

Evaluation of quality of life in dogs with atopic dermatitis and their owners after lokivetmab therapy

Avaliação da qualidade de vida em cães com dermatite atópica e seus tutores após terapia com lokivetmab

Evaluación de la calidad de vida en perros con dermatitis atópica y sus tutores después del tratamiento con lokivetmab

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Abstract

Canine atopic dermatitis is an inflammatory and pruritic skin disease, with clinical characteristics associated with IgE antibodies, most commonly directed against environmental allergens which impact the quality of life in affected animals and their owners. Treatment is multifaceted and must be adapted to each patient individually. Currently, a medication based on caninized monoclonal antibody (mAb), called lokivetmab, has shown promise for controlling the signs of the disease, as it neutralizes interleukin IL-31, a cytokine that plays an important role in the pathogenesis of atopy. The impact of dermatological diseases in the life of the dog and its owner has only been studied in recent years through validated questionnaires. This additional measurement tool is important for evaluating the therapeutic success of interventions in atopic dermatitis, as clinical improvement may not correlate with an increased quality of life. This study aimed to evaluate the quality of life in dogs with atopic dermatitis and their owners after lokivetmab therapy. Ten atopic dogs treated at the dermatology service of the Veterinary Hospital of the Veterinary School from UFMG were selected. Quality of life was assessed using a validated questionnaire, before and after lokivetmab therapy. It concludes that treatment with lokivetmab significantly improved the quality of life of dogs with atopic dermatitis and their owners.

Keywords: Monoclonal antibody; Atopy; Canine; IL-31; Questionnaire.

Resumo

A dermatite atópica canina (DAC) é uma doença inflamatória e pruriginosa da pele, com características clínicas associadas aos anticorpos IgE, mais comumente direcionados contra alérgenos ambientais e que impacta na qualidade de vida (QV) dos animais acometidos e de seus tutores. O tratamento é multifacetado e deve ser adaptado a cada paciente. Atualmente, uma medicação baseada em anticorpo monoclonal (mAb) caninizado, denominada lokivetmab, tem se mostrado promissora para o controle dos sinais da doença, pois neutraliza a interleucina (IL)-31, citocina que desempenha papel importante na patogênese da DAC. O impacto das doenças dermatológicas na vida do cão afetado e de seus tutores tem sido estudado apenas nos últimos anos, por meio de questionários validados. Essa ferramenta de medição adicional tem se mostrado importante para a avaliação do sucesso terapêutico das intervenções na dermatite atópica, já que a melhora clínica pode não se correlacionar com o aumento da qualidade de vida. Este trabalho teve como objetivo avaliar a qualidade de vida de cães com dermatite atópica e seus tutores após terapia com lokivetmab. Foram selecionados 10 cães atópicos atendidos no serviço de dermatologia do Hospital Veterinário da Escola de Veterinária da UFMG. Os pacientes e seus tutores foram avaliados quanto a qualidade de vida, por meio de um questionário validado, antes e após terapia com lokivetmab. Pode-se concluir que o tratamento com lokivetmab melhorou de forma significativa a qualidade de vida dos cães com dermatite atópica e de seus tutores.

Palavras-chave: Anticorpo monoclonal; Atopia; Canina; IL-31; Questionário.

Resumen

La dermatitis atópica canina es una enfermedad cutánea inflamatoria y pruriginosa, con características clínicas asociadas a los anticuerpos IgE, más comúnmente dirigidos contra alérgenos ambientales y que impacta en la calidad de vida de los animales afectados y sus guardianes. El tratamiento es multifacético y debe adaptarse a cada paciente. Actualmente, un medicamento basado en anticuerpos monoclonales caninizados (mAb), llamado lokivetmab, se ha mostrado prometedor para controlar los signos de la enfermedad, ya que neutraliza la interleucina (IL) -31, una citocina que desempeña un papel importante en la patogenia de la dermatitis atópica canina. El impacto de las enfermedades dermatológicas en la vida del perro afectado y sus tutores solo se ha estudiado en los últimos años, mediante cuestionarios validados. Se ha demostrado que esta herramienta de medición adicional es importante para evaluar el éxito terapéutico de las intervenciones en la dermatitis atópica, ya que la mejoría clínica puede no correlacionarse con una mejor calidad de vida. Este estudio tuvo como objetivo evaluar la calidad de vida de los perros con dermatitis atópica y sus tutores después de la terapia con lokivetmab. Se seleccionaron diez perros atópicos tratados en el servicio de dermatología del Hospital Veterinario de la Facultad de Veterinaria de la UFMG. Se evaluó la calidad de vida de los pacientes y sus tutores, mediante un cuestionario validado, antes y después del tratamiento con lokivetmab. Se puede concluir que el tratamiento con lokivetmab mejoró significativamente la calidad de vida de los perros con dermatitis atópica y sus guardianes.

