

Efficacy and safety of lokivetmab (Cytopoint®) for the control of pruritus and skin lesions in dogs with atopic dermatitis

Eficácia e segurança de lokivetmab (Cytopoint®) no controlo do prurido e lesões cutâneas em cães com dermatite atópica

Data de receção / Received in: 30/12/2020

Data de aceitação / Accepted for publication in: 25/4/2021

Rev Port Imunoalergologia 2022; 30 (1): 21-30

Marta Pinto^{1,*} , Maria Alice Silva^{1,*} , Beatriz Fernandes¹ , Ana Filipa Bizarro¹ , Hugo Pereira¹ , Ana Mafalda Lourenço¹ 

¹ University of Lisbon, Faculty of Veterinary Medicine, Centre for Interdisciplinary Research in Animal Health (CIISA), Lisbon, Portugal

* Marta Pinto and Maria Alice Silva equally contributed to this article.

ABSTRACT

Background and objective: Lokivetmab is the first anti-canine interleukin-31 monoclonal antibody approved in the European Union for Canine Atopic Dermatitis (CAD) management. This study aimed to assess the lokivetmab's efficacy and safety in treating CAD cases from a university reference service, as well as the dog's owner's overall opinion regarding therapy. **Methods:** Eighteen atopic dogs were enrolled to perform two subcutaneous injections of lokivetmab, according to the protocol. In order to determine the efficacy and safety of the treatment, skin lesions, pruritus score, blood count, liver parameters and adverse side effects were evaluated over 56 days. The overall pet owner's satisfaction about the therapy was assessed at the end of the study, and the number of animals that maintained the treatment three months after the end of the study was considered. **Results:** There was a significant reduction in pruritus score over the eight weeks, with 76.5% of the dogs showing a significant clinical improvement. Regarding the lesion score, 77.8% of the dogs achieved significant clinical improvement, with 61.1% reaching it in the first 4 weeks. There were no reported adverse side effects or changes in blood tests. Pet owner's opinion regarding the improvement of both the dog and its family's quality of life was very positive, and three months after the end of the study, 77.8% of the dogs continued their therapy with lokivetmab. **Conclusion:** Lokivetmab proved to be extremely effective and safe, in addition to sparing pet owners from at home drug administrations, which also

<http://doi.org/10.32932/rpia.2022.03.075>

contributes to their high satisfaction degree. The great specificity of this biological therapy makes it one of the most potent and promising in the CAD field.

Keywords: Canine atopic dermatitis, cytopoint, interleukin-31, lokivetmab, monoclonal antibody.

© 2022 Sociedade Portuguesa de Alergologia e Imunologia Clínica. Published by Publicações Ciência & Vida. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

RESUMO

Fundamentos e objetivo: O Lokivetmab é o primeiro anticorpo monoclonal anti-interleucina-31 canina aprovado na União Europeia para o tratamento da dermatite atópica canina (DAC). Este estudo teve o objetivo de avaliar a eficácia e segurança do lokivetmab no tratamento de casos de DAC de um serviço de referência universitário, bem como a opinião geral dos tutores dos animais em relação ao tratamento. **Métodos:** Foram recrutados dezoito cães atópicos para realizarem duas injeções subcutâneas de lokivetmab, de acordo com o protocolo. De modo a determinar a eficácia e segurança do tratamento, foram avaliados ao longo de 56 dias as lesões cutâneas, o grau de prurido, o hemograma, os parâmetros hepáticos e os efeitos adversos. A satisfação geral dos tutores relativamente ao tratamento foi aferida no final do estudo, e foram contabilizados os animais que mantiveram o tratamento três meses após o término do estudo. **Resultados:** Observou-se uma redução significativa do grau de prurido ao longo das oito semanas, sendo que 76,5% dos cães alcançou uma melhoria clinicamente significativa. Em relação ao quadro lesional, 77,8% dos cães teve uma melhoria clinicamente significativa, com 61,1% dos animais a manifestá-la nas primeiras 4 semanas. Não foram registados efeitos adversos ou alterações nos parâmetros sanguíneos. A opinião dos tutores dos animais foi muito positiva no que se refere à melhoria da qualidade de vida do cão e da família e, três meses após o término do estudo, 77,8% dos cães mantinham o tratamento com lokivetmab. **Conclusão:** O lokivetmab revelou-se extremamente eficaz e seguro, além de ter a vantagem de não requerer administração em casa por parte do tutor, o que também contribui para o seu elevado grau de satisfação. A grande especificidade desta terapêutica biológica torna-a uma das mais potentes e promissoras na área da DAC.

