 and A-18, respectively but there were no changes in Cases A-9 and A-10. In the remaining follow-up cases owners withdrew K71 therapy because of complete remission (Case A-3) and an unrelated complication (brain tumour in Case A-14) at 24 and 44 weeks, respectively.

Evaluation of safety

During the 12 week intervention period and the 48 week extension phase, no adverse events that could be linked to K71 therapy were observed. Two of 21 cases in the control group deteriorated. These events were judged as unrelated to the control agent (cetirizine) by the investigators but the trial was discontinued at the owners' requests.

Discussion

This randomized, double-blinded and active drug-controlled multicentre trial demonstrated the complementary efficacy of p.o. administration of K71 on cAD. Although CADESI and pruritus scores were not statistically different between the trial groups, medication scores in the K71 group decreased compared with the control group. In the K71 group, glucocorticoids and ciclosporin were tapered in six cases and glucocorticoids were completely withdrawn in two cases. In an extension phase where therapy was

continued for up to 48 weeks, all K71-treated dogs continued to improve, and medication scores decreased for an additional three cases. These results support the apparent steroid- and ciclosporin-sparing effect of K71.

In terms of trial design, it was a challenge to establish an appropriate system to evaluate the complementary effects of the investigational agent. All dogs enrolled had previously received various medical therapies (in particular, glucocorticoids) and were being maintained with anti-inflammatory and antipruritic drugs at the time of enrolment. As it was not realistic to compare the potency of all drugs administered to the participants, medication scores were calculated for those noted to have sufficient evidence of efficacy in the ITFCAD guidelines. The potency of drugs was converted into equivalent scores using previously reported data. Although not analysed formally, there was no clear discrepancy between the calculated medication scores and the owners' subjective evaluations of clinical signs.

There are various mechanisms by which K71 may potentially influence the atopic inflammatory cascade. In ovalbumin-immunized Balb/c mice, p.o. administration of K71 induced interleukin-12 and interferon- γ production, suppressed interleukin-4 production and reduced total and allergen-specific IgE levels.⁷ In a previous study inhibition of allergen-specific IgE (directed against *Dermatophagoides farinae*) by ingestion of *Lactobacillus rhamnosus* strain GG in dust mite-sensitized dogs was reported.¹⁷ Therefore, it is possible that lactic acid-producing bacteria downregulate IgE production via the induction of a T helper 1 cytokine milieu. Further investigations, such as large-scale, randomized trials with well-controlled breed, age and seasonality parameters, which include assays to assess the expression of cytokines and chemokines at the site of inflammation in cAD, will be needed to provide a better understanding of the effects of this agent.

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Supporting Information

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

Table S1. Clinical features of cases in the study.

Table S2. Medication scores and dosages in dogs of the K71 and control (cetirizine) groups.

Table S3. The medication scores in dogs of the K71 and control (cetirizine) groups.

Résumé

Contexte – La dermatite atopique est une dermatose fréquente chez le chien. Les corticoïdes sont fréquemment recommandés en traitements symptomatiques et des traitements adjuvants bien tolérés peuvent aider à diminuer les doses nécessaires et les risques associés à l'utilisation chronique de corticoïdes.

Hypothèses/Objectifs – Le but de cette étude est d'évaluer l'efficacité complémentaire de l'administration orale de *Lactobacillus paracasei* K71 dans la dermatite atopique canine (DAC).

Sujets – Quarante et un chiens atteints de DAC modérée à sévère ont été inclus par 19 hôpitaux vétérinaires.

Méthodes – Les chiens ont été répartis soit dans le groupe K71 (n = 20) soit dans le groupe contrôle recevant de la cétirizine (n = 20). Les traitements antérieurs étaient poursuivis à l'identique pendant les 12 semaines de l'étude. Les chiens ont été évalués par un CADESI (cAD Extent and Severity Index) et un système de notation des traitements. Les propriétaires évaluaient leur animal par une échelle visuelle analogue (VAS) et un score de prurit.

Résultats – Les scores CADESI, VAS et de prurit étaient améliorés à 12 semaines par rapport aux données initiales. Les scores de prurit et de CADESI étaient modérément plus faibles que ceux du groupe contrôle et la baisse des scores de traitements dans le groupe K71 était significatif par rapport au groupe contrôle ($P < 0.05$; Student's t-test).