Palabras clave: Anticuerpo monoclonal; Atopia; Canino; IL-31; Cuestionario.

1. Introduction

Atopic dermatitis (AD) is an extremely common, pruritic, and frustrating disease to treat (Marsella & De Benedetto, 2017). The findings in the clinical, histological, immunological, and epidemiological aspects of this dermatopathy led to the definition of canine atopic dermatitis (CAD) as an inflammatory and pruritic skin disease, with clinical characteristics associated with immunoglobulin E (IgE) antibodies, more commonly directed against environmental allergens (Halliwell, 2006) and that impacts the quality of life (QoL) of affected animals and, therefore, of their owners (Linek & Favrot, 2010).

CAD does not have pathognomonic clinical signs that allow a definitive diagnosis to be made after the initial anamnesis and clinical examination (Griffin & DeBoer, 2001). The most common clinical sign is pruritus, which precedes other signs and is responsive to the use of corticosteroids (Favrot, Steffan, Seewald & Picco, 2010a; Bruet, Bourdeau, Roussel, Imparato & Desfontis, 2012). The treatment of CAD is multifaceted and must be adapted to each patient depending on the stage of the disease, its severity, and distribution of lesions. The QoL of both, dogs and owners, must be considered (Medeiros, 2017).

Currently, lokivetmab (Cytopoint; Zoetis) has shown promise for controlling CAD signals (Souza, Rosychuk, Contreras, Schissler & Simpson, 2018). Composed of caninized monoclonal antibody (mAb), this medication neutralizes interleukin (IL)-31, a cytokine that plays an important role in the pathogenesis of atopy. Because it acts only on IL-31, lokivetmab has no direct effects on other cytokines, and therefore it is considered a safer therapy (Jackson & Forsythe, 2020). This medication is effective for the control of pruritus in CAD, with the onset of action often within twenty-four hours (Moyaert et al., 2017).

The complex impact of dermatological diseases on the life of the affected dog and its owners has until very recently been neglected (Noli, Minafò & Galzerano, 2011a). QoL in small animal dermatopathies has only been studied in recent years through, in most studies, validated questionnaires (Favrot, Linek, Mueller & Zini, 2010b; Linek & Favrot, 2010; Noli et al., 2011a; Noli et al., 2011b). In medicine, QoL tests have already been used as an additional measurement tool to assess the therapeutic success of medical interventions (Balkrishnan, Housman, Carroll, Feldman & Fleischer, 2003; Chamlin et al., 2007), since clinical improvement does not necessarily correlate with an increase in QoL.

This study aimed to evaluate the impact on the QoL of dogs with AD and their owners, after therapeutic interference with lokivetmab. The hypothesis of the present study considers that atopic dogs and their owners have a higher QoL after therapy with lokivetmab.

2. Methodology

To assess the impact of AD on the lives of dogs, their owners, and their families, a qualitative study was carried out through the application of a closed questionnaire with scaled questions (Pereira, Shitsuka, Parreira & Shitsuka, 2018).

Ten dogs with AD from the clinical routine of the dermatology service of the Veterinary Hospital from UFMG were evaluated. The diagnosis of canine AD was established by the history, clinical signs, and exclusion of other pruritic and inflammatory dermatoses through complementary examinations of the dermatological routine, in addition to having completed the allergic trial with the treatment of secondary infections, elimination of ectoparasites, and a restrictive hypoallergenic diet, commercial hydrolyzed protein or homemade with an unprecedented source of protein, for at least eight weeks.