Palavras-chave: Anticorpo monoclonal, cytopoint, dermatite atópica canina, interleucina-31, lokivetmab.

© 2022 Sociedade Portuguesa de Alergologia e Imunologia Clínica. Publicado por Publicações Ciência & Vida. Este é um artigo Open Access sob uma licença CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INTRODUCTION

Human and canine allergic diseases have become increasingly common in the last decades. Changes in both the environment and population's lifestyle, associated with increased exposure to allergens,

are factors implicated in their increased incidence⁽¹⁾. Canine atopic dermatitis (CAD) is one of the most common allergic skin diseases of dogs, and it is estimated to affect approximately 10-15% of the canine population worldwide^(2,3). CAD is currently defined as a “genetically predisposed inflammatory and pruritic allergic skin disease

with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens⁽⁴⁾.

In line with what has been demonstrated regarding the induced psychological stress and reduced well-being in human skin diseases, CAD also has a major impact on the quality of life for patients and their cohabiting families⁽⁵⁾. For dogs, the loss of quality of life is primarily related to the severity of pruritus, the main clinical manifestation of the disease, that often affects the dog's physiological activities, such as sleeping, walking, or playing⁽⁶⁻⁸⁾. This repeated behaviour damages the skin, perpetuating and increasing the inflammatory process, which in turn induces more pruritus, thus establishing a vicious cycle⁽⁹⁾. Pruritus is induced by several endogenous mediators, namely interleukins. In 2004, Dillon *et al.* identified the action of interleukin (IL) 31 in the development of pruritus, alopecia, and skin lesions in mice⁽¹⁰⁾. Since then, this interleukin has been used to induce pruritus in dogs experimentally⁽¹¹⁾. Currently, it is known that IL-31 plays a prominent role in the development of pruritus in CAD and its serum levels may be elevated in these dogs^(9,11,12). This interleukin is mainly secreted by activated T_H2 and memory T lymphocytes and its pruritogenic effect results from the activation of intracellular signalling pathways such as Janus kinase-signal transducer and transcription activator (JAK-STAT), mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)^(10,11). Although this interleukin belongs to a cytokine family with important roles in inflammation, immunity, hematopoiesis, development and metabolism, the function of IL-31 in the inflammatory process has been questioned⁽¹³⁾. In fact, a recent study demonstrated the action of IL-31 on pruritus and the lack of effect on skin inflammation in cases of contact hypersensitivity⁽¹⁴⁾.

Atopic dermatitis is commonly an incurable disease, therefore the ultimate goal of its management is to improve the dog's quality of life, achieving a reduction in pruritus, a longer interval between flares, as well as a lower degree of secondary complications, such as infec-

tions⁽¹⁵⁾. For pet owners, ease of drug administration and cost-related issues are also of matter. The International Committee on Allergic Diseases of Animals (ICADA) has updated the guidelines for the treatment of CAD (Treatment of canine atopic dermatitis: 2015 updated guidelines from ICADA), which include the detailed plan for the treatment of acute flares and chronic disease⁽¹⁶⁾.

Lokivetmab is the most recent and one of the most promising therapeutic tools for the treatment of CAD's pruritogenic manifestations. It is the first caninized monoclonal antibody, obtained by recombinant technology from Chinese hamster ovary cell, approved for veterinary medicine use in the European Union in 2017⁽¹⁷⁾. Despite this innovative biological therapy, which aims to neutralize canine IL-31, being highly specific, it is also very expensive (average of 90 euros per month, in Portugal). Moreover, it has an onset of action of only eight hours and a duration of effect of about a month⁽¹⁷⁾. Many studies have confirmed the antipruritic effect of this molecule and the therapeutic success associated with its use. Additionally, lokivetmab has a good reputation for safety, with fewer adverse events recorded when compared to other more conventional drugs and with rare induction of antibody-mediated reaction by the organism against lokivetmab⁽¹⁸⁾. This monoclonal antibody is, therefore, an advantageous therapeutic option for animals with concomitant systemic or dermatological diseases as it was shown to be effective, well-tolerated and safe⁽¹⁹⁾.

