VET EXPERT
BASED ON EVIDENCE

CLINICAL EVALUATION OF POLYUNSATURATED FATTY ACIDS IN COMBINATION WITH PALMITOYLETHANOLAMIDE (PEA) (VETOSKIN ULTRA) IN THE TREATMENT OF ATOPIC DERMATITIS SYMPTOMS IN DOGS.

SUMMARY

Atopic dermatitis is the most common allergic disease in dogs. The main symptom of the disease is severe pruritus and potential treatments include treating the causes or symptomatic treatment. As part of symptomatic treatment, glucocorticosteroids, oclacitinib and lokivetmab are used, while less severe symptoms can be treated using polyunsaturated fatty acids, antihistamines, cannabidol or palmitoylethanolamide.
The purpose of the study was to evaluate the effectiveness of palmitoylethanolamide in combination with polyunsaturated fatty acids in the symptomatic treatment of atopic dermatitis in dogs.
The study was performed in 16 dogs, divided into the study arm (10 animals) and control arm (6 animals). The study arm received palmitoylethanolamide in combination with polyunsaturated fatty acids, while the control arm received placebo. In all animals, the intensity of pruritus (pVAS) and the severity of skin lesions (CADESI 04) were assessed six times at weekly intervals.
In the study arm, there was a statistically significant reduction of pruritus after 4 weeks of treatment and a reduction of skin lesions was achieved after 2 weeks of treatment. Compared to the control arm, differences in both assessed parameters were observed after 4 weeks of treatment.
Palmitoylethanolamide combined with polyunsaturated fatty acids effectively reduces the intensity of skin lesions and pruritus.

Keywords: palmitoylethanolamide, polyunsaturated fatty acids, dogs, atopic dermatitis.

Atopic dermatitis in dogs is the most commonly diagnosed allergic disease in this species. It follows a typical course, with the predominant symptom being severe pruritus and skin inflammation, leading to post-pruritic lesions such as alopecia, scrapes, scabs or, in chronic cases, skin lichenification. Treatment of the disease is based on specific immunotherapy or symptomatic treatment with anti-inflammatory/antipruritic drugs. Several methods are used in symptomatic treatment. In cases of severe pruritus, it is interrupted with topical or systemic glucocorticosteroids, lokivetmab, oclacitinib or ciclosporin, while recent studies have also demonstrated the effectiveness of stem cells in such cases.
In case of less severe pruritus or in order to sustain the antipruritic effect achieved with more potent drugs, antihistamines and polyunsaturated fatty acids can be used, as well as baths in antipruritic shampoos. Since positive effects of polyunsaturated fatty acids will usually appear after prolonged use (measured in weeks), these acids cannot be used to stop severe pruritus in cases of acute AD, but rather when it is mild to moderate, or as one of the treatment components to prevent pruritus recurrence (15).
The primary mechanism of action for polyunsaturated fatty acids is the inhibition of arachidonic acid metabolism, which leads to a reduction in the levels of pro-inflammatory mediators (omega-6 acids) or conversion into anti-inflammatory mediators (omega-3). In addition, the effect of polyunsaturated fatty acids may affect the cell membranes of mast cells, reducing their degranulation (23, 25). In addition, it has been demonstrated that the administration of polyunsaturated fatty acids leads to mononuclear cell proliferation (26). An important mechanism of action of polyunsaturated fatty acids is their effect on the skin barrier, which consists in improving ceramide production. Ceramides are lipids whose effects are crucial for providing an effective skin barrier that determines the reduction of transepidermal water loss. They also exhibit a bacteriostatic effect. It has been demonstrated that polyunsaturated fatty acids supplementation leads to increased lipid content in the epidermis, thereby improving the state of the skin barrier and reducing transepidermal water loss (20,

9). Topical spot-on or spray application of polyunsaturated fatty acids onto the skin is also effective in reducing pruritus and skin lesions, as well as improving skin barrier integrity (27, 3). Furthermore, the use of polyunsaturated fatty acids improves hair quality, both in animals with atopic dermatitis and healthy animals (9).