The atopic patients selected for the study then received two doses of lokivetmab (2.2 – 3.1 mg/kg) subcutaneously at the following times: moment 0 (M0) – start of treatment, and moment 1 (M1) – 28 days after starting treatment. At M0, M1, and moment 2 (M2) - 56 days after the start of treatment, the owners of the animals were asked to fill out a quality of life questionnaire (figure 1), which was adapted from Noli et al. (2011a).

Figure 1. Questionnaire about the quality of life of dogs with skin disease and their owners.

<u>Questionnaire about the quality of life of dogs with skin disease and their owners</u>	
This questionnaire deals with the impact of your dog's skin disease on your dog's quality of life and that of his owners and family over the past week. Please read the questions carefully and tick only one answer.	
1. What is the severity and disorder of your dog's illness?	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
2. What was the impact of your dog's illness on his behavior and mood? (lazier, more nervous, more aggressive, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
3. How much was your dog's sleep disturbed by the illness?	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
4. How much were your dog's meals disrupted by the illness? (has no appetite, itches during meals, does not like special food, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
5. How much was your dog's play or work activities disrupted by the disease? (is more lazy, nervous, itchy, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
6. What was the impact of your dog's illness on your relationship with you, other family members, or other dogs? (due to mood swings, presence of skin lesions, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
7. How much has your dog's illness changed his habits? (change of place where you are allowed to sleep, live, eat, the way you walk, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
8. How much the dog was disturbed by the administration of therapies (shampoos, sprays, pills, drops, injections, ear cleaning, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
9. How much time did you lose because of your dog's illness? (administration of therapies, washing, household cleaning, cooking, veterinary consultations, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
10. What is the effect of your dog's illness on tiredness? (extra cleaning, cooking, washing, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
11. How much were your usual activities and/or those of your family disturbed by your dog's illness? (leisure, vacation, trips, work, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
12. What was the impact of your dog's illness on expenses? (cost of treatment, veterinarian, etc.)	<input type="checkbox"/> None <input type="checkbox"/> A little <input type="checkbox"/> Moderate <input type="checkbox"/> A lot
13. How much effect did your dog's illness have on causing emotional distress (guilt, helplessness, sadness, regret, anxiety, discomfort, disgust, anger, frustration, etc.)	

<input type="checkbox"/> None	<input type="checkbox"/> A little	<input type="checkbox"/> Moderate	<input type="checkbox"/> A lot
14. How much physical discomfort/restlessness do you experience due to your dog's illness? (offensive odor, feeling of dirt at home, aesthetic discomfort, etc.)			
<input type="checkbox"/> None	<input type="checkbox"/> A little	<input type="checkbox"/> Moderate	<input type="checkbox"/> A lot
15. What was the impact of your dog's illness on the relationship between family members? (between spouses, parents and children, relatives and friends, etc.)			
<input type="checkbox"/> None	<input type="checkbox"/> A little	<input type="checkbox"/> Moderate	<input type="checkbox"/> A lot

Fonte: adaptado de Noli et al. (2011a).

Answers were scored as 0, none (a); 1, a little; 2, moderate; and 3, a lot. The questionnaires were answered by only one owner of each dog, always prioritizing the same one. The 15 questions were subdivided into: a question about the general severity of the disease (S), score 0 to 3; seven questions about the dog's QoL (QoL1), total score from 0 to 21; and seven questions about the tutor's QoL (QoL2), total score from 0 to 21. The punctuation was then added (total from 0 to 45), and the higher the score the lower the QoL of the animals and their owners. The score thresholds for QoL1 and QoL2 considered for healthy dogs were 2 and 5 points, respectively (Noli, Della Valle, Miolo, Medori & Schievano, 2015).

To test the differences between the three moments of the variable: QoL questionnaire questions, generalized estimating equation models were adjusted for each response variable. The moment was used as a predictor (independent variable) and a composite symmetry temporal autocorrelation structure was used.

