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Original article

Evaluation of the clinical efficiency of lokivetmab in client privately owned atopic dogs – multicenter study

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Abstract

Atopic dermatitis (AD) is the most frequent allergic disease in dogs. AD can be treated using allergenspecific immunotherapy as well as symptomatic antipruritic treatment including the use of lokivetmab - caninized anti-interleukine-31 antibody.

The aim of the study was to evaluate the effectiveness of lokivetmab over 12 weeks of treatment. Studies have been carried out in 89 dogs. In all affected animals, the severity of lesions was assessed using the CADESI 04 and the pruritus was assessed using the VAS.

After the first dose of lokivetmab, both CADESI 04 and VAS statistical decreased by 4 weeks from 40.48 to 20.31, and from 7.42 to 2.48, respectively ($p = 0.0000001$) maintained significantly decresed values during the whole treatment period (CADESI 04 15.64, 15.07 after 8 and 12 weeks, respectively, PVAS 2.03, 1.95 after 8 and 12 weeks, respectively).

Lokivetmab leads to a significant reduction of CADESI 04 and pruritus, within four weeks and maximum effect is achived after the second dose.

Key words: atopic dermatitis, dog, lokivetmab

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Introduction

Allergic diseases in dogs belong to the most common skin diseases. Atopic dermatitis (AD) stands for the most frequent allergic disease in dogs. It is widely believed that cases of the disease constitute no less than 10% of all skin diseases in this species (Hiller and Griffin 2001).

Several treatments for atopic dermatitis are currently available. AD can be treated using allergen-specific immunotherapy as well as symptomatic antipruritic treatment including glucocorticoids, ciclosporin, oclacitinib or lokivetmab (Olivry et al. 2003, Forsythe and Paterson 2014, Gadeyne et al. 2014, Michels et al. 2016, Moyaert et al. 2017).

The last of these drugs, lokivetmab, is a caninized anti-interleukin-31 antibody that binds circulating IL-31, thereby preventing its binding to the receptor. In the study assessing the safety and efficancy of lokivetmab it was found that at a dose above 0.5 mg/kg it leads to a significant reduction of IL-31-dependent pruritus for at least four weeks (Michels et al. 2016). The resulting decreased pruritus directly correlated to improved skin condition as determined clinical assess using the CADESI 03 and PVS (Michels et al. 2016, Moyaert et al. 2017). The effectiveness of the drug was also evaluated using the transepidermal water loss test (TEWL) (Szczepanik et al. 2019).

The aim of this study was to assess the effectiveness of lokivetmab in dogs diagnosed with atopic dermatitis, at recommended (in Europe) by the manufacturer dose of 1mg/kg during 12-week treatment with VAS and the currently validated method of assessing the severity of clinical symptoms, CADESI 04.

Materials and Methods

89 client-owned dogs (39 males and 50 females) aged from 7 months to 10 years (median of 48 months) weighing from 4 kg to 60 kg (median 15.35) were enrolled from 9 clinics. The dogs were of the following breeds: French bulldog (18), crossbreed (11), bull terrier (8), labrador (6), golden retriever (4), Jack rusell rerrier (4), amstaff (3), German shepherd (3), Shith-tzu (3), whwt (3), Yorkshire terrier (3), Boston terrier (3), beagle (2), fox terrier (2), Swiss shepherd dog (1), English bulldog (1), giant schnauzer (1), pointer (1), Syberian husky (1), Rhodesian ridgeback (1), Dog de Bordeaux (1), pug (1), akita (1), Hungarian pointer (1), Weimar pointer (1), maltese (1), Polish hunting dog (1), bichon (1), dachshund (1).

The owners of the animals expressed their consent to participate in the research. The procedures used were non-invasive and in accordance with the law in Poland were classified as routine medical and veterinary procedures that do not require the consent of the ethics committee.

Dogs were diagnosed with atopic dermatitis on the basis of published diagnostic criteria. The second set of criteria was used (set 2) (Favrot et al. 2010). Other inflammatory pruritic skin diseases were excluded using trichoscopic examination, skin scrapings and cytology as well as a 6-week elimination diet trial. Allergic flea dermatitis was ruled out based on the use of appropriate anti-flea treatment. The animals were not treated prior to the start of the study and did not receive cyclosporin, oclacitinib, glucorticoids, antihistamines, polyunsaturated fatty acids or pentoxifylline for at least two months prior to the study.