Polyunsaturated fatty acids are often used in combination with quercetin, vitamins A, D, E or palmitoylethanolamide. Particularly interesting is their simultaneous use in combination with the latter substance, i.e. palmitoylethanolamide (6, 7, 19). Palmitoylethanolamide (PEA) is a naturally occurring bioactive lipid similar to endocannabinoids. Endocannabinoids and PEA are generated in response to stress and tissue damage and play an important role in regulating the skin's immune response. The effect of PEA most likely involves limiting mast cell degranulation. Studies have demonstrated that it is useful in reducing allergy symptoms in companion animals (22, 8, 28, 14). When used alone, PEA has been found to have an antipruritic effect following prolonged use, reducing skin lesions and pruritus intensity. It is primarily useful for treating patients with mild to moderate pruritus and skin lesions. In the studies by Noli et al. it was determined that after 8 weeks of PEA treatment (administered at a dose of 10 mg/kg), improvement was seen in most of the studied dogs, with the reduction in skin lesions being significant and without exceeding symptom aggravation as in the case of animals in remission.

In addition, polyunsaturated fatty acids can also be used to reduce the dose of potent antipruritic drugs such as glucocorticosteroids, ciclosporin or oclacitinib, with which they exhibit a synergistic effect (17, 18). Concomitant administration of polyunsaturated fatty acids and glucocorticosteroids has been demonstrated to reduce the dose of the latter by approximately twofold after 84 days of treatment (21). In other studies, combining polyunsaturated fatty acids with prednisolone reduced the dose of the latter by 24% to 100% in most of the animals involved in the experiment. Obviously, this reduction was achieved following prolonged polyunsaturated fatty acid use (12 weeks) (4). Polyunsaturated fatty acids are also effective in lowering ciclosporin doses. In a study conducted in 2016, their concomitant administration with ciclosporin, allowed for reducing the dose from 4.1 to 2.6 mg/kg of body weight, which is a statistically significant value. In addition, there was a greater decrease of pruritus in the group treated with ciclosporin with fatty acids compared to dogs treated with ciclosporin alone (11). The 2023 studies by Nishyjama et al. demonstrated that polyunsaturated fatty acids exhibit a synergistic effect with oclacitinib, leading to a significant reduction of pruritus and skin lesions compared to the group receiving oclacitinib alone. The positive effects of concomitant administration of both substances were evident already after 4 weeks of use (13). Moreover, concomitant use of polyunsaturated fatty acids with antihistamines exhibits a synergistic effect.

The products used for treatment contain various fatty acids, such as γ-linolenic acid (GLA) and eicosapentaenoic acid (EPA). There is no clear information on the recommended ratio between omega-6 and omega-3 fatty acids. For example, in 2003, a study was conducted using different ratios of fatty acids (ratios of omega-6 to omega-3 fatty acids ranging from 9.9:1 to 20.1:1), and in each case positive effects were observed, reducing the severity of skin lesions and pruritus after an eight-week treatment period (12). Scott is of the opinion that their efficacy increases with the dose and they are safe even after exceeding the manufacturer's recommended dose by 4–10 times (24).

MATERIALS AND METHODS

The study was performed in 16 dogs diagnosed with atopic dermatitis. The diagnosis was made after the patient met Favrot's diagnostic criteria (set no. 2). Each animal met at least 5 criteria. All dogs had been previously put on an elimination diet for no less than 6 weeks to rule out food allergies. The animals received regular antiparasitic prophylaxis with spot-on preparations. Fungal and bacterial infections, as well as parasitic invasions were ruled out on the basis of a microscopic examination of hair, scraping and cytological examination of impression preparations from the skin. Prior to treatment, the animals had not received glucocorticosteroids, lokivetmab, ciclosporin, oclacitinib or polyunsaturated fatty acids for at least a month. Animals with mild to moderate CADESI 04 disease severity (less than 60 points) and a pVAS pruritus score of less than or equal to 5 (16) were eligible for the study.

The group was randomly divided into two subgroups: a study arm of 10 individuals who received VetoSkin Ultra for 6 weeks at the dose recommended by the manufacturer and a control arm of 6 individuals who received placebo. Both VetoSkin Ultra and placebo were administered daily. Owners were blinded as to whether the animal was receiving VetoSkin Ultra or a placebo. All dog owners agreed to participate in the study. Dogs in the study arm (6 males, 4 females) were aged 2 to 6 years (median 3.5 years) with a body weight of 6 to 15 kg (median 11). The group included 3 French Bulldogs, 2 Maltese dogs, 1 West Highland White Terrier and 4 mixed-breed dogs. The control arm (3 males and 3 females) consisted of 2 French bulldogs, 2 West Highland White Terriers, 1 Maltese and 1 mixed-breed dog. The weight of the dogs in this group was between 6 and 15 kg (median 11.5), with the animals aged between 2 and 5 years (median 3.5).