Conclusion et importance clinique – L'administration orale de K71 peut être utile chez le chien atopique en tant que traitement complémentaire en permettant un effet d'épargne médicamenteuse.

Resumen

Introducción – la dermatitis atópica es una enfermedad de la piel bastante frecuente en perros. Los glucocorticoides están generalmente recomendados para el tratamiento sintomático, y otras terapias adyuvantes bien toleradas pueden ayudar a reducir la dosis necesaria de glucocorticoides y los riesgos asociados a su uso.

Hipótesis/Objetivos – el propósito este estudio fue evaluar la eficacia complementaria de la administración oral de *Lactobacillus paracasei* K71 en dermatitis atópica (cAD)

Animales – 41 perros con leve a moderada dermatitis atópica fueron incluidos en el estudio procedentes de 19 hospitales de animales

Métodos – los perros fueron asignados para recibir bien el agente bajo investigación (grupo K71; n = 20), o hidrocortisona (grupo control; n = 21). Medicamentos previamente recetados fueron continuados durante el período de prueba de 12 semanas. Los perros fueron evaluados por los investigadores utilizando el índice de severidad y la extensión de la dermatitis atópica canina (CADESI) y sistema de valoración de la medicación. Los propietarios evaluaron sus perros utilizando una escala análoga visual (VAS) y valores de prurito.

Resultados – Los valores de CADESI, VAS y prurito en ambos grupos mejoraron a las 12 semanas comparados con los valores basales. Los valores de CADESI y de prurito en el grupo K71 fueron ligeramente menores que los del grupo control y la reducción de los valores de medicación del grupo K71 fue más significativa que la del grupo control ($P < 0,05$; prueba t de Student).

Conclusiones e importancia clínica – la administración oral de K71 puede ser útil en perros con dermatitis atópica como terapia complementaria mediante la disminución de la dosis de corticoides.

Zusammenfassung

Hintergrund – Die atopische Dermatitis ist eine häufige, bei Hunden vorkommende, Hauterkrankung. Es werden häufig Glukokortikoide für eine symptomatische Behandlung empfohlen, und Zusatzbehandlungen, die gut vertragen werden, können die nötige Dosis und die damit verbundenen Risiken chronischer Glukokortikoidgabe vermindern helfen.

Hypothese/Ziele – Das Ziel dieser Studie war eine Evaluierung der Komplementärwirkung oraler Administration von *Lactobacillusparacasei* K71 bei der atopischen Dermatitis des Hundes (cAD).

Tiere – Einundvierzig Hunde mit mild bis moderater cAD wurden von 19 Tierkliniken rekrutiert.

Methoden – Die Hunde wurden in die Versuchsgruppe (K71 Gruppe; n=20), die den zu untersuchenden Wirkstoff erhalten sollte und die Kontrollgruppe (n=21), die Cetirizin Hydrochlorid erhalten sollte, eingeteilt. Die vorher verschriebenen Medikamente durften während der 12 wöchigen Versuchsdauer weiter gegeben werden. Die Hunde wurden von den UntersucherInnen mittels cADExtentandSeverity Index (CADESI) und einem Medikamentenbewertungssystem beurteilt. Die HundebesitzerInnen beurteilten ihre Hunde mittels einer Visual Analog Scale (VAS) und erfassten die Juckreizwerte.

Ergebnisse – Im Vergleich zu den Ausgangswerten verbesserten sich in beiden Gruppen am Ende der 12 Wochen die CADESI Werte, VAS und Juckreizwerte. Die CADESI und Juckreizwerte in der K71 Gruppe

waren geringfügig niedriger als die der Kontrollgruppe und die Reduzierung der Medikamentenwerte in der K71 Gruppe war signifikant im Vergleich zur Kontrollgruppe ($P < 0,05$; Student's t-Test).

Schlussfolgerungen und klinische Bedeutung – Eine orale Verabreichung von K71 kann bei Hunden mit cAD als komplementärmedizinische Behandlung nützlich sein, da es eine Steroid-sparende Wirkung aufweist.

