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Evaluation of Plasma C-Reactive Protein as a Biomarker in Dogs with Atopic Dermatitis Receiving Allergen-Specific Immunotherapy: A Pilot Study

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Evaluierung des C-reaktiven Proteins als Biomarker im Plasma bei Hunden mit atopischer Dermatitis unter allergenspezifischer Immuntherapie: Eine Pilotstudie

Das Ziel der vorliegenden Studie war es, C-reaktives Protein (CRP) im Plasma zu bestimmen und als Biomarker für Schweregrad und Behandlung der atopischen Dermatitis bei Hunden (AD) zu evaluieren. Neun atopische Hunde erhielten während eines Jahres eine allergenspezifische Immuntherapie. Vor Therapiebeginn und bei vier Nachuntersuchungen wurden jeweils die Hautläsionen mit dem «Canine Atopic Dermatitis Extent and Severity Index» (CADESI) 4 bewertet und den Tieren Blut entnommen. Die Plasma CRP-Spiegel wurden mittels Enzyme-linked Immunosorbent Assay (ELISA) gemessen. Wir fanden eine minimale signifikante Korrelation zwischen den CRP- und CADESI4-Werten. Die CRP-Werte unterschieden sich nicht signifikant zwischen den Hunden mit unterschiedlicher AD Schwere. Es konnte keine Korrelation zwischen der Prozentualen Veränderung der CADESI4- und CRP-Werte während der Immuntherapie festgestellt werden.
Zusammenfassend, das Fehlen eines signifikanten Unterschiedes zwischen den CRP-Werten bei Hunden mit unterschiedlichen AD-Schweregrade und das Fehlen einer Korrelation zwischen den prozentualen Hautläsionsveränderungen und den CRP-Werten zeigen, dass dieses Protein kein klinisch nützlicher Biomarker bei atopischen Hunden ist.

Schlüsselwörter: Neurodermitis, Biomarker, CRP, Hund

Abstract

In this pilot study, we wished to determine if C-reactive protein (CRP) levels could be a useful severity or treatment biomarker for canine atopic dermatitis (AD). Nine atopic dogs received allergen immunotherapy for 1 year. Blood was collected before and at four re-evaluation visits. At each time point, the skin lesions were graded with the Canine Atopic Dermatitis Extent and Severity Index (CADESI) 4, and the plasma CRP levels were measured by Enzyme-linked Immunosorbent Assay (ELISA). We found a significant yet minimal correlation between the CRP levels and the CADESI4 scores. The CRP levels were not significantly different between dogs with AD of increasing severity. Finally, there was no correlation between the percentage change in CADESI4 and CRP values during immunotherapy. In conclusion, the lack of significant difference in CRP levels between dogs of increasing AD severity and lack of correlation between percentage changes in skin lesion and CRP values suggest that this protein would not be a clinically-useful biomarker in atopic dogs.

Key words: atopic dermatitis, biomarker, CRP, dog

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Introduction

To assess the severity of skin lesions of canine atopic dermatitis (AD) for mechanistic studies or during clinical trials, lesion severity scales, such as one of the Canine Atopic Dermatitis Extent and Severity Index (CADESI) iterations or the Canine Atopic Dermatitis Lesion Index (CADLI) often are used.[12,14] Despite yielding a score that, at first, might appear as representing an objective measure of skin lesion severity, these time-consuming instruments only reflect the aggregation of subjectively-graded individual or grouped skin lesions on the entire body surface or at specific body sites.

