Ciência Rural, Santa Maria, v.53:8, e20220068, 2023
http://doi.org/10.1590/0103-8478cr20220068
ISSNe 1678-4596
CLINIC AND SURGERY

Canine atopic dermatitis: systemic immunomodulatory protocol based on clinical phenotype

Tiago Cunha Ferreira[1] Marina Gabriela Monteiro Carvalho Mori da Cunha[2] Diana Célia Sousa Nunes-Pinheiro[1]

[1]Programa de Pós-graduação em Ciências Veterinárias, Faculdade de Veterinária, Universidade Estadual do Ceará (UECE), 60914-703, Fortaleza, CE, Brasil. E-mail: tiago.cunha@uece.br. *Corresponding author.
[2]Laboratory of Translational Genetics, VIB-KU Leuven Center for Cancer Biology, Leuven, Belgium.

ABSTRACT: Canine atopic dermatitis (cAD) is a multifactorial allergic disease associated with immune dysfunction and abnormal skin barrier. Several immunological mediators play a role in its pathogenesis. Such molecules are produced by the activation of T helper lymphocytes (Th) through polarization to Th1 and/or Th2, which contributes to different lesion patterns. Acute lesions are mediated by an activation of the Th2 cytokine axis, which clinically induces erythema and pruritus. Conversely, in chronic injuries a mixed immune response of Th1/Th2 cytokines occurs, leading to hyperpigmented and lichenified skin. The clinical understanding of these patterns and the mode of action of immunomodulators are crucial for the best clinical management of the atopic patient. In this context, this review discussed the role of the immune response and the immunomodulatory drugs in dogs with atopic dermatitis and suggested a therapeutic protocol based on clinical phenotype. Based on the evidences showed in this review, it is considered appropriate to use immunomodulatory drugs that target cytokine spectrum related with the clinical phenotype of cAD.
Key words: canine atopy, inflammatory disease, immunomodulators.

Dermatite atópica canina: protocolos imunomodulatórios sistêmicos baseados no fenótipo clínico

RESUMO: A dermatite atópica canina (DAC) é uma doença alérgica multifatorial associada à disfunção imune e barreira cutânea anormal. Vários mediadores imunológicos desempenham um papel na sua patogênese. Tais moléculas são produzidas pela ativação de linfócitos T auxiliares (Th) por meio da polarização para Th1 e/ou Th2, o que contribui para diferentes padrões de lesão. Lesões agudas são mediadas pela ativação do eixo de citocinas Th2, que clinicamente induz eritema e prurido. Por outro lado, nas lesões crônicas ocorre uma resposta imune mista de citocinas Th1/Th2, levando à pele hiperpigmentada e liquenificada. O entendimento clínico desses padrões e o modo de ação dos imunomoduladores são cruciais para o melhor manejo clínico do paciente atópico. Esta revisão visa discutir o papel da resposta imune e das drogas imunomoduladoras em cães com dermatite atópica e sugerir um protocolo terapêutico baseado no fenótipo clínico. Baseado nas evidências apresentadas nessa revisão, é considerado apropriado utilizar drogas imunomoduladoras que abrangem o espectro de citocinas relacionadas ao fenótipo clínico da DAC.
Palavras-chave: atopia canina, doença inflamatória, imunomoduladores.

INTRODUCTION

Canine atopic dermatitis (cAD) is currently characterized as a clinical inflammatory syndrome whose development involves the interaction between genetic and environmental factors (MARSELLA, 2021). These factors are able to influence the immune response, the skin microbiome and the integumentary barrier, culminating in the synthesis of pro-inflammatory molecules that potentially perpetuate and aggravate skin inflammation (STEFANOVIC et al., 2021). These molecular mechanisms involved in a given group of individuals are defined as endotypes, while their observable clinical characteristics are known as phenotypes (EISENSCHENK, 2020). The characterization of these endotypes is the target of studies in human atopic dermatitis, as changes in endotypic patterns affect the clinical phenotypes (TOKURA & HAYANO, 2021).

The immunological alterations present in cAD involve different subpopulations of T helper effector lymphocytes (Th) and their related cytokines according to the disease stage (EISENSCHENK, 2020). In acute lesions there is a predominance of Th2 cells, while a mixed pattern of Th1 and Th2 lymphocytes is observed in chronic lesions (PUCHEU-HASTON et al., 2015). These cells are capable of producing cytokines that reproduce different clinical phenotypes in the skin (EISENSCHENK, 2020), which are currently the

Received 02.11.22 Approved 10.01.22 Returned by the author 11.19.22
CR-2022-0068.R1
Editors: Rudi Weiblen Felisbina Luisa Pereira Guedes Queiroga

target of studies in humans (TOKURA & HAYANO, 2021). It is noteworthy that other effectors Th cells are involved in cAD, such as Th17, Th22 and Treg lymphocytes. However, studies in the canine species are needed to define their real role in the phenotypic development of this disease (PUCHEU-HASTON et al., 2015; EISENSCHENK, 2020).

In canine patients with an acute phenotype, erythematous and pruritic lesions with rapid evolution are observed, while in a chronic phenotype, scaly, hyperkeratotic and hyperpigmented processes in skin are predominant. These clinical changes are related with an intensification of Th2 cytokine axis and a significant increase in the Th1 immune response (PUCHEU-HASTON et al., 2015; TOKURA & HAYANO, 2021).

Recognition of these injury patterns is important for the implementation of therapies capable of adequately encompassing the spectrum of cytokines and reversing the integumentary inflammatory process in cAD. Thus, this research discussed the role of the immune response in cAD and suggested a therapeutic protocol for the use of systemic immunomodulators based on the patient clinical phenotype.