要約

背景 – アトピー性皮膚炎はイヌで遭遇する一般的な皮膚疾患である。グルココルチコイドは対症療法として一般に推奨されるが、良好な耐容性を示す補助的療法により必要な用量と慢性的なグルココルチコイドの使用に関連するリスクを減らせる可能性がある。

仮説/目的 – この研究の目的はイヌアトピー性皮膚炎(cAD)において、*Lactobacillus paracasei* K71経口投与の補助的な効果を評価することである。

供与動物 – 19の動物病院で募集した、軽度から中程度のcADを示す41頭のイヌ。

方法 – イヌは治療群(K71群; $n=20$)あるいは塩酸セチリジン(コントロール群; $n=21$)のいずれかを投与するように振り分けられた。12週間の試験中、今まで処方されていた薬剤は使用を許可された。イヌはcAD Extent and Severity Index (CADESI)および薬剤スコアシステムを用いて試験担当者によって評価された。ペットの飼い主は彼らのイヌをビジュアルアナログスケール(VAS)と掻痒スコアを用いて評価した。

結果 – 12週間で両方の群において、CADESIスコア、VASおよび痒みスコアは基準値と比較し改善を示した。K71群において、CADESIおよび痒みスコアはコントロール群と比較しわずかに低く、K71群での薬剤スコアの減少はコントロール群と比較し有意であった($P < 0.05$; スチューデントのt検定)。

結論および臨床的な重要性 – K71の経口投与はcADのイヌで補助療法として、ステロイド節約効果をもたらすという点で役立つ可能性がある。

摘要

背景 – 异位性皮膚炎は犬常见的的皮肤疾病。对症治疗时常用糖皮质激素,良好的辅助治疗可帮助减少激素的使用剂量,降低长期使用糖皮质激素的风险。

假设/目的 – 本次研究的目的是评估口服副干酪乳杆菌K71,其在犬异位性皮膚炎上的辅助作用。

动物 – 来自19家医院41只轻度或中度的cAD患者犬。

方法 – 将犬分为两组,给予试验药(K71组; $n=20$)或盐酸西替利嗪(对照组; $n=21$)。给药12周。调查者用cAD程度和严重性评分表(CADESI)、药物评分系统来评估犬。宠物主人用视觉评估(VAS)和搔痒评分评估自己的犬。

结果 – 对比各自的基础值,两组在12周后的CADSIE评分、VAS和搔痒评分都有所改善。K71组CADSIE和搔痒评分稍低于对照组,K71组药物评分显著低于对照组($P < 0.05$; Student's t检验)。

总结与临床意义 – K71是cAD有效的辅助治疗口服药,可减少激素使用量。

Supporting Information Table 1. Clinical features of cases in the study

K71 group

CASE number	Age	Breed	Sex ^a	BW	CADESI
A-1	4	Shiba inu	CM	13.4	17
A-2	11	Shiba inu	SF	7.1	20
A-3	11	Beagle	SF	5.9	22
A-4	8	Golden retriever	SF	22.6	23
A-5	6	Shiba inu	SF	8.2	25
A-6	8	Beagle	SF	10.6	28
A-7	8	Shiba inu	SF	11.2	46
A-8	7	Shiba inu	SF	6.6	49
A-9	6	Miniature dachshund	SF	5.3	53
A-10	5	Chihuahua	CM	2.5	77
A-11	7	Cavalier King Charles spaniel	CM	8.9	111
A-12	12	Shiba inu	SF	8.6	123
A-13	7	Shiba inu	SF	7.6	57
A-14	10	French bulldog	CM	10.3	152
A-15	6	Shiba inu	SF	10.2	173
A-16	10	Shiba inu	CM	10.4	181
A-17	4	French bulldog	SF	10.0	205
A-18	12	Shiba inu	SF	9.8	226
A-19	12	Shih zu	SF	6.0	334
A-20	6	Beagle	CM	11.6	91

Control group

CASE Number	Age	Breed	Sex ^a	BW	CADESI
P-1	8	Shiba inu	CM	7.5	17
P-2	8	Shiba inu	SF	8.0	20
P-3	9	German shepherd	CM	40.2	30
P-4	5	Toy poodle	CM	3.4	26
P-5	11	Jack Russell terrier	CM	6.0	30
P-6	3	Shiba inu	CM	13.6	30
P-7	4	Beagle	SF	9.3	23
P-8	6	Miniature pinscher	SF	4.4	32
P-9	2	French bulldog	SF	9.5	62
P-10	6	Shiba inu	SF	8.2	68
P-11	12	Shiba inu	CM	13.8	76
P-12	4	Shiba inu	SF	9.2	76
P-13	9	Shiba inu	SF	11.5	149
P-14	6	Shiba inu	SF	8.0	127
P-15	9	Chihuahua	CM	3.4	151
P-16	11	Yorkshire terrier	CM	2.8	290
P-17	12	Shiba inu	SF	12.1	524
P-18	4	Cavalier King Charles spaniel	SF	9.2	28
P-19	10	Shiba inu	SF	13.7	47
P-20	9	Shiba inu	SF	8.5	46
P-21	11	Shiba inu	SF	14.0	527