A CADESI 04 clinical assessment of skin lesion severity and a pVAS assessment of pruritus severity were performed in all dogs in both the study and control arms. Assessment was performed on the day the study began and then at weekly intervals for 6 consecutive weeks.
Statistically significant differences between the results obtained during the study in both groups, as well as differences between groups at individual time intervals were calculated using the Mann-Whitney U test for $p<0.05$. Normal distribution of the sample was tested using the Kolmogorov-Smirnov test.

Animals in the study arm had an average CADESI 04 score of 32.81 on the day the study began. Over the course of the study, this score gradually decreased. A statistically significant decrease in CADESI 04 was determined after 2 weeks of product use ($p=0.036$). A statistically significant decrease in the parameter persisted until the end of observation and at Week 6 it was 17.9 ($p=0.003$).
A gradual decrease in pVAS pruritus severity was also noted. It averaged 3.2 on the day the observation started and decreased during the study, achieving a statistically significant difference compared to the baseline value at Week 4 of administration ($p=0.034$), which persisted until the end of the observation. At Week 6, the score was 1.1 and statistically different from baseline ($p=0.0004$).
In the control arm, there was no statistical reduction in the values of both skin lesion and pruritus severity. CADESI 04 values averaged 33.33 on the study's start date, reaching 35.33 on the day the observation ended ($p=1$). On the day the study started, pVAS scores averaged 3 and 3.33 on the day it ended ($p=0.91$).
While comparing the changes in skin lesion severity between the control and study arms at each time interval, it was determined that skin lesion severity was significantly lower in the study arm after Week 4 ($p=0.034$) as well as on the day the study ended ($p=0.02$).
Regarding pruritus severity, it was determined that pruritus statistically decreased in the study arm compared to the control arm after 4 weeks ($p=0.02$) and was also significantly lower on the day the study ended ($p=0.01$).
The results obtained are illustrated in Figures 1a, 1b, 2a and 2b.

Fig. 1a
Comparison of skin lesions severity (CADESI 04) in dogs in the study arm receiving VetoSkin Ultra and the control arm without the product – line graph.
*, # – indicate statistically significant differences.

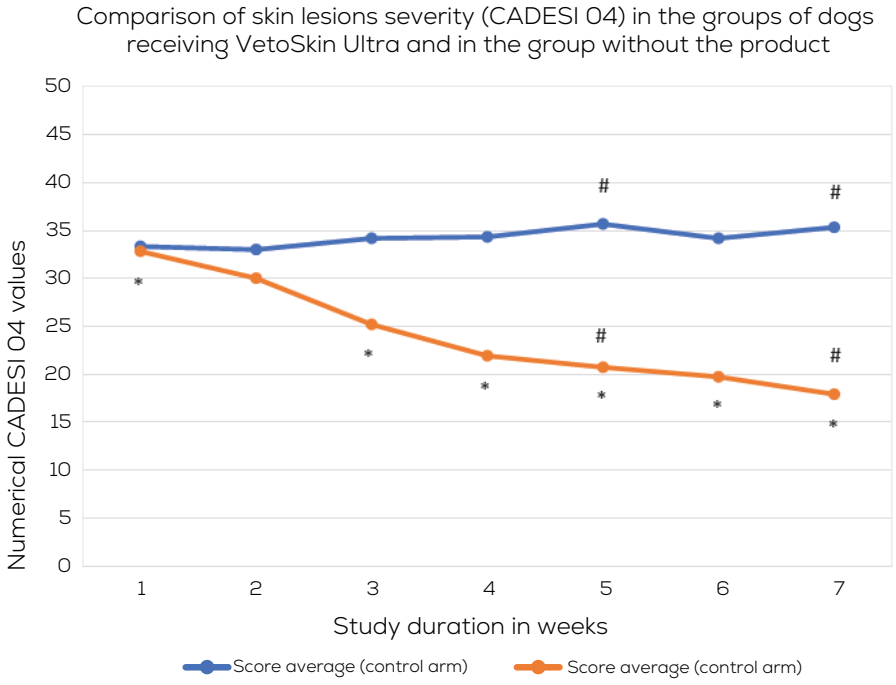


Fig. 1b
Comparison of skin lesions severity (CADESI 04) between the group receiving VetoSkin Ultra (study arm) and the group of dogs in which the product was not used (control arm).