To remedy the inherent subjectivity of clinician-assessed skin lesion scales, the search for more "objective" biomarkers of disease severity or treatment response in humans with AD has been ongoing for decades.[5] Commonly used biomarkers for human AD include histological lesions or immunostains from collected skin biopsies, or the serum levels of specific cytokines, chemokines or inflammation-associated proteins.[5] One such biomarker is the C-reactive protein (CRP), a liver-originating acute-phase protein whose blood levels increase during inflammation, including that which occurs during inflammatory skin diseases including AD, psoriasis and contact dermatitis.[17,20] First reported to parallel the response to antihistamine therapy in humans with AD in 2015, serum CRP levels were recently shown to positively correlate with both the skin lesion scores and the affected body surface area in human patients with moderate-to-severe AD.[8,19] In veterinary dermatology, the CRP serum level recently was found a valid disease severity biomarker for canine pemphigus foliaceus.[15]

To date, there is only one publication that reports a useful biomarker for canine AD.[2] In this paper, a specific ELISA was developed for the canine S100A8 (calgranulin A, one of the two calprotectin subunits), and serum levels of S100A8 rose with increasing levels of AD severity in 213 atopic dogs.[2] Furthermore, the correlation between the CADESI3 values and the S100A8 serum levels was 85% and highly significant.[2] Unfortunately, there is no validated commercially-available Enzyme-linked Immunosorbent Assay (ELISA) that would permit the use of such biomarker in veterinary dermatology research and practice.

At the time of this writing, we could only identify one study that reported, in abstract form, that CRP serum levels (assessed by latex coagulating nephelometry) were not elevated in canine AD.[16] This finding is surprising in light of the observation that acute allergen challenges in sensitized dogs lead to a rapid increase in the expression of pro-inflammatory cytokines (e.g., IL-6 among others) that should induce a rise in CRP production.[6,11] Furthermore, canine AD skin is known to have a high expression of the CRP-inducing cytokine TNF-alpha.[7,9,10] Therefore, we wished to determine if this acute-phase protein could be used as a biomarker of disease severity or immunotherapy efficacy in dogs with AD.

Materials and methods

The collection of blood samples in this study was approved beforehand by our institution's Animal Care and Use Committee.

Atopic dogs

Client-owned dogs with AD presented to the University of Zurich Small Animal Internal Medicine Clinic were selected. In these dogs, the diagnosis of AD was made based on a compatible history, characteristic clinical signs and the exclusion of resembling pruritic dermatoses (e.g. ectoparasitoses, yeast, and bacterial infections, and so on) using standard methods.[3,4]

All dogs had been treated with allergen immunotherapy (AIT) as part of another study during which they were bled on five separate occasions: at the initiation of AIT and at re-evaluation visits scheduled at approximately 1, 3, 6 and 12 months after beginning this intervention. The present study was consequently retrospective. The blood was centrifuged, and the plasma was isolated and stored at -80°C until used. At each visit, the extent and severity of AD skin lesions were assessed using the CADESI4, a complete general examination was carried out and all anti-allergic medications (e.g., cyclosporine, oclacitinib, prednisolone, topical glucocorticoids)–as well as those used for other problems–taken in the last two weeks were also recorded.[12]

Plasma CRP levels

The CRP plasma levels were measured using the TECO canine CRP ELISA (TECO medical, Sissach, Switzerland) by the Laboratoire Cerba (Saint-Ouen-l'Aumône, France). This assay has reported inter- and intra-assay coefficients of variations lower than 5% and a limit of detection of 30 ng/ml; the proposed cut-off value in healthy dogs is 10 µg/ml; this cut-off value is similar to that proposed in a recent paper.[15]

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Statistics

Statistical analyses were performed using Graphpad 8.0 (GraphPad, La Jolla, California, USA). After determining that the CADESI4 and CRP values did not have a normal distribution, non-parametric analyses were used. The correlation between the CADESI4 and the CRP plasma levels was assessed using a one-tailed Spearman Rank correlation test using the single assumption that the correlation would be positive. Additionally, comparisons were made between the CRP plasma levels of dogs in groups of different CADESI4-based skin lesion severity, that is, in dogs with AD in remission (CADESI4 < 10), and those with mild (11-34), moderate (35-59) and severe disease (> 59). For this, we used the Kruskal-Wallis test and repeated the two tests with two different subpopulations: 1) in dogs not treated with anti-allergic drugs, and 2) in dogs with active AD (i.e., after removal of the dogs with AD in remission). Finally, we assessed if there was a correlation between the percentage change in CADESI4 values (a proxy for treatment response) and those of plasma CRP levels.