The animals were treated with lokivetmab (Cytopoint Zoetis Rue Laid Burniat, Belgium). Lokivetmab was supplied as 1 ml single-use vials. The vials contained the solution at one of four concentrations: 10, 20, 30, 40 mg / ml. Dogs weighing up to 10 kg received 10 mg of lokivetmab, 10-20 kg - 20mg, 20-30 kg - 30 mg, 30-40 kg - 40 mg, according to the manufacturer's instructions. The dose of the drug administered was from 1 to 2.22 mg/kg of body weight. (mean 1.32 mg/kg of body weight). Lokivetmab was given subcutaneously, three times at 4-week intervals.

In all affected animals, the severity of lesions was assessed using the CADESI 04 method and the pruritus intensity was assessed. The CADESI 04 was performed in dogs with AD before treatment (week 0), and three times at four week intervals after 4 weeks, 8 weeks, and 12 weeks.

CADESI 04 system was used to determine CADESI (Olivry et al. 2014). The severity of pruritus was assessed according to the numerical scale of VAS (0-10) (Hill et al. 2007, Rybnicek et al. 2009).

Statistical analysis

The statistical differences between the individual measurements (before the start of the treatment and after 4, 8 and 12 weeks) for the CADESI 04 and the severity of pruritus scores were calculated. Differences in statistical significance between the results were calculated based on the U-Mann-Whitney test. Bonferroni corrections were made in all cases. $P<0.05$ values were considered significant.

In addition, the effectiveness of the treatment was evaluated by assessing the number of dogs who achieved more than 50% pruritus reduction (assessed with VAS) and clinical symptoms (assessed using CADESI 04). The results were expressed as the percentage of dogs whose state improved in comparison to the entire study population. Statistically significant differences were calculated between treatment intervals

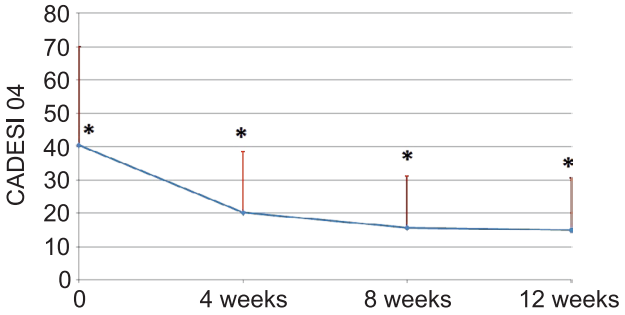

Fig. 1. Average values of CADESI 04 in dogs treated with lokivetmab (with marked standard deviation), * significant differences.

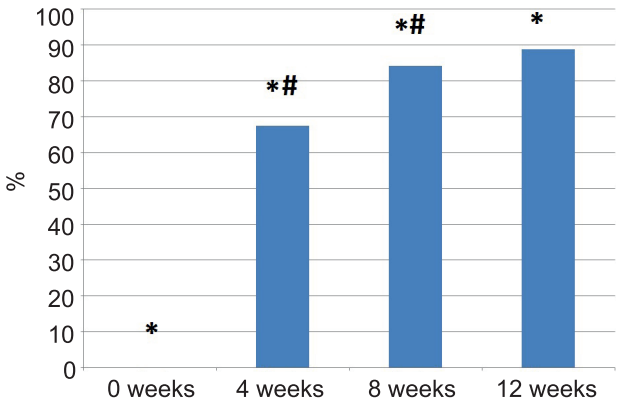

Fig. 3. Percentage of dogs with more than 50% reduction in CADESI 04 during treatment with lokivetmab, *, # significant differences.

(before the start of the treatment after 4, 8 and 12 weeks). To calculate significant differences, the Chi square test was used at $p<0.05$.

All analyses were performed using Statistica 10 software (Statsoft, Tulsa, OK, USA).

