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Dogs with Atopic Dermatitis: Effects of Oclacitinib Maleate on Serum Total Antioxidant and Total Oxidant Status Levels

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ABSTRACT

***Background*:** Canine atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease associated with epidermal barrier dysfunction, immune dysregulation, and oxidative stress. Total antioxidant status (TAS) and total oxidant status (TOS) are useful biomarkers for assessing systemic redox balance. Oclacitinib maleate, a selective Janus kinase 1 (JAK1) inhibitor, is widely used to control pruritus and inflammation in canine AD; however, its effects on oxidative balance remain unclear. This study aimed to evaluate the effects of short-term oclacitinib treatment on serum TAS and TOS levels in dogs with AD.

***Materials, Methods & Results*:** Dogs diagnosed with AD (n = 10) according to Favrot criteria and age-matched healthy control dogs (n = 10; 1-3 years-old) were included in the study. To ensure that oxidative parameters reflected primary atopic disease rather than concurrent conditions, secondary bacterial, fungal, and parasitic infections were excluded through detailed microbiological, mycological, and parasitological examinations. Dogs in the AD group received oral oclacitinib maleate at a dose of 0.5 mg/kg twice daily (q12h) for 7 days. Blood samples were collected from the control group once and from the AD group at three time points: before treatment (day 0), day 7, and day 14. Serum TAS and TOS levels were determined spectrophotometrically using commercially available ELISA kits. Pre-treatment TAS levels in dogs with AD were significantly higher than those of healthy controls and post-treatment values ($P < 0.05$). During the treatment period, TAS levels showed a significant progressive decrease and reached values comparable to those of healthy dogs by day 14. In contrast, no statistically significant differences were detected in TOS levels either between groups or across sampling time points ($P > 0.05$).

***Discussion*:** The elevated pre-treatment TAS levels observed in dogs with AD may represent a compensatory upregulation of systemic antioxidant defenses in response to chronic inflammation and increased oxidative burden. Inflammatory cytokines and activated immune cells promote reactive oxygen species (ROS) production, which can stimulate antioxidant mechanisms. Therefore, increased TAS levels before treatment may reflect an adaptive response to ongoing systemic inflammation. The significant decline in TAS during oclacitinib therapy suggests reduced inflammatory activity and, consequently, a decreased requirement for compensatory antioxidant defense. By inhibiting JAK1-dependent cytokine signaling, oclacitinib suppresses mediators involved in inflammation and pruritus and may thereby indirectly reduce oxidative stress. Moreover, its reported suppressive effects on $CD4^+$ and $CD8^+$ T lymphocytes suggest that the reduction in TAS may also be associated with modulation of immune-mediated antioxidant responses. Thus, decreased TAS following treatment may reflect both attenuation of inflammatory stimuli and immunomodulatory effects on effector immune cells. In contrast, the absence of significant changes in TOS throughout the study suggests that oclacitinib may not directly affect oxidant production or ROS generation. Its influence on redox balance may therefore occur mainly through modulation of inflammatory and immune pathways rather than through direct alteration of oxidant status. Overall, these findings suggest that oclacitinib treatment may modify systemic antioxidant balance in dogs with AD by reducing inflammation and immune activation. Further large-scale, long-term, and mechanistic studies are needed to clarify the relationship between JAK1 inhibition, immune modulation, and redox homeostasis in canine AD. Additional oxidative biomarkers may help characterize these treatment-related changes furthe.

Keywords: atopic dermatitis, canine, total antioxidant status, total oxidant status, oclacitinib.

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INTRODUCTION

Atopic dermatitis is a chronic, pruritic, inflammatory skin disease in dogs that develops on a genetic basis and is commonly associated with IgE-mediated hypersensitivity to environmental allergens, characterized by epidermal barrier dysfunction and immune dysregulation [5,8,10,16]. Diagnosis is primarily based on characteristic clinical findings, detailed anamnesis, and the Favrot criteria, which demonstrate high sensitivity and specificity, are widely used in clinical practice [2,4,6,16]. The main goals of treatment are to control inflammation and pruritus, restore skin barrier integrity, and prevent secondary infections [10]. Accordingly, immunosuppressive and immunomodulatory agents such as cyclosporine, oclacitinib, and corticosteroids are commonly used [3,11-14,16].