The goal of our study was to evaluate the efficacy and safety of lokivetmab (Cytopoint®) in the treatment of dogs with atopic dermatitis and to assess their owners' overall opinion regarding this therapy.

MATERIALS AND METHODS

Participant enrolment criteria

Eighteen client-owned dogs (irrespective of breed or sex) with perennial atopic dermatitis were selected at

the Dermatology Service of the Hospital of the Faculty of Veterinary Medicine of the University of Lisbon and enrolled in the study after the owners' written informed consent has been obtained.

All dogs had undergone standard diagnostic evaluation and fulfilled criteria for the clinical CAD diagnosis, based on the history, clinical signs and according to the recommended criteria by Favrot⁽²⁰⁾. All differential diagnoses were excluded, namely the possibility of external parasites, by establishing an antiparasitic protocol for each animal, which was maintained throughout the trial. Maintaining other concomitant pre-established medications (including antibiotics, antifungals, ectoparasiticides, fatty acids, vitamin E and therapeutic shampoos) was allowed, provided they had been instituted before the start of lokivetmab and the dosing regimen was maintained during the trial. Allergen immunotherapy was permitted if it had been used for more than twelve months, in an unchanged dose for six months, and the regimen was maintained throughout the study.

Exclusion criteria included the interruption of treatment before the end of the study, the non-compliance of the owners in filling out the scale for the classification of pruritus, the lack of attendance to the proposed evaluation consultations and pregnant/lactating bitches.

This study was approved by the Faculty of Veterinary Medicine's Ethics and Animal Welfare Committee.

Study protocol

This study was designed as an eight-week clinical trial. Throughout the study period (56 days), dogs have received two subcutaneous administrations of lokivetmab, on days 0 and 28, with the appropriate dose for their weight, according to the licensed dosage of the drug (Figure 1).

The efficacy of lokivetmab was determined by the clinical evolution of the skin lesions, assessed by the veterinarian, using the validated Canine Atopic Dermatitis Extent & Severity Index (CADESI)-04 scale, and by the quantitative evaluation of the pruritus by the owners, using the validated Pruritus Visual Analogue Scale (PVAS). The evaluation of skin lesions occurred at four stages in the hospital, on days 0, 14, 28, 56. The pruritus score was assigned 14 times, on days 0, 1, 2, 3, 4, 5, 6, 13, 20, 27, 34, 41, 48 and 55, in a notebook provided to the owners for that purpose.

The safety of the treatment was assessed using analytical parameters of liver function (ALT – alanine aminotransferase – and ALP – alkaline phosphatase) and blood count, with blood sampling performed on days 0 and 56. Besides, owners were provided with a diary to record potential adverse effects presented by the animals.

The general owners' satisfaction regarding the treatment was evaluated during the follow-up visits and based on the number of animals that maintained the therapy after the end of the study.

Dog body weight (kg)	CYTOPOINT dosage (mg) to be administered			
	10	20	30	40
3.0-10.0	1 bottle			
10.1-20.0		1 bottle		
20.1-30.0			1 bottle	
30.1-40.0				1 bottle
40.1-50.0	1 bottle			1 bottle
50.1-60.0			2 bottles	
60.1-70.0			1 bottle	1 bottle
70.1-80.0				2 bottles

Figure 1. Description of the dose of lokivetmab (Cytoint[®]) to be administered depending on the dog's body weight. Recommended minimum dose: 1 mg/kg. (Image adapted from European Medicines Agency 2018).

Statistical analysis

The collected data were organized in the Microsoft Office 365 program, Excel® (version 16.19) and the statistical analysis was performed using the R® program (version 3.5.1). Pruritus' serial classifications were assessed using the Kaplan-Meier method. To compare some of the curves obtained by this method, the non-parametric Log-Rank test was used. To assess the difference between the pruritus and CADESI-04 values at different times, the Wilcoxon non-parametric test was used for paired samples that do not follow a normal distribution. For all analysis, values of $p < 0.05$ were considered statistically significant. Confidence intervals (CI) were calculated using the Wilson method of the EpiTools Epidemiological Calculators website, developed by Ausvet®.

RESULTS

Pruritus score evolution

Due to lack of sufficient data, one of the dogs had to be excluded from the sample prior to the results' analysis.

The pruritus score values recorded on day 0 had a median of 7. After four weeks (day 27), the median pruritus score decreased to 4. In the last evaluation, eight weeks after the start of treatment (day 55), the median pruritus score had been reduced to 3.