Results

Before the start of the study in dogs, their CADESI 04 score ranged from 2 to 187 (mean 40.48) and VAS ranged from 4 to 10 (mean 7.32). During the use of lokivetmab, both CADESI 04 and VAS decreased. The statistical decrease in the values of both parameters was found as soon as after 4 weeks ($p=0.0000001$ for both assessed parameters) and was maintained throughout the entire treatment period ($p=0.0000001$ for both assessed parameters for differences between measurements before treatment and measurements at 8th and 12th week). There was no statistically significant reduction in the values of the parameters evaluated between 4th and 8th week ($p=0.061$ for VAS and $p=0.089$ for CADESI). There was also no significant reduction in the parameters between 8th and 12th week ($p=0.92$ for VAS and $p=0.89$ for CADESI 04). There was no statistically significant difference regarding CADESI

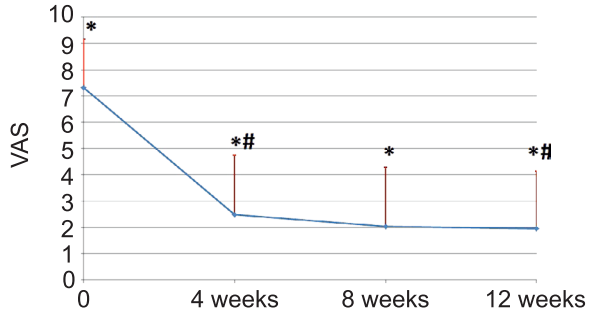

Fig. 2 PVAS mean values in dogs treated with lokivetmab (with a standard deviation marked),*, # significant differences.

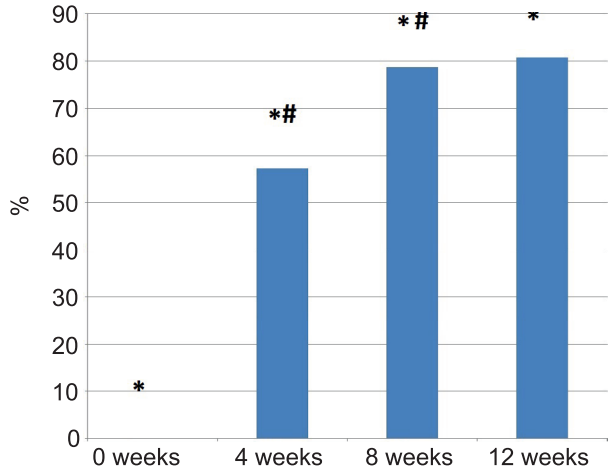

Fig. 4. Percentage of dogs with more than 50% reduction in pruritus during treatment with lokivetmab, *, # significant differences.

between the measurements at 4 and 12 weeks ($p=0.053$), whereas the difference was in the case of VAS ($p = 0.045$). The results obtained are presented in Figs. 1 and 2.

With regards to the effectiveness of the treatment as measured by owner-assessed VAS, it was found that 67.4% of dogs experienced a more than 50% reduction in pruritus after four weeks, 84.26% after 8 weeks and 88.76% after 12 weeks. When assessing the severity of skin lesions using CADESI 04 method, over 50% reduction in clinical symptoms was measured in 57.3% of dogs after 4 weeks, 78.77% after 8 weeks and 80.83%, after 12 weeks. The results are shown in Figs. 3 and 4. Statistically, there were differences between the start of treatment and the number of individuals whose condition improved at 4th, 8th and 12th week (for both parameters assessed $p=0.05$). The difference was noted also between the number of individuals whose conditions improved at 4th and 8th week for both parameters assessed ($p=0.05$). It was not noted that the number of individuals who showed improvement varied between 8th and 12th week.

Discussion

Lokivetmab administered subcutaneously at the average dose of 1.32 mg/kg once every four weeks, caused significant decreases in CADESI 04 and VAS. The most significant effect in reducing pruritus and CADESI 04 was found after four weeks of treatment. In subsequent measurements, after 8 and 12 weeks, we noted further reduction in pruritus and CADESI 04 values, however, the decrease was not significant (only significant reduction of VAS between week 4 and 12 was noted) . The decrease in the values evaluated after 12 weeks no longer showed differences significant in relation to the values of these parameters at week 8, which points to the fact that after the second administration of the drug the maximum therapeutic effect of lokivetmab was already obtained. Similar conclusions can be drawn by assessing the effectiveness of treatment based on the number of animals that improved both in the assessment of pruritus and CADESI 04; the most significant effect occurs after 4 weeks, after 8 weeks there is a certain increase in the number of individuals who improved, after 12 weeks the increase in the numbers of animals is minor and does not differ statistically from the number of individuals whose condition improved during the 8th week.