Immunosuppressive conditions may alter oxidative balance. TAS and TOS are important biomarkers of oxidative stress, reflecting overall antioxidant capacity and oxidant burden, respectively. Studies have reported decreased TAS and increased TOS levels during immunosuppressive therapy, particularly following organ transplantation and in autoimmune diseases [1,7]. However, the direct effects of oclacitinib, whose immunomodulatory effects are well defined, on TAS and TOS have not yet been scientifically clarified, and a lack of literature in this area has been observed [14]. The aim of this study was to evaluate the effects of systemic oclacitinib treatment on TAS and TOS levels at days 0, 7 and 14 in dogs with AD.

MATERIALS AND METHODS

Animals

In this study, the animal material consisted of a total of 10 dogs of different breeds and sexes, aged 1-3 years, which were brought to Dicle University Animal Hospital due to recurrent chronic dermatological problems, had not received any treatment in the past month, were diagnosed with AD according to Favrot criteria, and showed no signs of systemic infection (fever, nasal/ocular discharge, vomiting, diarrhea, etc.) or superficial/deep pyoderma.

The control group, on the other hand, consisted of 10 healthy dogs of different breeds and sexes, aged 1-3 years, which showed no clinical signs of dermatological manifestations (alopecia, scaling, erythema, lichenification, etc.) or systemic diseases. In both the patient and control groups, animals were selected taking into account similar age range and breed diversity, ensuring comparability between the groups.

Clinical examination

After taking the anamnesis of the dogs in the patient group, their routine physical, microbiological, and dermatological examinations were carried out in detail. Based on the clinical evaluations performed, AD was diagnosed according to Favrot criteria.

Collection of blood, skin scrapings, and swab samples

During routine clinical examinations, blood samples were collected from the control group dogs, and from the dogs diagnosed with AD before treatment and on days 0, 7, and 14 after treatment, from the *vena cephalica antebrachii* into anticoagulant-free tubes. The collected blood samples were centrifuged at 1,650 × *g* for 10 min. He obtained serum samples were stored at -80°C until the day on which TAS and TOS analysis were to be performed. In addition, swab and skin scraping samples were collected from the lesional areas of dogs suspected of AD using sterile swabs. Skin scraping samples were prepared with a KOH 10% solution and examined under a microscope for *Demodex* spp. and *Sarcoptes* spp. The collected swab samples were sent to the laboratory of the Department of Microbiology, Faculty of Veterinary Medicine, Dicle University for bacteriological and mycological analyses.

As a result of the analysis, 10 dogs with AD in which no growth was detected in bacteriological and mycological cultures were included in the study. Accordingly, only dogs that yielded negative results for secondary infection agents, and thus whose dermatological presentations could be primarily associated with AD, were evaluated in the study. This selection was made to provide more accurate and reliable results in comparisons between healthy and diseased groups.

Drug administration

All dogs diagnosed with AD were administered PO oclacitinib[1] [0.5 mg/kg, p.o., BID].

Total antioxidant status and total oxidant status measurement

In the obtained serum samples, the levels of TAS and TOS were measured spectrophotometrically using commercial ELISA kits[2] in accordance with the manufacturer's instructions. The measurements were carried out in the laboratory environment in compliance with the kit protocol, and the obtained data were used in the statistical analysis of the study.

Statistical analysis

The TAS and TOS levels of dogs with AD and healthy dogs were compared using statistical methods. All analysis were performed using SPSS 24.0 software[3]. In the comparison of the patient and control groups, the Mann-Whitney U test was applied considering the distribution characteristics of the data. In addition, One-Way ANOVA was used to evaluate the time-dependent changes in TAS and TOS values obtained in dogs with AD before treatment (day 0), and on days 7 and 14 after treatment.