Considering a reduction of at least 50% in the pruritus score value as a clinically significant improvement, this was observed in 76.47% of the dogs, 95% CI [52.74%-90.44%], over the eight-study weeks (between days 0 and 55). If we only consider the first four weeks (between days 0 and 27), there was a clinically significant improvement in the pruritus in 64.71% of the dogs, 95% CI [41.30%-82.69%]. Of those who did not significantly improve after the first injection of lokivetmab, 33.33% (95% CI [9.68%-70%]) improved in the following four weeks. The results of the efficacy of lokivetmab in reducing the dog's pruritus over the eight weeks and after the first and second injections are summarized in Table 1. Although

Table 1. Percentage of dogs that achieved clinically significant improvement in pruritus over 8 weeks (total), after the first injection and after the second injection of lokivetmab

Percentage of dogs with clinically significant improvement in pruritus		
Total	After the 1 st injection	After the 2 nd injection
76.47%	64.71%	33.33%

clinically significant improvement was not achieved by all animals ($n=4$), there was a consistent reduction in the pruritus value in 75% of these dogs ($n=3$) over the study time, 95% CI [30.06%-95.44%].

The pruritus score values' reduction between day 0 and day 55 was statistically significant ($W=125$, $p=0.023$), as well as the decrease in the value in the first four weeks, between day 0 and 27 ($W=90$, $p=0.02$). It was also observed that more than 50% of the dogs with clinically significant improvement reached it before the seventh day after the first injection.

Lesional score evolution

The CADESI-04 values in the first evaluation (day 0) had a median of 23.5. After four weeks, on the second injection of lokivetmab, the median value decreased to 12. In the last evaluation, eight weeks after the start of treatment (day 56), the median value was 12.5.

As with pruritus, a reduction of at least 50% in the CADESI-04 value was considered to be clinically significant. During the total eight-weeks period, there was an improvement in 77.78% of the dogs, 95% CI [54.79%-91%]. If we only take into account the first four weeks (between days 0 and 28), there was a clinically significant improvement in 61.11% of the animals, 95% CI [38.62%-79.69%]. Of those who did not improve after the first injection of lokivetmab, 42.86% improved in the following four weeks (after the second injection), 95% CI [15.82%-74.95%]. The results of the efficacy of lokivetmab in reducing dog's skin lesions over the eight weeks and after the first and second injections are summarized in Table 2. Of the animals that did not

Table 2. Percentage of dogs that achieved clinically significant improvement in skin lesions over 8 weeks (total), after the first injection and after the second injection of lokivetmab

Percentage of dogs with clinically significant improvement in skin lesions		
Total	After the 1 st injection	After the 2 nd injection
77.78%	61.11%	42.86%

achieve a clinically significant improvement in the lesional score ($n=4$), 75% ($n=3$), 95% CI [30.06% -95.44%] recorded a decrease in the CADESI-04 value over the study period.

The reduction in CADESI-04 values between day 0 and day 56 was statistically significant ($W=150$, $p=0.005$). There was also a statistically significant difference between days 0 and 14 ($W=108$, $p=0.007$) and between day 0 and day 28 (after four weeks of the first injection) ($W=148.5$, $p=0.006$). However, the decrease in CADESI-04 values between four weeks after the start of treatment (day 28) and the last evaluation (day 56) was not statistically significant ($W=78$, $p=0.96$).

Adverse effects and laboratory analysis

During the eight weeks, there were two episodes of vomiting in different animals and one episode of vomiting and diarrhoea in another dog. None of these events required medical intervention. Regarding blood tests, no clinically significant changes were detected in the results of the second collection (after two administrations of lokivetmab).

Although the development of antibodies against lokivetmab has not been investigated, there were two animals (11.76%, 95% CI [3.29%-34.34%]) whose progression of the pruritus over the two months could be compatible with this situation.

Follow-up after project completion

Upon study completion, 14 dogs (77.78%, 95% CI [54.79%-91%]) continued to receive monthly lokivetmab administrations, as part of CAD's therapeutic control, for at least the following three months.

DISCUSSION

Evaluation of the pruritus score evolution

Pruritus progressed positively over time, with a reduction that proved to be statistically significant both at the end of the first (day 27) and second months (day 55), concerning the beginning of treatment (day 0). The median pruritus value decreased more than half, with just two injections of lokivetmab.