Results

We included nine dogs in this study; seven of them had blood collected at the time of starting AIT and at four re-evaluation visits, while the other two missed a scheduled visit and had only three post-treatment samples; details on the enrolled dogs, their CADESI4 and corresponding CRP plasma levels are presented in the Table 1. Altogether, we collected CADESI4 and CRP plasma level pairs from 43 dog-visits. General examination was carried at all time points and were unremarkable.

On nine occasions, the dogs had been receiving anti-allergic drugs known to affect inflammation (cyclosporine, oclacitinib, prednisolone, topical glucocorticoids); these visits are colored red in the Table 1 and in the two figures). No other treatments, except dewormers, had been administered during the study.

At baseline, the dogs' CADESI4 skin lesion scores ranged from 20 to 60 (median: 24) and after intra-lymphatic (four dogs), subcutaneous (two dogs), and sublingual AIT (three dogs) their final CADESI4 grades varied between 0 to 78 (median: 4). The corresponding CRP plasma levels varied between 0.1 and 12.9 µg/ml (median 1.6) when starting the AIT, and 0.2 and 6.1 µg/ml (median: 2.4) after one year of this intervention. Of note is that in only 2/9 atopic dogs (22%) were CRP plasma levels consistently above the upper threshold for healthy dogs with this assay (10 µg/ml) when their AD was active during the first months of AIT (values in blue in Table 1).

The correlation between the CADESI4 and CRP plasma levels was significant but weak (Figure 1; Spearman r = 0.27; $P = 0.040$). After removal of the dogs concurrently treated with anti-allergic drugs, the correlation was

Table 1: Characteristics, Canine Atopic Dermatitis Extent and Severity Index 4 (CADESI4) and C-reactive protein (CRP) plasma levels of dogs (n=9) involved in a pilot study on atopic dermatitis (AD). Results of animals with allergen-specific immunotherapy a shown in red and without treatment in black.

Supplementary Material 1: characteristics of study subjects, CADESI4 and CRP plasma levels

				Initial		after 1 month		after 3 months		after 6 months		after 12 months		Change during AIT	
AIT	Breed	Age (yrs)	Sex	CADESI4	CRP (µg/ml)	CADESI4	CRP (µg/ml)	CADESI4	CRP (µg/ml)	CADESI4	CRP (µg/ml)	CADESI4	CRP (µg/ml)	CADESI4	CRP
ILIT	Labrador	6.9	FS	24	1.6	2	8.9	7	3.1	0	12.4	0	1.5	–100%	–6%
ILIT	West Highland white terrier	8.7	MC	54	0.2	28	0.7	13	0.6	4	0.7	11	NC	–80%	–
ILIT	crossbred	2.5	FS	23	1.2	6	4.1	7	0.8	4	1.2	4	2.1	–83%	+75%
ILIT	Boston terrier	2.8	FS	20	0.1	0	0.0	0	0.0	4	0.4	0	0.2	–100%	+100%
SCIT	French bulldog	5.1	FS	60	10.4	36	2.0	13	4.9	12	14.4	0 2.6	2.6	–100%	–75%
SCIT	Jack Russell terrier	4.4	FS	52	7.8	5	15.4	5	15.6	23	1.5	7	4.5	–87%	–42%
SCIT	Boxer	8.0	MI	23	6.3	12	0.4	9	ND	9	1.7	3	3.3	–87%	–48%
SLIT	boxer	2.0	MC	30	12.9	41	46.0	158	62.7	20	0.9	78	6.1	+160%	–53%
SLIT	West Highland white terrier	2.0	FS	20	0.6	5	0.0	4	1.8	2	0.6	10	1.6	–50%	+167%