Cytokines and their impact on canine atopic dermatitis

Cytokines are defined as protein molecules with cell signaling capacity, responsible for exerting biological effects on the immune system. In this context, these molecules can have pro-inflammatory or anti-inflammatory activities, depending on the stimulus involved for their production (NAKAJIMA et al., 2021). In atopic dermatitis, the cytokines tend to amplify the inflammatory process, being produced by different populations of lymphocytes. Among them, the Th1 and Th2 lymphocytes are reported as the main effector cell groups in canine atopy (PUCHEU-HASTON et al., 2015).

Th1-type immune response is characterized by the production of cytokines capable of activating cellular mechanisms of inflammation. Interferon-γ (IFN-γ) and interleukin-12 (IL-12) are the main proteins that act together for the progression of the inflammatory response in the skin of atopic animals (SCHLOTTER et al., 2011). In an acute phase of cAD there is a predominance of Th2 type cytokines (PUCHEU-HASTON et al., 2015), while in a chronic phase the production of IFN-γ and IL-12 tends to increase, due to the largest participation of Th1 cells. However, there is no significant reduction in Th2 cells activation (Figure 1), characterizing a mixed-pattern cytokine response in the chronic phase of atopic disease (SCHLOTTER et al., 2011; CZARNOWICKI et al., 2019).

Regarding to the Th2-type response, it is responsible for the development of an inflammatory process associated with IgE-mediated hypersensitivity reactions (PUCHEU-HASTON et al., 2015). It is noteworthy that human and canine atopic dermatitis are not considered diseases with strict Th2 polarization (SCHLOTTER et al., 2011; CZARNOWICKI et al., 2019). Other lymphocytes populations, such as Th22, may play role in acute phase of atopic dermatitis (OLIVRY et al., 2016). However, evidence suggested the main contribution of the Th2 pattern of immune response and its cytokines in the development and perpetuation of atopic dermatitis, particularly in the early stages of disease and acute lesions (PUCHEU-HASTON et al., 2015). The main cytokines involved in cAD and their functions will be better explained below.

Interferon-gamma (IFN-γ) is one of the most potent cytokines produced by Th1 cells (TAWADA et al., 2014). This cytokine is related with skin lipid abnormalities (TAWADA et al., 2014) and was identified in skin of atopic dogs with chronic and lichenified lesions (OLIVRY et al., 1999; SCHLOTTER et al., 2011). Besides, this cytokine also has the ability to activate lymphoid cells, thus intensifying the Th1 pattern and the inflammatory process (ALSPACH et al., 2019).

Interleukin-12 (IL-12) is a pro-inflammatory cytokine produced by macrophages, dendritic cells, mast cells and various other cell types (YAWALKAR et al., 2000). This cytokine polarizes immune responses to the Th1 pathway, activates $CD8^+$ T lymphocytes and regulates the production of IFN-γ, being highly expressed in the skin of patients with atopic dermatitis (SCHLOTTER et al., 2011; CHYUAN & LAI, 2020).

Interleukin-4 (IL-4) is a classic example of a Th2 pathway cytokine (PUCHEU-HASTON et al., 2015) and it is produced by Th2 lymphocytes, mast cells and basophils and innate type 2 lymphocytes (ILC2) (MASHIKO et al., 2017). This cytokine regulates gene expression related to the production of chemokines and pro-inflammatory factors and negatively regulates the synthesis of antimicrobial peptides and glucocorticoid receptors, favoring the skin dysbiosis and impairing the glucocorticoid effects (BAO et al., 2013).

Interleukin-5 (IL-5) is an important Th2 protein produced by T cells and granulocytes (TAKATSU, 2011). This cytokine is related to

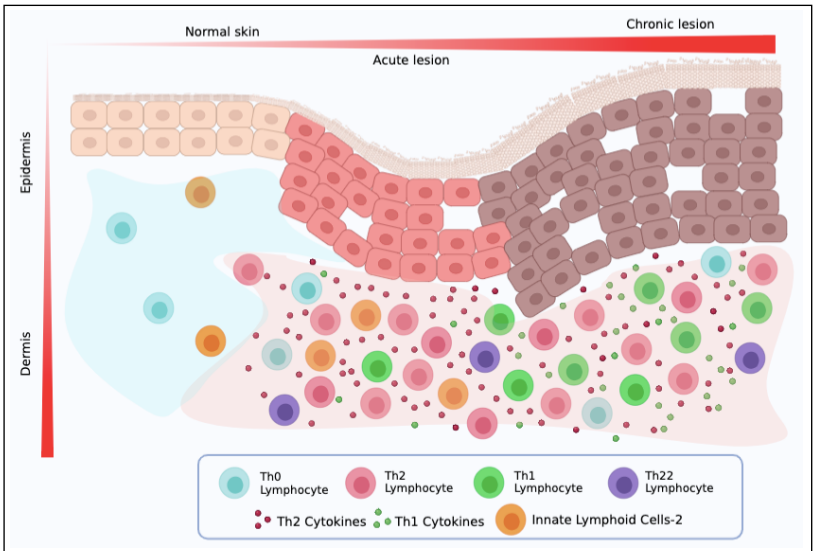

Figure 1 - Effector cell populations and cytokines involved in canine atopic dermatitis (cAD) according to lesion chronicity. Different cell populations and their cytokines are involved on the progression of the inflammatory process. In an acute phase of cAD there is a predominance of Th2 response, while in a chronic phase both Th1 and Th2 response.

the development, survival and proliferation of eosinophil populations (SIMON et al., 2004). Although, the participation of IL-5 in human allergic diseases is evidenced, studies are needed to assess its relationship and with phenotypes in canine atopic dermatitis (BRANDT & SIVAPRASAD, 2011; TENERO et al., 2020).