The decision to consider the criterion of clinically significant improvement only for value reductions of at least 50%, to assess the efficacy and treatment success with lokivetmab, was based on its previous use in several similar clinical studies, as in the works of Michels and his collaborators and Cosgrove *et al.*, respectively related to lokivetmab and oclacitinib^(12,18,21). The use of this criterion was an attempt to obtain more demanding results regarding the efficacy of lokivetmab. Consequently, the results suggest the efficacy of lokivetmab in reducing pruritus in most animals (76.47% during the total time under study). This value is similar to that obtained (77%) by Souza and collaborators in their retrospective study regarding the use of lokivetmab in allergic pruritus' management in dogs⁽¹⁹⁾.

ICADA has recently developed a Core Outcome Set for therapeutic clinical trials enrolling dogs with CAD (COSCAD'18)⁽²²⁾. According to these new recommendations, the pruritus outcome measure would be the percentage of dogs with owner-assessed pruritus score in the range of normal dogs or the mild CAD range at the end of the study⁽²²⁾. If this therapeutic success criterion had been adopted in this study, better results would probably have been obtained. Namely, a greater number of animals with clinically significant improvement in the pruritus score would have been found.

The effect of lokivetmab in pruritus' reduction was evident in the first 24 hours (at the day-1 evaluation), which is in line with the results of other studies^(18,19). It was possible to notice from the owners' report that, in some cases, lokivetmab took effect a few hours after its

administration. Moreover, before the seventh day after the first injection, a clinically significant improvement had already been achieved in more than half the animals.

Although a clinically significant improvement, according to our established criteria, was not achieved by all animals, all but one dog showed a decrease in the initial pruritus score. This only dog already had a pruritus score within the normal range (2 out of 10) to begin with, as he had been treated with oclacitinib before its inclusion in this study. To be able to provide such a comfortable level of pruritus under Cytopoint® therapy was, therefore, considered a therapeutic success.

The fact that some animals (n=4) did not achieve satisfactory results can be justified for several reasons. The formation of antibodies against lokivetmab, although it was not tested in this study, could explain two (11.76%) of these cases, where the pruritus score increased after the second administration. Despite being caninized antibodies, there is the possibility of creating antibodies directed against the 10% hamster antibody residue, which would neutralize the lokivetmab effect^(17,23). These antibodies were researched and quantified in a 2016 study, which evaluated this molecule's safety, and were found in 2.5% of the animals that received the treatment⁽¹²⁾. Another study, from 2018, found loss of pruritus control after the second injection of lokivetmab in 2.6% of the animals under treatment. In the latter, antibodies directed against lokivetmab were not researched. However, the authors considered this a plausible hypothesis to justify the results⁽¹⁹⁾. Additionally, the lack of response to lokivetmab or the less pronounced response may also be related to the complexity of this syndrome and the combination of multiple pruritus mediators involved in the CAD pathogenesis, with a predominance of different mediators over IL-31⁽⁹⁾.

Evaluation of the skin lesions score evolution

The progress of CADESI-04 classifications was satisfactory, with a statistically significant reduction in values between the day of the first administration (day

0) and the final of the study (day 56). The decrease in these values was observed shortly after two weeks since the first injection. The reduction was also statistically significant both between days 0 and 14 and between days 0 and 28. The median skin lesion value decreased by almost half, with only two injections of lokivetmab.

If we consider the same criterion used for the pruritus score, this study suggests that lokivetmab is efficient in reducing skin lesions since there was a clinically significant improvement in the CADESI-04 value in 77.78% of the animals over the total period under study. In the first month, 61.11% of the dogs reached a clinically significant improvement, a value higher than those recorded by Michels *et al.* in a similar time interval but based on CADESI-03 (46% in the dog group receiving 2 mg/kg of lokivetmab and 22% in the group of 0.5 mg/kg)⁽¹⁸⁾.

According to COSCAD'18, the lesional outcome to be considered would be the percentage of dogs with veterinarian-assessed skin lesions in the range of normal dogs or the mild CAD range at the end of the study⁽²²⁾. Once again, if this criterion had been assumed in this study, better results regarding a greater number of dogs with clinically significant improvement in the lesional score would probably have been reported.