3. Results and Discussion

A total of 10 dogs (five females and five males) were included in this study, eight sterilized (four females and five males) and two not sterilized (one female and one male). The age and weight of the animals ranged from 6.15 ± 4.85 years and 6.75 ± 2.85 kg, respectively. The breeds were: shih tzu (4), pug (2), french bulldog (1), lhasa apso (1), mixed breed (1), and yorkshire terrier (1). All selected atopic dogs had skin lesions, with scores between 10 and 35 on CADESI-04 (Olivry et al., 2014), at the time of the first application of lokivetmab (M0).

In some cases, it was necessary the concomitant use of other medications, such as oral and topics antibiotics and antifungals, and topics antiseptics and allergic anti-inflammatory drugs. Some of the dogs included in the study would not have completed it if they were not using these other therapies. The most plausible explanation would be a limited improvement in clinical signs, due to complications secondary to CAD, which would not be enough to lead to an improvement in QoL that is prominent enough to be noticed by the owners. The most common complications reported in dogs throughout this study were: otitis externa (3/10), two by bacteria and one by yeast, and superficial pyoderma (2/10), both common in AD (Griffin & DeBoer, 2001).

About the QoL of atopic dogs before lokivetmab therapy (M0), QoL1 scores (0-21) ranged from 6 to 18 (median 9) and QoL2 scores (0-21) from 8 to 21 (median 13,5), indicate that the questionnaire reveals a range of impacts on QOL. The general severity of the disease perceived by the tutor (possible range 0-3) ranged from 2 to 3 (median 2,5) (Table 1).

Table 1. Scores from the quality of life questionnaire applied to 10 atopic dog owners, before (moment 0) and after (moment 1 and 2) therapy with lokivetmab.

Dog	Moment 0			Moment 1			Moment 2		
	S	QoL1	QoL2	S	QoL1	QoL2	S	QoL1	QoL2
1	3	8	11	2	4	4	2	1	4
2	2	12	10	2	6	6	1	3	7
3	3	8	15	3	8	11	2	3	15
4	2	6	8	1	3	5	1	3	6
5	3	18	21	2	8	12	2	11	19
6	3	16	14	2	9	10	2	5	6
7	2	10	18	0	1	2	1	8	7
8	2	7	13	1	3	9	2	9	12
9	3	6	10	2	15	13	2	8	12
10	2	10	14	1	4	13	1	4	9

S, disease severity; QoL1, dog quality of life; QoL2, owner quality of life. Fonte: arquivo pessoal.

When evaluating the relative frequency, 60% of the dogs reduced the QoL1 score by at least 50% between M0 and M2, with two showing a reduction above 90%. Of these, one reached a score below the threshold for healthy dogs ($QoL1 < 2$) in M1 and another in M2, a result lower than that found in another study (Noli et al., 2015). While in the present work the selected dogs had mild signs of AD, in the study by Noli et al. (2015) dogs with moderate AD were used, which may have contributed to a greater relative reduction in the QoL1 score after therapy in these patients. Thus, the difference found between the two studies can be justified by the different populations of dogs used.

At M1 and M2, 80% of the owners observed a positive impact on the QoL of their animals, compared to the moment before therapy (M0). Similar results were found in the study by Cosgrove et al. (2015), in which owners observed a positive impact on QoL in more than 91% of all dogs, after therapy with oclacitinib maleate. Therefore, the results found in the present study suggest that the use of lokivetmab generates a positive impact on the QoL of patients similar to the impact caused by therapy with oclacitinib maleate (Apoquel; Zoetis). A controlled study comparing groups of atopic dogs in different therapies (Cytopoint® and Apoquel®) is needed to prove this hypothesis.

Using the individual mean score of the questions (range 0-3), the highest-scoring items in QoL1 were: disturbances caused by therapies, followed by disturbances in the animal's sleep and behavior/mood. In QoL2, the highest scores were related to concerns about expenses, lost time, and emotional distress. Such results are consistent with other studies (Favrot et al., 2010b; Linek & Favrot, 2010; Noli et al., 2011a).