Interleukin-13 (IL-13) is a critical mediator in inflammation of allergic origin, being present in acute and chronic conditions related to atopic dermatitis (BRANDT & SIVAPRASAD, 2011; PUCHEU-HASTON et al., 2015). This protein is a Th2 cytokine produced by T cells, basophils, mast cells and ILC2 (BIEBER, 2020). Due to the functional similarity with IL-4, *in vitro* studies usually compare the activity of both cytokines concomitantly (ESCHE et al., 2004). IL-13 attenuates the expression of genes associated with the production of filaggrin, loricrin and involucrin, directly affecting the integrity of the skin barrier and favoring allergen penetration. In addition, it has a pro-fibrotic effect leading to lichenification usually present in the chronic atopic dermatitis (MITAMURA et al., 2018; FURUE et al., 2020).

Interleukin-22 (IL-22) is a Th2/Th22 pro-inflammatory cytokine produced by mast cells, natural killer T cells, Th22 cells and $CD8^+$ T cells (FARD et al., 2016), and acts through an upregulation of epithelial derived cytokines in keratinocytes (LOU et al., 2017). Those in turn are critical molecules for promoting type 2 immune responses (LOU et al., 2017). In dogs; however, there was no difference in the expression of this cytokine between healthy and atopic skin (SHIOMITSU et al., 2021), making its role unclear in pathogenesis of cAD.

Interleukin-31 (IL-31) is produced by Th2 cells and also by mast cells (BRANDT & SIVAPRASAD, 2011), being largely expressed in damaged skin of atopic animals (GONÇALVES et al., 2018; SHIOMITSU et al., 2021). It is associated with pruritus through a neurological stimulation and elongation of sensory fibers (GONZALES et al., 2013). Additionally, IL-31 reduces the expression of filaggrin in the epidermis, affecting the skin structure (FURUE et al., 2018).

Taken together, the aforementioned cytokines influence the skin structure and clinical phenotype of the patient. Cytokines present in both acute and chronic response in dogs and their phenotypes are summarized in figure 2.

Clinical phenotypes in canine atopic dermatitis

The clinical phenotypes represent a group of individuals who share similar characteristics. This

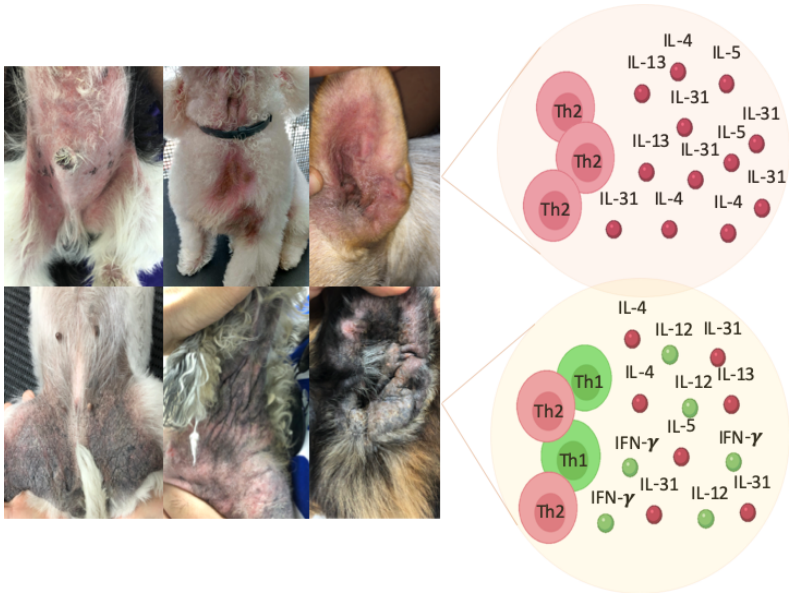

Figure 2 - Clinical lesion variation according to the profile of cells and cytokines. In acute injuries (first line), there is a predominance of Th2-type responses, leading to erythematous and scaling processes. In chronic injuries (second line) there is a predominance of mixed Th1-Th2 responses, increasing epidermal differentiation which is clinically evidenced by hyperkeratotic and lichenified lesions.

definition favors the identification of genetic factors that contribute with disease particularities, as well as the establishment of prognosis and adoption of therapies (EISENSCHENCK, 2020).

In human atopic dermatitis, lesion distribution varies according to age, race/ethnicity, sex, age of onset, and global region (NOMURA et al., 2020). Conversely, those definitions are scarce and restricted to breed and acute/chronic stages in cAD (WILHEM et al., 2011; EISENSCHENK, 2020). Acute lesions are expected to be erythematous, wet and highly inflammatory, turning lichenified, dry, thick and hyperpigmented in dogs with chronic disease (EISENSCHENK, 2020). These phenotypic patterns reflect the cytokines activities.

Comparing cytokine and cell profiles of acute/chronic stages of canine atopic skin, it is possible to understand the changes and immune disparities between disease stages. Th2 cytokines, such as IL-4, IL-13 and IL-31 contribute to erythema, pruritus and structural abnormalities even in the absence of skin lesions. With the progression of the inflammatory process, a high expression of IL-13 induces skin thickening, IL-4 and IL-31 increase pruritus and promote epidermal dysfunctions and, finally, other cell signaling pathways are activated culminating in Th1 cells differentiation. Those, in turn, synthesize pro-inflammatory cytokines, such as IL-12 and IFN-γ which maintain the skin inflammatory status. The clinical features of acute/chronic atopic skin are shown in figure 2.