Abbreviations: AIT: allergen immunotherapy; FS: female spayed; ILIT: intralymphatic immunotherapy; M: male; MC: male castrated; NC: not collected; SCIT: subcutaneous Immunotherapy; SLIT: sublingual immunotherapy

red text: treated with anti-allergic drugs

blue text: CRP values above the upper limit for healthy dogs (i.e., 10 µg/ml)

Originalarbeiten | Original contributions

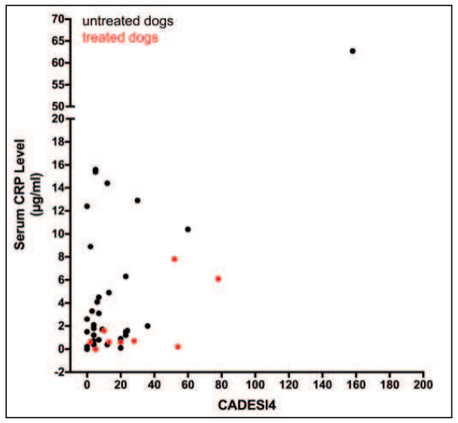

Figure 1: Correlation between Canine Atopic Dermatitis Extent and Severity Index 4 (CADESI4) and C-reactive protein (CRP) plasma levels in untreated (black dots) and with anti-allergic drugs treated (red dots) dogs with canine atopic dermatitis at the time of blood collection. Spearmann test showed a low correlation (r = 0,27, P = 0.04), which was increased (r = 0,36, P = 0.02) when treated dogs were removed (red dots).

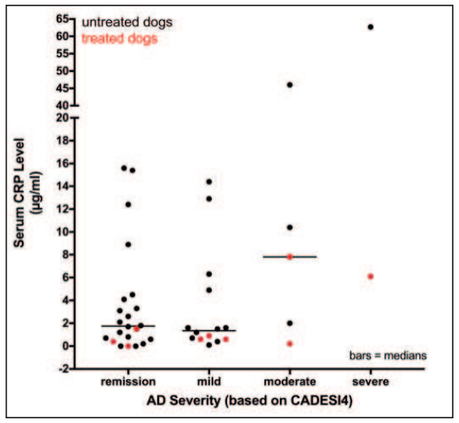

Figure 2: C-reactive protein (CRP) plasma levels in dogs with increasing Canine Atopic Dermatitis Extent and Severity Index 4 (CADESI4) based on Atopic dermatitis (AD) severity categories. Dogs treated with anti-allergic drugs at the time of blood collection are shown in red. Bars represent medians. CRP levels were not significantly different between severity groups (Kruskal-Wallis ANOVA, P = 0.169)

slightly stronger (Spearman r = 0.36; P = 0.026). The correlation was highest when we compared the values of dogs with active AD, that is after removing those with scores of disease remission (Spearman r = 0.44; P = 0.027).

We then grouped the CRP plasma levels based on the canine AD severity category of their corresponding CADESI4 (Figure 2).[12] The CRP levels were not significantly different between AD severity groups (Kruskal-Wallis test, P = 0.169). When removing the values from dogs treated with anti-allergic drugs or those from dogs with AD in remission, the values were not significantly different between groups, either.

Finally, we compared the percentage change in CADESI4 values with those of CRP plasma levels during AIT in eight dogs. While the percentage change in skin lesion scores suggested a strong improvement of AD in 7/8 dogs (88%) after treatment with AIT (median: -87%; range: -100 to +160%), there was no such corresponding change in CRP plasma levels (median: -24%; range: -75 to +167%). The percentage change in CADESI4 and CRP values were not significantly correlated (Spearman r = 0.13; P = 0.744).