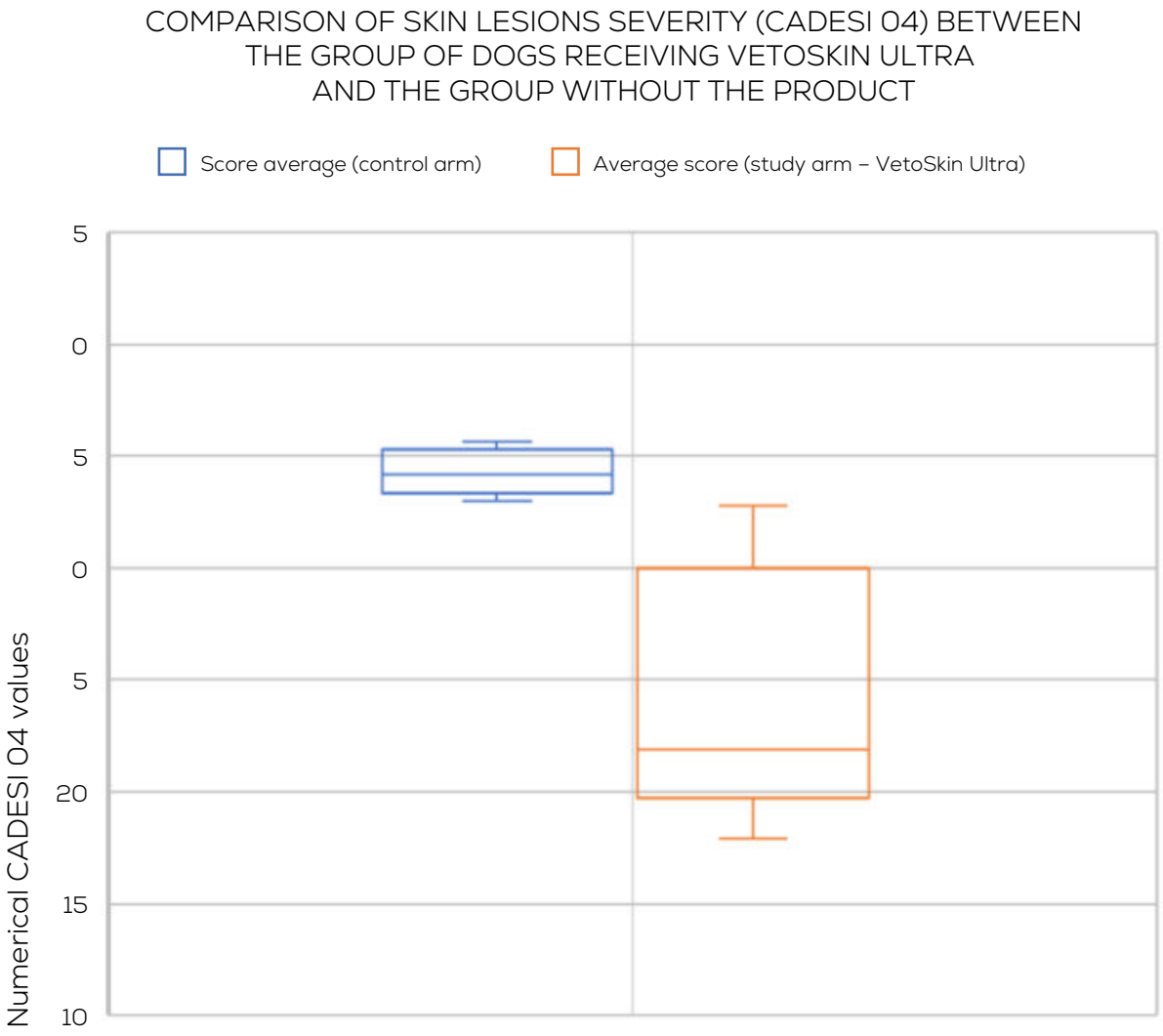


Fig. 2a
Comparison of pruritus severity (pVAS) in the group of dogs receiving VetoSkin Ultra (study arm) and in the group without the administration of the product (control arm) – line graph.
*, # – indicate statistically significant differences