Although, atopic dogs are expected to follow a pattern of response as previously mentioned, cAD is known to have wide individual clinical variation (FERREIRA et al., 2022). Based on these evidences, it is hypothesized that canine response to the abovementioned mechanisms can vary according to the type of stimulus and its intensity which can induce the overproduction of inflammatory cytokines. Thus, the understanding of this cytokine storm and its relation with clinical lesions can be a potential roadmap toward a precision medicine approach in cAD.

Systemic immunomodulators and canine atopic dermatitis

Currently, there are four immunomodulatory commercially available group of drugs for cAD treatment (OLIVRY & BANOVIC,

2019). These drugs differ in its mechanism and spectrum of action, time to onset of therapeutic response and side effects (EISENSCHENK, 2020). Details of each drug and their different targets will be described below and summarized in figure 3.

Glucocorticoids

Glucocorticoids (GCs) are considered a group of essential hormones that physiologically play fundamental roles in the processes of homeostasis, cognition, cell proliferation, growth of puppies, and reproduction (CAIN & CIDLOWSKI, 2017). Corticoid-mediated immunomodulation has been classically attributed to the induction of alterations in gene expression in various cell groups (RATMAN et al., 2013). GCs interfere in the activation of transcription factors, such as NF-kB, AP-1, NF-AT, and STAT, culminating in the reduction of pro-inflammatory cytokine synthesis such as IL-2, IL-5, IL-6, IL-13, IFN-γ, and TNF-α (RATMAN et al., 2013; CAIN & CIDLOWSKI, 2017).

It is also known that GCs are capable of altering leukocyte mobilization within blood vessels in different ways. This property is attributed to the inhibition of phospholipase A2 (KIM et al., 2001), the reduction in production of chemokines (CAIN & CIDLOWSKI, 2017) and expression of adhesion molecules in vascular endothelium (CRONSTEIN et al., 1992; ATSUTA et al., 1999).

Due to this broad spectrum of action on the immune system, GCs are recommended as first choice drugs to remove the patient from the pruritus crisis associated with canine atopic dermatitis (OLIVRY & BANOVIC, 2019). Later on, a dose reduction and therapy switching are recommended to avoid potential side effects (OLIVRY et al., 2015; OLIVRY & BANOVIC, 2019).

The side-effects of GCs are common and can sometimes become problematic, ranging from mild cases, which courses with polyphagia and polydipsia, to a more severe case, such as Cushing syndrome, posing a life-threatening risk to the patient (ORAY et al., 2016). Moreover, GCs can also affect musculoskeletal, circulatory and gastrointestinal systems (VANDEWALLE et al. 2018). In skin, corticosteroids can cause skin atrophy and fragility (KAYA & SAURAT, 2007) as well as impair cutaneous healing through blockage of collagen genes expression (SCHACKE et al., 2002).

Cyclosporine A

Cyclosporine A (CsA) is a polypeptide produced from the fungus *Cylindrocarpon lucidum* (BOREL et al., 1994), being used in clinical medicine for the control of immune-mediated diseases due to its immunosuppressive potential (OLIVRY et al., 2015; GANUGULA et al., 2020).

Within its spectrum of action, CsA acts mainly by binding to cyclophilin. The resultant

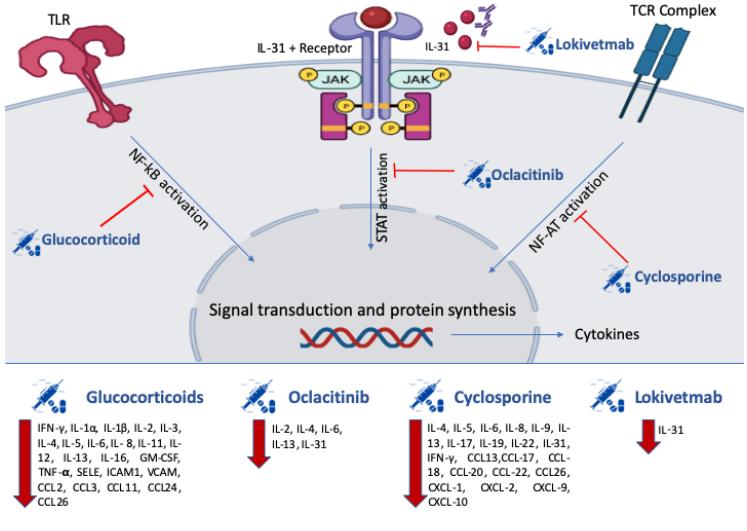

Figure 3 - Immunomodulators as targeted agents (blue) of canine atopic dermatitis (cAD). Schematic representation on various antagonistic strategies used for regulation of cytokine signaling acting in cAD.

complex cyclosporine/cyclophilin inhibits calcineurin, which is a protein that mobilizes the NF-AT from cytoplasm to the nucleus (HAWKSHAW & PAUS, 2021). As NF-AT is a key molecule related to IL-2 synthesis (VINH et al., 2019), its inhibition affects the lymphocytes proliferation and culminates in the general regulation of the immune system (ARCHER et al., 2014; FELLMAN et al., 2019). Additionally, this drug is able to inhibit the prolongation of nerve endings in the epidermis and normalize keratinocyte proliferation and keratin production (KO et al., 2016).