^a CM: Castrated male, SF: Spayed female BW Body weight kg

Supporting Information Table 2. Medication scores and dosages in dogs of the K71 and Control (Cetirizine) groups

K71 group					
Case No.	medicine	Scores and Dosage			
		0-4 w	4-8 w	8-12 w	
A-1	Ciclosporin	0.37 (25 mg once daily)	0.37 (25 mg once daily)	0.19 (25 mg eod)	
A-2	Prednisolone	1.13 (8 mg eod)	1.13 (8 mg eod)	1.13 (8 mg eod)	
	Ciclosporin	0.10 (25 mg 4 days)	0.20 (25 mg 8 days)	0.20 (25 mg 8 days)	
A-3	Prednisolone	0.17 (1 mg eod)	0.17 (1mg eod)	0.17 (1 mg eod)	
	Ciclosporin	1.19 (35 mg once daily)	1.19 (35 mg once daily)	1.19 (35 mg once daily)	
A-4	Ciclosporin	0.44 (50 mg once daily)	0.44 (50 mg once daily)	0.44 (50 mg once daily)	
	Hydrocortisone aceponate	0.05 (16 g)	0.01 (2.6 g)	0.00 (1.3 g)	
	Mometasone furoate	0.02 (5.3 g)	0.02 (4.2 g)	0.00 (0.5 g)	
A-5	Prednisolone	0.61 (2.5 mg once daily)	0.61 (2.5 mg once daily)	0.61 (2.5 mg once daily)	
A-6	Prednisolone	0.70 (7.5 mg eod)	0.70 (7.5 mg eod)	0.70 (7.5 mg eod)	
	Hydrocortisone aceponate	0.02 (2.08 g)	0.02 (2.08 g)	0.02 (2.08 g)	
A-7	—	—	—	—	
A-8	Prednisolone	1.15 (3.75 mg once daily)	1.15 (3.75 mg once daily)	0.57 (3.75 mg eod)	
A-9	—	—	—	—	
A-10	Prednisolone	0.50 (1.25 mg eod)	0.50 (1.25 mg eod)	0.50 (1.25 mg eod)	
A-11	Prednisolone	0.32 (5 mg 8 days)	0.32 (5 mg 8 days)	0.32 (5 mg 8 days)	
A-12	Ciclosporin	0.29 (25 mg eod)	0.29 (25 mg eod)	0.29 (25 mg eod)	
A-13	Prednisolone	0.33 (2.5 mg eod)	0.33 (2.5 mg eod)	—	
	Mometasone furoate	—	0.03 (0.1 g)	—	
A-14	—	—	—	—	
A-15	Prednisolone	0.49 (5 mg eod)	0.49 (5 mg eod)	0.25 (2.5 mg eod)	
	Hydrocortisone aceponate	0.00 (1.04 g)	0.00 (1.04 g)	0.00 (1.04 g)	

A-16	Prednisolone	0.48 (5 mg eod)	—	—
A-17	Prednisolone	1.00 (5 mg once daily)	0.50 (5 mg eod)	—
	Mometasone furoate	0.05 (6.7 g)	0.01 (1.8 g)	0.00 (0.2 g)
A-18	Prednisolone	0.51 (5 mg eod)	0.51 (5 mg eod)	0.51 (5 mg eod)
	Hydrocortisone aceponate	0.85 (27.26 g)	0.17 (5.55 g)	0.35 (11.16 g)
	Mometasone Furoate	—	0.11 (14.66 g)	—
A-19	Ciclosporin	0.83 (25 mg once daily)	0.83 (25 mg once daily)	0.83 (25 mg once daily)