Similarly to what was observed in pruritus, despite an improvement of at least 50% in the value of CADESI-04 not being seen in all animals, there was a reduction in its initial value in all dogs except one. Nevertheless, the CADESI-04 values of this last animal have always remained low, in the interval classified as mild, throughout the study period. Looking at intervals for CAD severity classification using CADESI-04 values (<10: normal dogs or remission, 10-34: mild CAD, 35-59: moderate CAD, 60: severe CAD)⁽²⁴⁾, it is possible to verify that the majority of dogs were classified within the mild range, in the first evaluation (day 0), with only one severe case and three moderate cases. In the following clinical evaluations, no severe cases were registered. In the last evaluation (day 56), most animals were in the mild range,

with only one moderate case and six animals evolving to the remission group.

Therefore, lokivetmab was found to be effective in reducing CADESI-04 values for most animals, and in maintaining low scores between administrations (for at least four weeks). The effect of lokivetmab in pruritus may have favoured the improvement of skin lesions, by interrupting the itching and the inflammation – pruritus vicious cycle. While pruritus decreases rapidly with treatment, skin lesions may take longer to resolve. Therefore, in short-term studies, as the current one, the evaluation of the effect of a therapeutic approach may not fully represent reality.

Adverse effects and laboratory analysis assessment

During the two months, only three cases of adverse events were recorded. The three animals presented episodes of vomiting, and one of them also had diarrhoea. In all cases, the situation was resolved without the need for intervention. These side effects in animals being treated with lokivetmab have been described in the drug's safety study. Lethargy and vomiting were the most common adverse reactions observed by Souza and collaborators, in their retrospective study in 2018, and in the present study, situations were solved without the need for medical intervention⁽¹⁹⁾.

Regarding physical examinations and blood tests performed before and after treatment, there were no changes with clinical significance. These observations are in line with the results obtained in the study by Michels *et al.* in which no analysis' changes recorded in animals treated with lokivetmab⁽¹²⁾. Although drug interactions were not actively investigated, they were not observed, similarly to what was seen in a previous study⁽¹²⁾.

The absence of interaction with other medications and the specific action to a single interleukin suggest that lokivetmab may be an excellent option for dogs with concomitant diseases that make treatment with other molecules unfeasible. More specifically, in case of dogs

with neoplasia to which oclacitinib must not be administered. The results of this study indicate a high safety standard for lokivetmab, with no record of serious adverse effects or the need for veterinary intervention.

General owner's satisfaction and treatment maintenance after project completion

CAD's emotional and physical challenge for the owners, as well as the implications of its management, both financially and in the time invested, greatly influence their quality of life^(5,8). Owners' satisfaction regarding the therapeutic plan is, therefore, paramount to maintain their compliance and, ultimately, achieve therapeutic success⁽⁷⁾.

The owners' opinion was inquired during the follow-up consultations and a high satisfaction's degree was found regarding the lokivetmab clinical results. This biological therapy has the great advantage of controlling the patients' clinical condition over about a month, with just one injection. Since it does not require daily home drug administration, which could lead to stress for both owners and dogs and ultimately deteriorate their relationship⁽²⁵⁾, this therapeutic option proves to be very convenient and attractive for many owners. The high number of dogs that, after three months from the end of the study (77.78%), maintained treatment with lokivetmab reflects the most-owners' satisfaction. Moreover, some of the owners testified that lokivetmab provided a great improvement in their dogs' and families' quality of life. There were only four owners who did not notice a significant difference with the use of lokivetmab in their animals. Two of these dogs were under treatment with other molecules before the study started, and, in the owners' opinion, lokivetmab has achieved similar control of clinical signs compared to previous treatment. For economic reasons, these four animals returned to their previous therapy at the end of the study.

Long-term treatment with lokivetmab turns out to be costly and unaffordable for some owners, who have to choose other treatment options to best suit their financial

condition. Even so, in this Portuguese Dermatology Service, since April 2018, an average of twenty-five patients are undergoing monthly treatment with Cytopoint®.

Study limitations and future research

Ideally, to assess the effects of lokivetmab, no other medication should have been simultaneously used. However, the main concern of this project was the welfare of the animals and, given the real clinic scenario and the severe clinical presentation of some cases, there was a need to implement a multimodal and individualized therapeutic plan. In order to avoid this inconvenience, all medications used concurrently with lokivetmab were registered and administered to interfere as minimum as possible with the results.