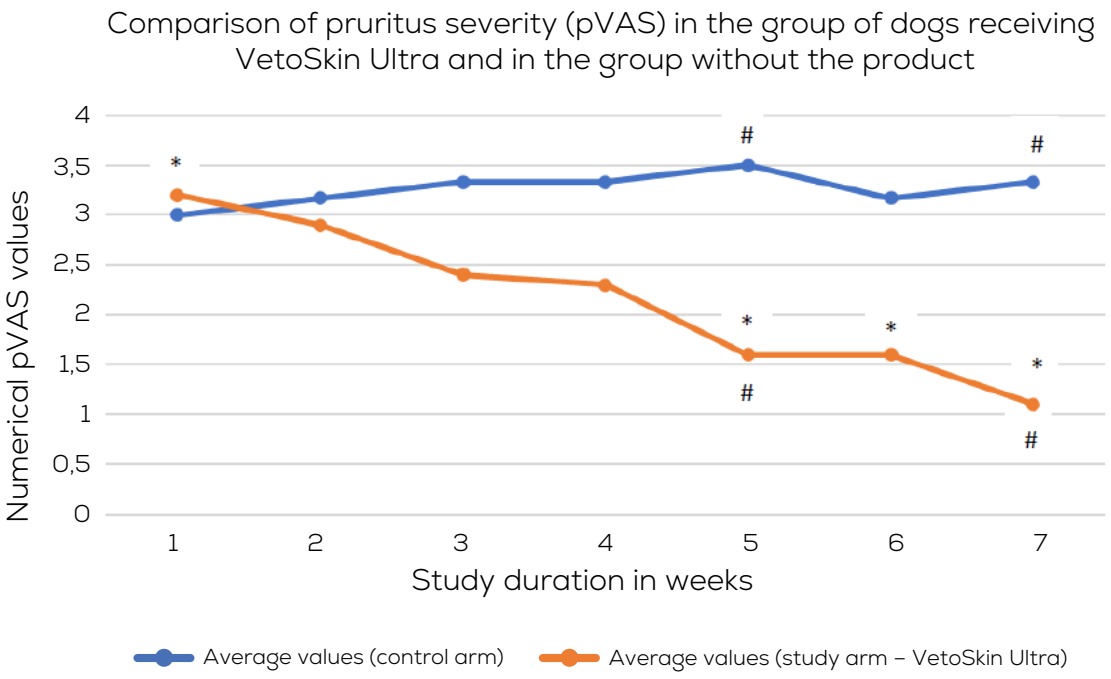
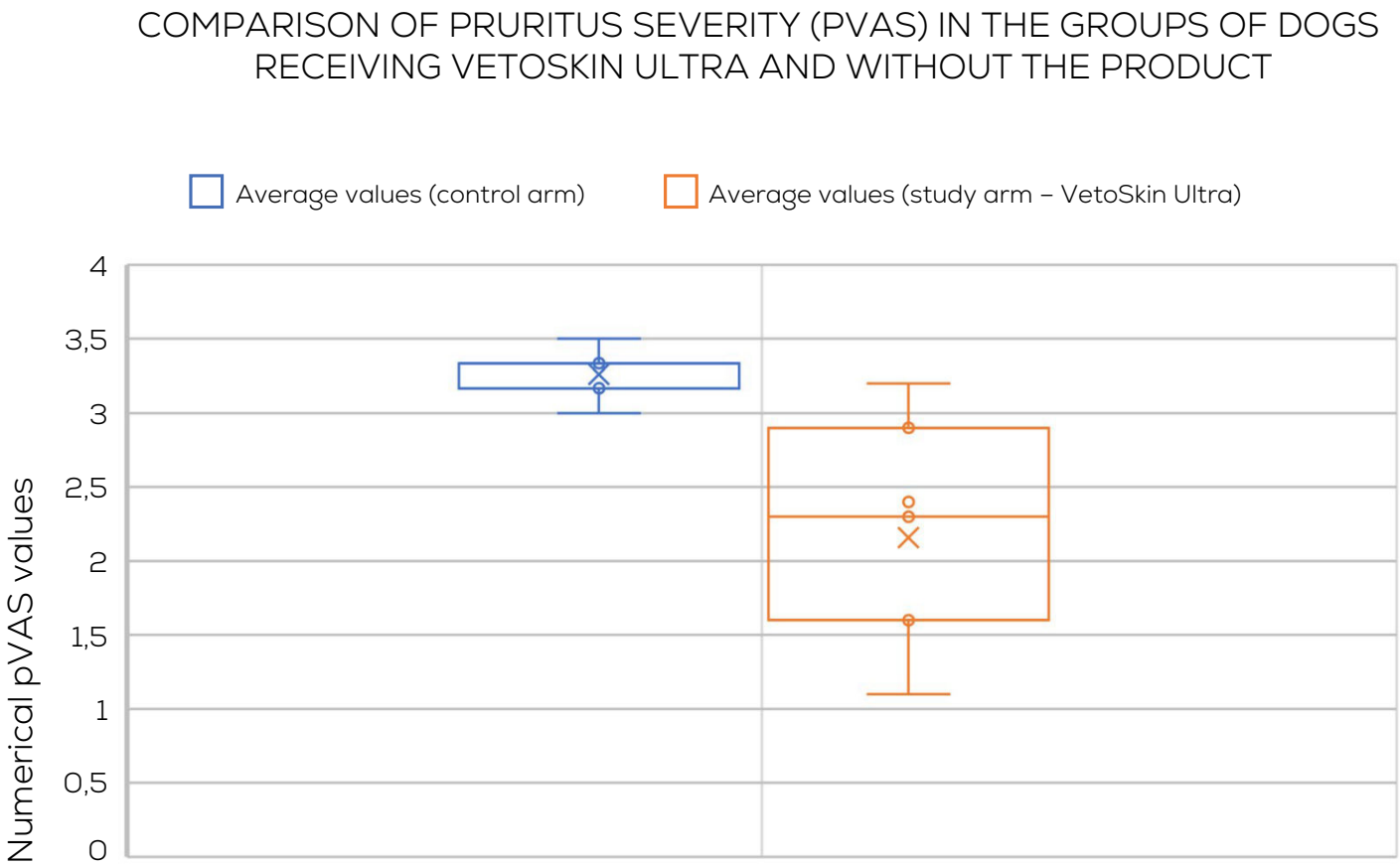