Control (Cetirizine) group

Case No.	medicine	scores and dosage		
		0-4 w	4-8 w	8-12 w
P-1	Prednisolone	0.22 (1.67 mg eod)	0.22 (1.67 mg eod)	0.22 (1.67 mg eod)
P-2	—	—	—	—
P-3	Prednisolone	0.12 (2.5 mg once daily)	0.02 (2.5 mg 4 days)	0.04 (2.5 mg 9 days)
	Hydrocortisone aceponate	0.01 (6.2 g)	—	0.02 (8.8 g)
P-4	—	—	—	—
P-5	Prednisolone	—	0.42 (2.5 mg eod)	0.42 (2.5 mg eod)
	Ciclosporin	—	0.30 (25 mg 10 days)	0.30 (25 mg 10 days)
	Hydrocortisone aceponate	0.03 (4.0 g)	0.01 (1.4 g)	0.03 (3.4 g)
	Betamethasone	0.06 (3.0 g)	0.00 (0.23 g)	0.02 (0.96 g)
P-6	Ciclosporin	0.74 (50 mg once daily)	0.37 (50 mg eod)	0.26 (50 mg 10 days)
P-7	Ciclosporin	1.08 (50 mg once daily)	1.08 (50 mg once daily)	1.08 (50 mg once daily)
	Hydrocortisone aceponate	0.02 (2 push once daily)	0.02 (2 push once daily)	0.02 (2 push once daily)
P-8	Prednisolone	0.85 (3.75 mg eod)	0.85 (3.75 mg eod)	0.85 (3.75 mg eod)
P-9	Prednisolone	0.53 (5 mg eod)	0.53 (5 mg eod)	0.53 (5 mg eod)
P-10	Prednisolone	0.30 (2.5 mg EOD)	0.30 (2.5 mg EOD)	0.30 (2.5 mg EOD)
P-11	Prednisolone	0.18 (5 mg EOD)	0.18 (5 mg EOD)	0.18 (5 mg EOD)

	Ciclosporin	0.20 (100 mg 8 days)	0.20 (100 mg 8 days)	0.20 (100 mg 8 days)
P-12	Prednisolone	0.27 (2.5 mg EOD)	0.27 (2.5 mg EOD)	0.27 (2.5 mg EOD)
P-13	Prednisolone	0.43 (5 mg EOD)	0.43 (5 mg EOD)	0.43 (5 mg EOD)
P-14	Methylprednisolone	0.79 (2 mg ONCE DAILY)	0.79(2 mg ONCE DAILY)	1.57 (4 mg ONCE DAILY)
	Ciclosporin	1.26(50 mg ONCE DAILY)	1.26(50 mg ONCE DAILY)	2.52(100 mg ONCE DAILY)
P-15	—	—	—	—
P-16	Ciclosporin	0.73(10 mg ONCE DAILY)	0.73(10 mg ONCE DAILY)	0.73(10 mg ONCE DAILY)
	Mometasone Furoate	0.05 (2.65 mg)	—	—
P-17	Prednisolone	—	0.41(2.5 mg ONCE DAILY)	0.41(2.5 mg ONCE DAILY)
	Ciclosporin	—	0.41(25 mg ONCE DAILY)	0.41(25 mg ONCE DAILY)

Supporting Information Table 3. The medication scores in dogs of the K71 and Control (Cetirizine) groups

K71 group				Control group			
No.	Scores			No.	Scores		
	0-4 w	4-8 w	8-12 w		0-4 w	4-8 w	8-12 w
A-1	0.37	0.37	0.19	P-1	0.22	0.22	0.22
A-2	1.23	1.33	1.33	P-2	0	0	0
A-3	1.36	1.36	1.36	P-3	0.13	0.02	0.06
A-4	0.51	0.47	0.44	P-4	0	0	0
A-5	0.61	0.61	0.61	P-5	0.09	0.73	0.77
A-6	0.72	0.72	0.72	P-6	0.74	0.37	0.26
A-7	0	0	0	P-7	1.10	1.10	1.10
A-8	1.15	1.15	0.57	P-8	0.85	0.85	0.85
A-9	0	0	0	P-9	0.53	0.53	0.53
A-10	0.5	0.5	0.5	P-10	0.30	0.30	0.30
A-11	0.32	0.32	0.32	P-11	0.38	0.38	0.38
A-12	0.29	0.29	0.29	P-12	0.27	0.27	0.27
A-13	0.33	0.36	0	P-13	0.43	0.43	0.43
A-14	0	0	0	P-14	2.05	2.05	4.09
A-15	0.49	0.49	0.25	P-15	0	0	0
A-16	0.48	0	0	P-16	0.78	0.73	0.73
A-17	1.05	0.51	0	P-17	0	0.82	0.82
A-18	1.36	0.79	0.86				
A-19	0.83	0.83	0.83				