The small sample size was a limiting factor, making certain investigations impossible, such as comparing the efficacy of lokivetmab among different breeds and between animals with high and low initial pruritus values. Larger future investigations could fruitfully explore these issues further. The owner's motivation in filling out the scales for pruritus assessment also limited the sample size, resulting in the exclusion of some dogs from the study, whose owners did not respect the number of requested evaluations. Besides, although a detailed and described scale was provided to all owners for determining pruritus' value at each evaluation time, the interpretation and consistency of its filling may vary between people and by the same person over time. Lokivetmab cost, considered by many owners to be high and beyond their financial means, was also a limiting factor for the inclusion of animals in the study.

Although the clinical efficacy and safety of this biological therapy have been described, long-term studies to assess these issues as a chronic treatment approach are urgently needed. Furthermore, despite a recent study has demonstrated that Lokivetmab can be used as a proactive regimen for pruritus control (and not successfully for lesion's prevention), further studies are welcome to identify the most likely responder dogs⁽²⁶⁾. Moreover,

although treatment-induced immunogenicity has been discussed in previous works, further research on this topic would provide insight into the clinical relevance of this finding and whether it interferes with the long-term treatment response rate.

CONCLUSIONS

The use of lokivetmab proves to be an extremely effective and safe strategy for controlling CAD. The significant clinical reduction in pruritus and skin lesions scores, the absence of relevant side effects, and the great specificity directed at IL-31 make this therapeutic tool one of the most potent and promising in the CAD's field. Furthermore, since it spares daily home drug administration and allows for a month to control the patient's pruritus, the use of lokivetmab becomes very convenient and leads to a high owner's satisfaction degree. Nevertheless, its high cost associated with the need to maintain long-term treatment may, in some cases, restrict its adoption, even when the therapeutic success and owners' satisfaction are high.

Conflict of interest

The authors state no conflict of interest.

ORCID:

Marta Pinto  0000-0002-6991-8704

Maria Alice Silva  0000-0001-8980-7502

Beatriz Fernandes  0000-0001-5398-673X

Ana Filipa Bizarro  0000-0001-9282-2949

Hugo Pereira  0000-0001-8005-2043

Ana Mafalda Lourenço  0000-0002-4747-2086

Corresponding author:

Marta Pinto

E-mail: marta.pinto.5@hotmail.com

REFERENCES

- Marsella R, De Benedetto A. Atopic dermatitis in animals and people: an update and comparative review. *Vet Sci.* 2017; 4(3):37. DOI: 10.3390/vetsci4030037.
- Marsella R, Girolomoni G. Canine models of atopic dermatitis: a useful tool with untapped potential. *J Invest Dermatol.* 2009; 129: 2351-2357. DOI: 10.1038/jid.2009.98.
- Gedon N, Mueller R. Atopic dermatitis in cats and dogs: a difficult disease for animals and owners. *Clin Transl Allergy.* 2018; 8(1):41. DOI: 10.1186/s13601-018-0228-5.
- Halliwell R. Revised nomenclature for veterinary allergy. *Vet Immunol Immunopathol.* 2006;114(3-4):207-8. DOI: 10.1016/j.vetimm.2006.08.013.
- Noli C. Assessing quality of life for pets with dermatologic disease and their owners. *Vet Clin North Am Small Anim Pract.* 2019; 49(1):83-93. DOI: 10.1016/j.cvsm.2018.08.008.
- Favrot C, Linek M, Mueller R, Zini E. Development of a questionnaire to assess the impact of atopic dermatitis on health-related quality of life of affected dogs and their owners. *Vet Dermatol.* 2010;21(1):64-70. DOI: 10.1111/j.1365-3164.2009.00781.x.
- Linek M, Favrot C. Impact of canine atopic dermatitis on the health-related quality of life of affected dogs and quality of life of their owners. *Vet Dermatol.* 2010;21(5). DOI: 10.1111/j.1365-3164.2010.00899.x.
- Noli C, Minafò G, Galzerano M. Quality of life of dogs with skin diseases and their owners. Part I: Development and validation of a questionnaire. *Vet Dermatol.* 2011;22(4):335-43. DOI: 10.1111/j.1365-3164.2010.00954.x.
- De Lucia M. Recent advances in the pathophysiology of pruritus. In *Proceedings da Sociedade Portuguesa de Dermatologia Veterinária – Prurido em Pequenos Animais.* Lisbon, May 2018 (1-5).
- Dillon S, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell S, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol.* 2004; 5(7):752-60. DOI: 10.1038/ni1084.
- Gonzales A, Humphrey W, Messamore J, Fleck T, Fici G, Shelly J, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol.* 2013;24(1). DOI: 10.1111/j.1365-3164.2012.01098.x.
- Michels G, Walsh K, Kryda K, Mahabir S, Walters R, Hoeyers J, et al. A blinded, randomized, placebo-controlled trial of the safety of lokivetmab (ZTS-00103289), a caninized anti-canine IL-31 monoclonal antibody in client-owned dogs with atopic dermatitis. *Vet Dermatol.* 2016;27(6):505-e136. DOI: 10.1111/vde.12364.
- Jones S, Jenkins B. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. *Nat Rev Immunol.* 2018;18(12):773-89. DOI: 10.1038/s41577-018-0066-7.
- Takamori A, Nambu A, Sato K, Yamaguchi S, Matsuda K, Numata T, et al. IL-31 is crucial for induction of pruritus, but not inflammation, in contact hypersensitivity. *Sci Rep.* 2018;8(1). DOI: 10.1038/s41598-018-25094-4.
- Saridomichelakis M, Olivry T. An update on the treatment of canine atopic dermatitis. *Vet J.* 2016;207:29-37. DOI: 10.1016/j.tvjl.2015.09.016.
- Olivry T, Deboer D, Favrot C, Jackson H, Mueller R, Nuttall T, et al. Treatment of Canine Atopic Dermatitis: 2015 Updated Guidelines from the International Committee on Allergic Diseases of Animals (ICADA). *BMC Vet Res.* 2015;11:1-15. DOI: 10.1186/s12917-015-0514-6.
- European Medicines Agency (EMA). Summary of product characteristics – Cytoint. 2018. Consulted on September 15th, 2020, in https://www.ema.europa.eu/en/documents/product-information/cytopoint-epar-product-information_en.pdf
- Michels G, Ramsey D, Walsh K, Martinon O, Mahabir S, Hoeyers J, et al. A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client-owned dogs with atopic dermatitis. *Vet Dermatol.* 2016;27(6):478-e129. DOI: 10.1111/vde.12376.
- Souza C, Rosychuk R, Contreras E, Schissler J, Simpson A. A retrospective analysis of the use of lokivetmab in the management of allergic pruritus in a referral population of 135 dogs in the western USA. *Vet Dermatol.* 2018; 29(6): 489-e164. DOI: 10.1111/vde.12682.
- Favrot C, Steffan J, Seewald W, Picco F. A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. *Vet Dermatol.* 2010;21(1):23-31. DOI: 10.1111/j.1365-3164.2009.00758.x.
- Cosgrove S, Cleaver D, King V, Gilmer A, Daniels A, Wren J, et al. Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life. *Vet Dermatol.* 2015;26(3):171-e35. DOI: 10.1111/vde.12194.
- Olivry T, Besignor E, Favrot C, Griffin C, Hill P, Mueller R, et al. Development of a core outcome set for therapeutic clinical trials enrolling dogs with atopic dermatitis (COSCAD'18). *BMC Vet Res.* 2018;14:238. DOI: <https://doi.org/10.1186/s12917-018-1569-y>.
- Souza C. Biologic therapy for companion animals – what is it? In *World Small Animal Veterinary Association Congress Proceedings, El Dorado Hills, CA, USA.* El Dorado Hills, CA, USA, 2017.
- Olivry T, Saridomichelakis M, Nuttall T, Besignor E, Griffin C, Hill P. Validation of the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4, a simplified severity scale for assessing skin lesions of atopic dermatitis in dogs. *Vet Dermatol.* 2014;25(2): 77-86. DOI: 10.1111/vde.12107. Epub 2014 Jan 25.
- Noli C, Sartori R, Cena T. Impact of a terbinafine-florfenicol-betamethasone acetate otic gel on the quality of life of dogs with acute otitis externa and their owners. *Vet Dermatol.* 2017;28: 386-e90. DOI: 10.1111/vde.12433.
- Tamamoto-Mochizuki C, Paps J, Olivry T. Proactive maintenance therapy of canine atopic dermatitis with the anti-IL-31 lokivetmab. Can a monoclonal antibody blocking a single cytokine prevent allergy flares? *Vet Dermatol.* 2019; 30: 98-e26. DOI: 10.1111/vde.12715.