Fig. 2b
Comparison of pruritus severity (pVAS) in the group of dogs receiving VetoSkin Ultra (study arm) and in the group without the product (control arm).



In our studies, a significant reduction in pruritus and skin lesion severity compared to the control arm was observed already after 4 weeks of treatment (and in case of skin lesions severity compared to the baseline value already after 2 weeks). This result is better than the ones obtained by other authors who used polyunsaturated fatty acids and palmitoylethanolamide separately.
In the studies by Cambell et al. who used a commercial product containing polyunsaturated fatty acids with a 5:1 ratio of omega-6 to omega-3 fatty acids, a statistically significant pruritus reduction was determined in 40% of treated dogs only after 8 weeks of its administration (assessed with the PICAD system), and a skin lesion reduction in more than 55% of animals over the same time (assessed with the LICAD system) (5). Although a decrease in the values of both parameters assessed in these studies was already evident after 4 weeks of use, it was not yet statistically significant, which is different from
our observations, where a statistically significant difference was determined during this period.
Similarly, a 2005 study by Abba et al. showed the efficacy of polyunsaturated fatty acids after 8 weeks, where the condition of 53% of animals in the early stages of the disease improved, and only 14%
in chronic cases. Evaluation was also performed by the authors after one month of treatment but they do not report the effectiveness of treatment after this period (1). The results obtained in our study are inconsistent with the authors' observations, as we determined significant improvement during a twice shorter period.
In a 2004 study by Mueller et al. administration of polyunsaturated fatty acids produced positive effects only after 10 weeks of use. The authors did not evaluate clinical effects at shorter time intervals. Also referring to these results, the effects

obtained in our studies were faster (10).
Positive effects were observed in animals receiving polyunsaturated fatty acids in their diet. The dogs were fed commercial foods containing high levels of polyunsaturated fatty acids, leading to a significant pruritus and skin lesion reduction. In observations carried out in 2008, where polyunsaturated fatty acids were administered in this way, it was determined that pruritus was reduced after 30 days of their use; the severity of skin lesions was reduced, but without a statistically significant difference after both 30 and 60 days. (2) The results obtained by these authors with regard to pruritus are comparable to those obtained by us, whereas the ones regarding skin lesions are inconsistent (a decrease in this parameter was determined in our studies).
Regarding the efficacy of palmitoylethanolamide used alone,
the results obtained in our studies are also better than those obtained by other authors. Noli et al. in 2015 determined that when administering palmitoylethanolamide alone to atopic dogs, significant improvement occurred only after 8 weeks of using the substance (14).
To summarize the results of our observations on the concomitant use of polyunsaturated fatty acids in combination with palmitoylethanolamide in dogs with atopic dermatitis, significantly better results were obtained compared to using these active substances separately, exhibiting in a more rapid clinical improvement in both skin lesion severity (assessed by the CADESI 04 system) and the reduction in pruritus severity (assessed by the pVAS system). Therefore, the combination of palmitoylethanolamide and polyunsaturated fatty acids works synergistically to accelerate the effect of these substances. It is therefore reasonable to use such a combination concomitantly, which allows for significant pruritus and skin lesion severity reduction in cases of mild or moderate clinical signs in the course of atopic dermatitis in dogs.

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