Due to this set of factors, CsA has been widely used in the treatment of atopic dermatitis in dogs (OLIVRY et al., 2015). In a clinical study using 12 dogs, the drug was related to a clinical improvement in pruritus and lesions associated with cAD; although, less effective when compared to GCs (NETO et al., 2017). However, in another comparative study between drugs, with 20 dogs in each group, there was no statistical difference between animals treated with prednisone and animals treated with CsA (TASZKUN, 2010). It is noteworthy that, as it has a lower intensity of side effects when compared to corticosteroids, CsA becomes an option for continuous control of pruritus in animals with cAD (OLIVRY & BANOVIC, 2019).

With regard to the side effects associated with the use of CsA, gastrointestinal changes are mentioned, such as nausea, vomiting and diarrhea, (NUTTALL et al., 2014). The increased susceptibility to the development of infectious processes in the bladder (PETERSON et al., 2012), skin (NUTTALL et al., 2014) and respiratory tract (SALANT et al., 2021) is also noteworthy and possibly associated with reduced activity of the immune system, favoring the proliferation of opportunistic microorganisms.

Oclacitinib

Oclacitinib is a drug recently introduced in veterinary medicine for the treatment of allergic pruritus in dogs. Its mechanism of action involves the inhibition of Janus Kinase (JAK) receptors (GONZALES et al., 2014; DENTI et al., 2022). In mammalian cells there are 4 JAK groups that play important pathophysiological roles. JAK-1 is associated with the inflammatory process, while JAK-2, JAK-3 and TYK-2 are involved in cell differentiation and hematopoiesis (SCHWARTZ et al., 2017). Oclacitinib is able to block the activation of these signaling pathways, having a high affinity for JAK-1 and JAK-2, and a lower affinity for JAK-3 and TYK-2 (GONZALES et al., 2014; SCHWARTZ et al., 2017). Blocking JAK-1 and JAK-2 directly affects the synthesis of pro-inflammatory cytokines, such as IL-2, IL-4, IL-6, IL -13 and IL-31 (SCHWARTZ et al., 2017).

In the first studies related to oclacitinib, side effects in the digestive system, such as vomiting and diarrhea, urinary system, such as urinary tract infections, and integumentary system, such as otitis and pyoderma, were reported (COSGROVE et al., 2015). However, another research on long-term use of oclacitinib in dogs concluded that the presence of bacteriuria was not an expected side effect, as long as this animal did not have a previous history of urinary infection or predisposing condition during the treatment period (SIMPSON et al., 2017).

Lokivetmab

Lokivetmab was the first commercially available immunobiological for the treatment of allergic disease in dogs. This monoclonal antibody acts by directly blocking IL-31, making it unavailable to bind to its receptor and trigger itching. As it is a synthetic antibody, the technology for its manufacture involves the caninization of its molecular structure to avoid recognition and destruction by the immune system (MICHELS et al., 2016).

These IL-31 antibodies promote a rapid itching control response (FLECK et al., 2021), which can last between 30 to 60 days, depending on the degree of itching stimulus and the presence of secondary infections (TAMAMOTO-MOCHIZUKI et al., 2019). The high specificity of lokivetmab gives it advantages such as mild side effects, usually associated with pain at the application site and hypersensitivity reactions (MICHELS et al., 2016; SOUZA et al., 2018).

Among the limitations of this immunobiological agent, the low ability to control skin lesions is cited, even with stabilized pruritus. This fact reflects the need for attention to the early treatment of lesions, preventing their development and progression of the inflammatory process. Furthermore, due to its specificity in blocking IL-31, the possibility of low therapeutic response in animals whose IL-31 does not act as the main pruritogenic molecule is considered (TAMAMOTO-MOCHIZUKI et al., 2019). Therefore, further clinical trials are needed to investigate the applicability of the drug based on patient individuality.

Phenotype based therapy

Although, veterinary medicine has an arsenal of drugs available to control the signs associated with cAD, it is known that the therapeutic response in this disease varies according to the individual and the drug (SANTORO, 2019; MARSELLA et al., 2020; FERREIRA et al., 2022). Among the various reasons that would explain these differences in the treatment of atopic dermatitis, the possibility of variations in cytokine groups based on the geographical location of the animal and the affected breeds should be considered (WILHEM at al., 2011; SANTORO, 2019; EISENSCHENCK, 2020). These variables would potentially modify the immune system polarization, generating different cell and cytokine profiles involved in the hypersensitivity response, as occurs in human atopic dermatitis (STEFANOVIC et al., 2021).

Currently, in human medicine, studies are focused on defining the phenotypes and endotypes of atopic dermatitis in different countries and differentiated by age (TOKURA & HAYANO, 2021). With these studies, there is a better targeting of the pattern of cytokines involved in the disease and, thus, a targeted therapeutic approach is favored (NOMURA et al., 2020). In veterinary medicine, these studies are scarce, being restricted to phenotypic differences between acute and chronic injuries (WILHEM et al., 2011; EISENSCHENK, 2020).

In acute lesions, an immune response composed of Th2 cells and their related cytokines is expected (PUCHEU-HASTON et al., 2015). In the absence of secondary infections, treatments with corticosteroids, oclacitinib and lokivetmab can be benefitial to this type of phenotype (SANTORO, 2019; MARSELLA et al., 2020). However, we should also consider the severity of the injury and the intensity of the crisis to decide which of them are the most suitable. Therefore, due to its broader spectrum of action, animals with severe lesions will have a better response to the use of GCs and, when the crisis becomes stable, a switch to other drugs can be adopted (OLIVRY & BANOVIC, 2019; MARSELLA et al., 2020). Due to the mechanism of action of CsA (HAWKSHAW & PAUS, 2021), it would also be a viable possibility. However, it should not be used alone during the remission of clinical signs (e.g pruritus) as it may take up to six weeks to reach its maximum effect (OLIVRY & BANOVIC, 2019; MARSELLA et al., 2020).