Lokivetmab was evaluated for the effectiveness of treating atopic dermatitis in client-owned animals. The evaluation was performed with the use of VAS and CADESI 03 - an older clinical assessment system. Michels et al. (2016) showed a decrease in the value of CADESI 03, as well as pruritus, after the use of the drug, finding its greatest effectiveness at the dose of 2 mg/kg. The authors, however, did not use the drug in the dose we utilized (according to the manufacturer's recommendations, i.e. 1 mg/kg of body weight), and the administration was performed only once. The effect of the drug was observed for two months, therefore, one cannot compare the results directly with those obtained in our study. According to the study cited above, the anti-pruritic effects of the drug (at a dose of 2 mg/kg of body weight) is maintained (superior to placebo) for 49 days, and reduction of the CADESI 03 score for 56 days.

In a later study conducted by Moyaert et al. (2017), the assessment of the clinical effectiveness of lokivetmab (CADESI 03 and VAS) was carried out in a similar way as compared to our studies after using the drug on a monthly basis. These authors found a significant reduction in CADESI 03 (from 184 to 57) after 12 weeks of treatment. Similarly to our studies, where the largest decrease was noted after 4 weeks (from 40.48 CADESI 04 to 20.31 after 4 weeks - a decrease by almost 50%) in Mayaert studies, the decrease was most significant after the first administration of the drug (CADESI 03 from 184 to 76 - after 4 weeks the decrease was reported by over 56%). Similarly, in the case of pruritus assessment, the most significant decrease was observed by the authors at the beginning of treatment (after 4 weeks, a decrease by over 43% as compared to a 66% decrease in our study). When assessing the number of individuals in which clinical improvement with regards to 4-week pruritus treatment was observed in the study of the abovementioned authors, it occurred in 39% of animals; after 12 weeks it occurred in 49% of the animals. Similarly, when using the CADESI system as a criterion for clinical improvement, the authors observed it in 12.7% of cases after 4 weeks and almost in 37% of cases after 12 weeks. These results are slightly lower than those obtained by us, which results from slightly different criteria used by Mayaert et al. (2017) who assessed the percentage value of individuals with remission (arbitrarily determining the values of CADESI and PVS) while our studies assessed the number of individuals with more than 50% reduction of clinical symptoms and pruritus. However, it can be stated that in both Mayert's and our studies, a gradual increase in the number of animals that recover or improve in clinical condition is evident and administration of lokivetmab can stopped disease flares in dogs with the spontaneous disease.

The CADESI 04 system was used to assess the effectiveness of treatment with Lokivetmab in 2019 (Szczepanik et al. 2019). The authors found the highest reduction of this parameter (from 36.3 to 11.1) after four weeks of treatment, similarly to current studies. The decrease in the assessed parameter after 8 and 12 weeks was not as significant. The results obtained, regarding the effectiveness of treatment, are in line with ours. A drawback at Szczepanik et al. (2019) research is that it was carried out on a relatively small number of animals. In the studies of the above authors, the effectiveness of lokivetmab was also assessed by measuring transepidermal water loss (TEWL) with results similar to those obtained by clinical methods (the highest reduction after 4 weeks).

Tamamoto-Mochizuki et al. (2019) conducted research on the use of lokivetmab in proactive therapy, in which it was subjected for one year at 4 weeks intervals. The average time without time-to-flare reaction was 63 days, but 28% of dogs did not exhibit a flare for at least one year. After 3 months of use, no symptoms of atopic dermatitis were found in 1/3 of the tested animals. There are no known reasons why this form of proactive therapy is more effective in some individuals and this requires further research. The observations cited above are not fully consistent with our re-

search because we did not observe recurrence of the disease during 3 months of lokivetmab use. Moyaert et al. (2017) also observed a gradual increase in the number of animals that recovered and no relapses of disease was seen during three months of treatment. In the study conducted by Tamamoto-Mochizuki et al. (2019) different criteria of severity assessment of the disease was used, so this may explain of different result. Criteria for exclusion from the trial were also different and this may influence for results.

In conclusion, lokivetmab administered at a dose of 1.26 mg/kg at 4-week intervals leads to a significant reduction of CADESI 04 and pruritus, while the most visible improvement occurs after the first dose; further administration brings less reduction of pruritus and lesion severity while after the second dose the maximum effectiveness of treatment is achieved; further administration no longer leads to significant reduction in the assessed parameters. In this study, we also proved the ability of the anti-IL-31 lokivetmab to prevent the development of clinical signs in atopic dogs. In 3 months of therapy any relapses of clinical signs were not observed . In concussion, lokivetmab may be used in proactive therapy in canine atopic dermatitis for flare prevention.

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