Discussion

A biomarker is a parameter that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacologic responses to treatment.[1] Biomarkers can be used as a tool for diagnosis, for predicting the severity of a disease, as an indicator for disease prognosis or to monitor the clinical response to an intervention.[1]

We could not find a set of criteria that defines the characteristics of a useful biomarker for canine AD. Nevertheless, one could envision that such a biomarker should allow the separation of dogs with a controlled AD from those with an active disease, as well as distinguish between dogs of increasing disease severity categories; its values should also strongly correlate with skin lesion scores graded with validated instruments and the evolution of this biomarker should mirror that of skin lesions during treatment.

In spite of the limitation of having followed only a small number of dogs – albeit having done so over one year with 43 value pairs – we found that the CADESI4 skin lesion scores were correlated significantly with the CRP plasma levels, but this positive correlation was minimal. Even when only considering dogs with active AD or those untreated with anti-allergic drugs, the correlation remained weak at best. Importantly, when segregating the dogs among CADESI-based categories of increasing AD severity, there was no significant difference in CRP plasma levels. Altogether, these observations suggest that CRP plasma levels cannot serve as a useful biomarker for the severity of canine AD. That the percentage change in CADESI4 scores and those of the CRP plasma levels during AIT were not correlated suggest that the CRP might not be a useful treatment biomarker either.

Our results are consistent with those of the abstract reporting that CRP levels were not raised in canine AD, even though details were not provided on the number of dogs assessed and whether or not they were receiving treatment. Nevertheless, from the information contained in that abstract, one can infer that all dogs with AD had CRP values in the range of those of healthy dogs (i.e., up to 0.1 mg/dl = 10 µg/ml).[18] One should also keep in mind that these values are low when compared to those of dogs with inflammatory gastro-intestinal disease, such as inflammatory bowel disease or pancreatitis.[13,21]

Of interest is that the range of CRP plasma levels in our seven dogs with moderate-to-severe AD was identical to that determined in the serum of human atopic patients with a disease of similar severity (0.02 to 6.2 mg/dl = 0.2-62.0 µg/ml).[19] While only 39% of human patients with moderate-to-severe AD had a CRP serum level superior to the upper reference range for humans (0.5 mg/dl = 5.0 µg/ml), 5/7 (71%) of our dogs with the same severity had plasma levels above that threshold. [19] However, only 2/9 atopic dogs (22%) would have CRP plasma levels above the cut-off for healthy dogs using this assay (i.e., 10 µg/ml), a threshold twice that of humans.

Conclusion:

In summary, the results of our pilot study established a weak correlation between CRP levels and the CADESI4 scores. However, the lack of separation of CRP levels between dogs of increasing AD severity, and the absence of correlation between the percentage change in atopic skin lesion and those of CRP values suggest that the CRP plasma levels would unlikely form a valid severity and treatment biomarker for canine AD.

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Das Ziel der vorliegenden Studie war es, C-reaktives Protein (CRP) im Plasma zu bestimmen und als Biomarker für Schweregrad und Behandlung der atopischen Dermatitis bei Hunden (AD) zu evaluieren. Neun atopische Hunde erhielten während eines Jahres eine allergenspezifische Immuntherapie. Vor Therapiebeginn und bei vier Nachuntersuchungen wurden jeweils die Hautläsionen mit dem «Canine Atopic Dermatitis Extent and Severity Index» (CADESI) 4 bewertet und den Tieren Blut entnommen. Die Plasma CRP-Spiegel wurden mittels Enzyme-linked Immunosorbent Assay (ELISA) gemessen. Wir fanden eine minimale signifikante Korrelation zwischen den CRP- und CADESI4-Werten. Die CRP-Werte unterschieden sich nicht signifikant zwischen den Hunden mit unterschiedlicher AD Schwere. Es konnte keine Korrelation zwischen der Prozentualen Veränderung der CADESI4- und CRP-Werte während der Immuntherapie festgestellt werden.
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Mots clés: *Coxciella burnetii*, avortement, mortalité périnatale, chèvre, zoonose

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Parole chiave: *Coxiella burnetii*, aborto, nati morti, capra, zoonosi

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