In chronic phase lesions, on the other hand, due to increased activation of Th1 cells and proliferative changes in the epidermis (CZARNOWICKI et al., 2019; EISENSCHENK, 2020), it is considered that GCs and CsA can bring greater benefits to the patient when compared to oclacitinib or lokivetmab. This fact is due both to the broader blockade in the synthesis of pro-inflammatory cytokines, and also to the regulation of keratinocyte proliferation, culminating in the normalization of epidermal cell kinetics (KAYA & SAURAT, 2007; KO et al., 2016). After reestablishing homeostasis, it is possible to consider maintaining a long-term control with CsA or switching to oclacitinib or lokivetmab (OLIVRY & BANOVIC, 2019). Different strategies of the use immunomodulatory drugs are proposed on figure 4.

With regard to maintenance therapy, the importance of preventing or delaying the onset of the integumentary inflammatory process is emphasized (OLIVRY & BANOVIC, 2019). Therefore, a multimodal therapeutic approach is needed (OLIVRY et al., 2015; BENSIGNOR & VIDEMONT, 2022) and, considering the individuality of each patient, the combined use of immunomodulators can be appreciated. It is also noteworthy that, as this is a chronic disease (MARSELLA, 2021), affected dogs undergo long-lasting treatments (OLIVRY et al., 2015) and; therefore, patients should be regularly followed up to avoid serious side effects associated with the chosen drugs. Moreover, the regular use of skin care and mostuirizing products, identification and allergen avoidance and dysbiosis control are also important strategies to improve cAD maintenance (OLIVRY et al., 2015). However, we will focus only on the systemic immunomodulatory therapy, since it is the aim of this review.

In the near future, further research on the molecular profiles of dogs with cAD in different regions of the world is expected, similarly to studies on atopic dermatitis in humans (NOMURA et al., 2020). Furthermore, it is not yet known whether there is variation in the immune response based on the type of antigen involved in cAD, which could potentially characterize the influence of the environment on the endophenotypic development. With such information, it will be possible to consider personalized and selective drug strategies (PESCITELLI et al., 2021), minimizing the occurrence of extensive side effects and optimizing therapeutic responses.

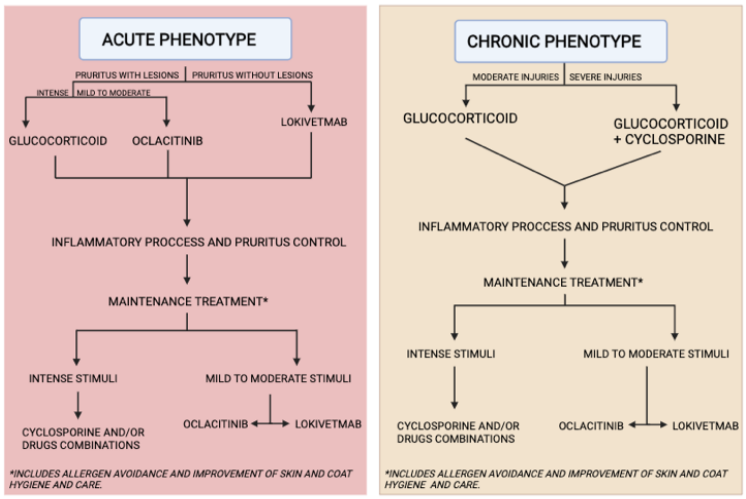

Figure 4 - Guidance flowchart for systemic immunomodulatory use according to clinical phenotype and severity. While in an acute phenotype patient, there is a variety of treatments to control the flare crisis, in a chronic phenotype there is a more restrict protocol. Later on, a maintenance treatment is proposed according to stimuli intensity. It is important to note that a therapeutic protocol to prevent crisis includes a multimodal approach with the use of other products besides the immunomodulators.

CONCLUSION

Based on this review, it is appropriate to consider the use of immunomodulatory therapies aimed at the clinical phenotype of cAD. The management should target the cytokine spectrum involved with the inflammatory process, thus driving the therapeutic choices toward precision medicine. Furthermore, more in-depth studies of canine atopic dermatitis phenotypes and endotypes are encouraged, bringing answers to the following questions: which dog will respond best to which therapy? How long the therapy should be continued? Which allergens induce which signaling pathways? These answers may allow a more precise definition of different clinical endo/phenotypes as key elements for successful development of new therapeutic options and implementation of targeted therapy in dogs with cAD.

AUTHORS' CONTRIBUTION

All authors contributed equally to the conception and writing of this manuscript. The authors have critically revised the manuscript and approved the final version.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

ALSPACH, E. et al. Interferon-γ and its importante roles in promoting and inhibiting spontaneous and therapeutic cancer immunity. **Cold Spring Harbor Perspectives in Biology**, v.11, p.1-20, 2019. Available from: <https://pubmed.ncbi.nlm.nih.gov/29661791/>. Accessed: Nov. 03, 2021. doi: 10.1101/cshperspect.a028480.

ARCHER, T. M. et al. Oral cyclosporine treatment in dogs: a review of the literature. **Journal of Veterinary Internal Medicine**, v.28, p.1-20, 2014. Available from: <https://pubmed.ncbi.nlm.nih.gov/24341787/>. Accessed: Sept. 04, 2021. doi: 10.1111/jvim.12265.

ATSUTA, J. et al. Inhibition of VCAM-1 expression in human bronchial epithelial cells by glucocorticoids. **American Journal of Respiratory Cell and Molecular Biology**, v.20, p.643–650, 1999. Available from: <https://www.atsjournals.org/doi/full/10.1165/ajrcmb.20.4.3265>. Accessed: Nov. 10, 2021. doi: 10.1165/ajrcmb.20.4.3265.