RESULTS

Clinical examination findings

In the clinical examinations of 10 dogs brought to Dicle University Animal Hospital with complaints of skin lesions and severe pruritus, dermatological findings such as erythema accompanying pruritus, localized or generalized alopecia, and lichenification were detected. These findings were clinical signs consistent with AD and made a significant contribution to the diagnostic process in the evaluation of the cases. In addition, the fact that these signs were observed in a similar manner in all cases revealed that the disease followed a systematic pattern.

Blood, skin scrapings, and swab samples findings

Microscopic, bacteriological, and mycological analysis of skin scrapings and swab samples obtained from dogs suspected of atopic dermatitis revealed no ectoparasitic agents such as *Demodex* spp. or *Sarcoptes* spp., and no bacterial or fungal pathogens were detected.

Total antioxidant status and total oxidant status measurement findings

Significant differences were observed between the groups in terms of TAS. The pre-treatment period (day 0) of the patient animals showed statistically significantly higher TAS values compared to both day 7 and day 14 after treatment and healthy animals ($P < 0.05$). This indicates that there was a significant decrease in TAS levels as the treatment progressed, and by day 14, the values reached levels similar to those of healthy animals. In contrast, no significant difference in TAS was detected between the patient animals on days 7 and 14 after treatment and the healthy animals ($P > 0.05$) [Figure 1]. These findings indicate that the treatment had an effect on antioxidant levels. On the other hand, multiple comparisons regarding the TOS variable revealed no statistically significant differences between the groups ($P > 0.05$) [Figure 2]. This result indicates that the treatment process did not cause a significant change in TOS levels.

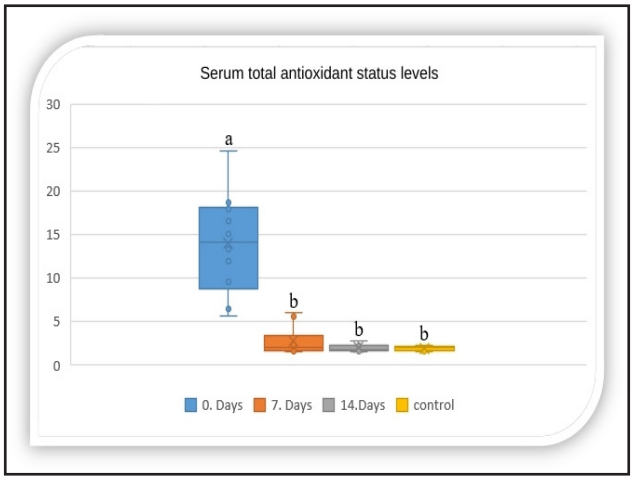

Figure 1. Distribution of the patient group by day and serum TAS levels of the healthy group. [a,b]The different statements in the header are statistically significant ($P < 0.05$).

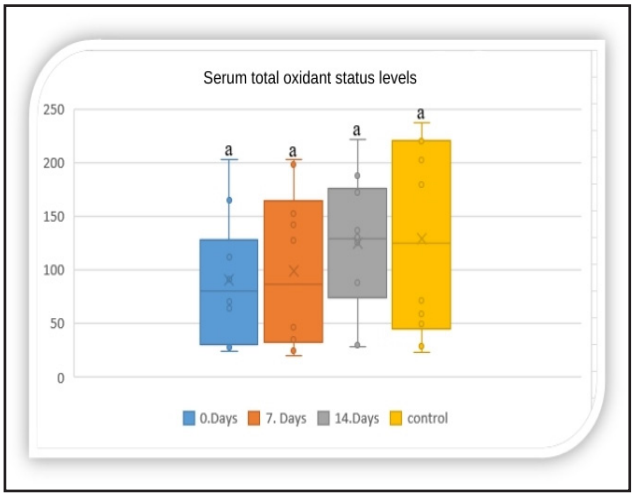

Figure 2. Distribution of the patient group by day and serum TOS levels of the healthy group.