When the answers to the individual questions were compared before (M0) and after the second application of lokivetmab (M2), all questions showed a decrease in mean scores, although of different magnitudes (Table 2). This suggests that both the QoL of dogs and their owners were positively influenced after therapy with lokivetmab

Table 2. The mean and relative improvement observed in the scores for each question of the quality of life questionnaire, applied to handlers of dogs with atopic dermatitis, before (day 0) and after (day 56) therapy with lokivetmab.

Question	Mean			Positive answers			
	Day 0	Day 56	Improvement (%)	Day 0	Day 56	Reduction of positive answers (%)	
S							
1	Disease severity	2,5	1,6	36	100	100	-
QoL1							
2	Behavior/mood	1,7	0,8	52	80	80	-
3	Sleep	1,7	1,0	41	80	70	10
4	Meals	0,9	0,5	55	70	40	30
5	Play/work	1,0	0,6	40	70	50	20
6	Social interaction	1,5	0,6	60	80	50	30
7	Changes in habits	1,2	0,6	50	70	50	20
8	Therapies	2,1	1,4	33	90	100	-10
QoL2							
9	Lost time	2,4	1,7	29	100	100	-
10	Physical exhaustion	1,6	1,2	25	100	80	20
11	Usual activities	1,3	0,7	46	80	40	20
12	Expenditure	2,7	2,3	14	100	100	-
13	Emotional suffering	2,3	2,0	13	100	100	-
14	Physical restlessness	1,6	1,0	37	80	70	10
15	Family relationship	1,5	0,8	46	70	50	20

Fonte: arquivo pessoal.

The mean percentage improvement between M0 and M2 was 36% for disease severity (S), 45% for QoL1, and 27% for QoL2. Similar results were found in the study by Noli et al. (2011b); however, the therapies used in dogs were not specified in that study, which suggests that other medications administered in the treatment of CAD cause impacts of similar magnitudes on the patients' QoL. In contrast, another study noted improvement only in QoL2 after using lokivetmab in atopic dogs (Nguyen et al., 2018). This observation can be explained by the high level of QoL that patients already had at the beginning of the study or by the patient population used.

When considering the QoL1, the disturbance caused by the administration of the therapy had the lowest mean improvement (33%), in addition to a 10% increase in positive responses. In the owners' QoL, issues related to loss of time, physical exhaustion, expenses, and emotional suffering were the ones that had the least improvement. Similar observations were made in both studies of Noli et al. (2011b) and in a study in humans, in which child care efforts and financial concerns about treatment had the greatest impact (Balkrishnan et al., 2003).

In another study (Noli, Sartori & Cena, 2017), QoL was assessed in dogs with otitis externa before and after treatment and, interestingly, while QoL1 seemed to improve with time, QoL2 did not occur until the last day of medication, possibly reflecting the burden on owners of home-administered therapy. A similar discrepancy between improvements in values for QoL1 and QoL2 after clinically successful therapies has been described in dogs and cats treated for allergic dermatitis (Noli et al., 2011b; Noli et al., 2015; Noli, Borio, Varina & Schievano, 2016). Therefore, although lokivetmab reduces the burden of owner-administered medications, the value of treatment and the burden of maintenance therapy, such as bathing and other medications, is likely responsible for the smaller improvement in QoL2 compared to QoL1.

4. Conclusion

According to the results, it can be concluded that treatment with lokivetmab significantly improved the QoL of dogs and their owners. Furthermore, the study clearly shows that the QoL of atopic dogs and their owners is profoundly and negatively affected by the disease and demonstrates the importance of measuring QoL1 and QoL2 not only in the context of clinical trials but also in daily practice. Understanding for better tutor support and better assessment of treatment options.

In this study, other variables such as the degree of proximity between the owner and his animal and the age of the owners were not evaluated. Some studies have shown that the closer the owner-pet relationship, the greater the impact of the animal's disease on QoL2 (Linek & Favrot, 2010), and significant differences were found between younger and older owners in the perception of dog disease (Favrot et al., 2010b). Therefore, it is suggested that future research also consider the age of the owners and the degree of proximity to their animal when using questionnaires to assess QoL.

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