BAO, L. et al. IL-4 up-regulates epidermal chemotactic, angiogenic, and pro-inflammatory genes and down-regulates antimicrobial genes in vivo and in vitro: relevant in the pathogenesis of atopic dermatitis. **Cytokine**, v.61, p.419-425, 2013. Available from:

<https://pubmed.ncbi.nlm.nih.gov/23207180/>. Accessed: Oct. 12, 2021. doi: 10.1016/j.cyto.2012.10.031.

BENSIGNOR, E.; VIDEMONT, E. Weekly topical therapy based on plant extracts combined with lokivetmab in canine atopic dermatitis. **Veterinary Dermatology**, v.33, p.68-e22, 2022. Available from: <https://pubmed.ncbi.nlm.nih.gov/34414621/>. Accessed: Sept. 07, 2021. doi: 10.1111/vde.13004.

BIEBER, T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. **Allergy**, v. 75, p.54-62, 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/31230370/>. Accessed: Jun. 08, 2022. doi: 10.1111/all.13954.

BOREL, J. F. et al. Biological effects of cyclosporin A: A new antilymphocytic agent. **Agents and Actions**, v.43, p.179-186, 1994. Available from: <https://pubmed.ncbi.nlm.nih.gov/8969/>. Accessed: Oct. 20, 2021. doi: 10.1007/BF01986686.

BRANDT, E. B.; SIVAPRASAD, U. Th2 Cytokines and Atopic Dermatitis. **Journal of Clinical and Cellular Immunology**, v.2, p.1-25, 2011. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189506/>. Accessed: Sept. 03, 2021. doi: 10.4172/2155-9899.1000110.

CAIN, D. W.; CIDLOWSKI, J. A. Immune regulation by glucocorticoids. (2017). **Nature Reviews Immunology**, v.17, p.233-247, 2017. Available from: <https://pubmed.ncbi.nlm.nih.gov/28192415/>. Accessed: Nov. 10, 2021. doi: 10.1038/nri.2017.1.

CHYUAN, I. T.; LAI, J. H. New insights into the IL-12 and IL-23: From a molecular basis to clinical application in immune-mediated inflammation and cancers. **Biochemical Pharmacology**, v.175, p.1-9, 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/32217101/>. Accessed: Nov. 10, 2021. doi: 10.1016/j.bcp.2020.113928.

COSGROVE, S. B. et al. Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life. **Veterinary Dermatology**, v.26, p.171-e35, 2015. Available from: <https://pubmed.ncbi.nlm.nih.gov/25688708/>. Accessed: Sept. 07, 2021. doi: 10.1111/vde.12194.

CRONSTEIN, B. N. et al. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. **Proceedings of the National Academy of Sciences of the United States of America**, v.89, p.9991-9995, 1992. Available from: <https://pubmed.ncbi.nlm.nih.gov/1279685/>. Accessed: Nov. 10, 2021. doi: 10.1073/pnas.89.21.9991.

CZARNOWICKI, T. et al. Atopic dermatitis endotypes and implications for targeted therapeutics. **Journal of Allergy and Clinical Immunology**, v.143, p.1-11, 2019. Available from: <https://pubmed.ncbi.nlm.nih.gov/30612663/>. Accessed: Sept. 07, 2021. doi: 10.1016/j.jaci.2018.10.032.

DENTI, D. et al. Prolonged twice-daily administration of oclacitinib for the control of canine atopic dermatitis: a retrospective study of 53 client-owned atopic dogs. **Veterinary Dermatology**, s/v., p.1-8, 2022. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/vde.13053>. Accessed: Jan. 20, 2022. doi: 10.1111/vde.13053.

EISENSCHENK, M. Phenotypes of Canine Atopic Dermatitis. **Current Dermatology Reports**, v.9, p.1-6, 2020. Available from: <https://link.springer.com/article/10.1007/s13671-020-00303-4>. Accessed: Oct. 12, 2021. doi: 10.1007/s13671-020-00303-4.

ESCHE, C. et al. Keratinocytes in atopic dermatites: inflammatory signals. **Current allergy and asthma reports**, v.4, p.276-284, 2004. Available from: <https://pubmed.ncbi.nlm.nih.gov/15175141/>. Accessed: Sept. 07, 2021. doi: 10.1007/s11882-004-0071-8.

FARD, N. A. et al. The potential role of T helper cell 22 and IL-22 in immunopathogenesis of multiple sclerosis. **Innovations in Clinical Neuroscience**, v.13, p.30-36, 2016. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5022987/?report=reader>. Accessed: Jun. 24, 2022. PMCID: PMC5022987.

FELLMAN, C. L. et al. Effects of cyclosporine and dexamethasone on canine T cell expression of interleukin-2 and interferon-gamma. **Veterinary Immunology and Immunopathology**, v.216, p.109892, 2019. Available from: <https://pubmed.ncbi.nlm.nih.gov/31446206/>. Accessed: Nov. 12, 2021. doi: 10.1016/j.vetimm.2019.109892.

FERREIRA, T. C. et al. Canine atopic dermatitis: report of ten cases. **Research, Society and Development**, v.11, p.1-6, 2022. Available from: <https://rsdjournal.org/index.php/rsd/article/view/27258>. Accessed: Jun. 28, 2022. doi: 10.33448/rsd-v11i4.27258.