DISCUSSION

In this study, the effects of oclacitinib maleate treatment on serum TAS and TOS were evaluated in dogs diagnosed with AD. The findings showed that, in the pre-treatment period, dogs with AD had significantly higher TAS levels compared to healthy controls; however, as the treatment progressed, TAS levels significantly decreased and by day 14 reached levels similar to those of healthy dogs. On the other hand, no statistically significant change was detected in TOS levels throughout the treatment process. Atopic dermatitis is a complex disease that arises from the interaction of multiple factors such as genetic predisposition, epidermal barrier dysfunction, immune dysregulation, and microbial colonization [9,16]. Oxidative stress, which plays an important role in the pathogenesis of AD, is considered both a cause and a consequence of the inflammatory process [15]. In this context, TAS and TOS levels, which reflect the oxidative balance status of the organism, are considered important biomarkers in terms of disease activity and response to treatment.

In this study, the high TAS levels found in dogs with AD before treatment may be an indicator of an enhanced antioxidant response against systemic inflammation. This finding supports the role of oxidative stress in the pathogenesis of AD [5,10]. It has been reported in the literature that inflammatory processes activate antioxidant defense and this may cause a temporary increase in TAS levels [13]. However, the significant decrease observed in TAS levels during the treatment process indicates a reduction in inflammation and consequently in oxidative stress. Oclacitinib maleate, through its JAK1 inhibitory effect, suppresses both pruritus and inflammation by blocking the signal transduction of inflammatory cytokines such as IL-2, IL-4, IL-6, IL-13, and IL-31 [1]. However, it has also been shown to exert immunosuppressive effects on effector cells of the immune system in parallel with this activity [7]. In the current study, the decrease observed in TAS levels may be related not only to the suppression of inflammation but also to the suppressive effects of oclacitinib on the immune response.

The *in vitro* studies revealed that oclacitinib suppressed $CD4^+$ and $CD8^+$ T cells both in terms of number and activation [7]. This situation may also indirectly lead to a weakening of the antioxidant response at the cellular level. On the other hand, the fact that no statistical change was detected in TOS levels in the study is noteworthy. This finding suggests that oclacitinib treatment does not have a significant effect on oxidant production. The stability of oxidant levels may indicate that the treatment does not have a direct effect on increasing ROS production. In the literature, there are limited data regarding the direct effects of oclacitinib on the oxidative system, and this study can be considered one of the 1st steps toward filling this gap [3,14].

In this study, the performance of detailed microbiological and parasitological examinations to exclude secondary infections in the diagnosis of AD is important in terms of demonstrating that the obtained biochemical results are specific to the primary disease. Disruption of the skin barrier and microbial colonization are among the important triggers of oxidative stress in AD [15], and controlling these factors has increased the reliability of the study.

CONCLUSIONS

This study demonstrated the effects of oclacitinib maleate treatment on oxidative balance in dogs diagnosed with AD, showing that there was a significant decrease in TAS levels during the treatment process, whereas no marked change was observed in TOS levels. The findings suggest that while oclacitinib is effective in controlling inflammation and pruritus, it may weaken the antioxidant defense system due to its immunomodulatory effects. Therefore, considering the possible effects of oclacitinib on oxidative stress in the treatment of AD, it may be beneficial to plan antioxidant support, especially in long-term treatment applications.

In addition, the long-term effects of oclacitinib on redox balance should be evaluated through further studies with larger sample groups and supported by different clinical presentations.

MANUFACTURERS

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Ethical approval. Ethical approval was obtained from the Local Ethics Committee for Animal Experiments, XXX University (10-03/26.03.2025).

Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Artificial intelligence statement. The authors declare that no Artificial Intelligence (AI) was used in this study. The authors are solely responsible for all aspects of the work.

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