FLECK, T. J. et al. Onset and duration of action of lokivetmab in a canine model of IL-31 induced pruritus. **Veterinary Dermatology**, v.32, p.681-e182, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33830571/>. Accessed: Sept. 07, 2021. doi: 10.1111/vde.12943.

FURUE, K. et al. Pathogenic implication of epidermal scratch injury in psoriasis and atopic dermatitis. **The Journal of Dermatology**, v.47, p.979-988, 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/32677165/>. Accessed: Sept. 07, 2021. doi: 10.1111/1346-8138.15507.

FURUE, M. et al. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. **Allergy**, v.73, p.29-36, 2018. Available from: <https://pubmed.ncbi.nlm.nih.gov/28670717/>. Accessed: Nov. 12, 2021. doi: 10.1111/all.13239.

GANUGULA, R. et al. A highly potente lymphatic system-targeting nanoparticle cyclosporine prevents glomerulonephritis in mouse model of lupus. **Science Advances**, v.12, p.1-13, 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/32582860/>. Accessed: Nov. 12, 2021. doi: 10.1126/sciadv.abb3900.

GONÇALVES, B. H. R. et al. Correlation between clinical findings, mast cell count and interleukin 31 immunostaining in the skin of dogs with atopic dermatitis. **Ciência Rural**, v.48, p.1-8, 2018. Available from: <https://www.scielo.br/j/cr/a/gf43H6bdCv69S84bNNsPtNn/?lang=en>. Accessed: Nov. 12, 2021. doi: 10.1590/0103-8478cr20189994.

GONZALES, A. J. et al. Oclacitinib (APOQUEL®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. **Journal of Veterinary Pharmacology and Therapeutics,** v.37, p.317-324, 2014. Available from: <https://pubmed.ncbi.nlm.nih.gov/24495176/>. Accessed: Oct. 12, 2021. doi: 10.1111/jvp.12101.

GONZALES, A. J. et al.Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. **Veterinary**

Dermatology, v.24, p.48-53, 2013. Available from: <https://pubmed.ncbi.nlm.nih.gov/23331679/>. Accessed: Sept. 07, 2021. doi: 10.1111/j.1365-3164.2012.01098.x.

HAWKSHAW, N. J.; PAUS, R. Beyond the NF-AT horizon: From Cyclosporine A induced adverse skin effects to novel therapeutics. **Trends in Pharmacological Sciences**, v.42, p.316-328, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33752908/>. Accessed: Oct. 15, 2021. doi: 10.1016/j.tips.2021.02.001.

KAYA, G.; SAURAT, J. H. Dermatoporosis: a chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. **Dermatology**, v.215, p.284-294, 2007. Available from: <https://pubmed.ncbi.nlm.nih.gov/17911985/>. Accessed: Aug. 20, 2021. doi: 10.1159/000107621.

KIM, S. W. et al. Inhibition of cytosolic phospholipase A2 by annexin I. Specific interaction model and mapping of the interaction site. **The Journal of Biological Chemistry**, v.276, p.15712-15719, 2001. Available from: <https://pubmed.ncbi.nlm.nih.gov/11278580/>. Accessed: Aug. 20, 2021. doi: 10.1074/jbc.M009905200.

KO, K. C. et al. Possible antipruritic mechanism of Cyclosporine A in Atopic Dermatitis. **Acta Dermato Venereologica**, v.96, p.624-629, 2016. Available from: <https://pubmed.ncbi.nlm.nih.gov/26671728/>. Accessed: Sept. 07, 2021. doi: 10.2340/00015555-2318.

LOU, H. et al. Expression of IL-22 in the skin causes Th2-biased immunity, epidermal barrier dysfunction and pruritus via stimulating epithelial Th2 Cytokines and the GRP pathway. **Journal of Immunology**, v.198, p.2543-2555, 2017. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360537/>. Accessed: Jun. 24, 2022. doi: 10.4049/jimmunol.1600126.

MARSELLA, R. Advances in our understanding of canine atopic dermatitis. **Veterinary Dermatology**, 32, p.547-e151, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33891338/>. Accessed: Nov. 12, 2021. doi: 10.1111/vde.12965.

MARSELLA, R. et al. Comparison of various treatment options for canine atopic dermatitis: a blinded, randomized, controlled study in a colony of research atopic beagles. **Veterinary Dermatology**, v.31, p.284-e69, 2020. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/vde.12849>. Accessed: Nov. 12, 2021. doi: 10.1111/vde.12849.

MASHIKO, S. et al. Increased frequencies of basophils, type 2 innate lymphoid cells and Th2 cells in skin of patients with atopic dermatitis but not psoriasis. **Journal of Dermatological Science**, v.88, p.167-174, 2017. Available from: <https://www.jdsjournal.com/article/S0923-1811(17)30701-6/fulltext>. Accessed: Nov. 12, 2021. doi: 10.1016/j.jdermsci.2017.07.003.

MICHELS, G. M. et al. A blinded, randomized, placebo-controlled trial of the safety of lokivetmab (ZTS-00103289), a canonized anti-canine IL-31 monoclonal antibody in client-owned dogs with atopic dermatitis. **Veterinary Dermatology**, v.27, p.505-e136, 2016. Available from: <https://pubmed.ncbi.nlm.nih.gov/27647513/>. Accessed: Sept. 07, 2021. doi: 10.1111/vde.12364.

MITAMURA, Y. et al. NRF-2 activation inhibits both TGF-b1 and IL-13-mediated periostin expression in fibroblasts: benefit of cinnamaldehyde for antifibrotic treatment. **Oxidative Medicine and Cellular Longevity**, v.2018, p.1-10, 2018. Available from: <https://www.hindawi.com/journals/omcl/2018/2475047/>. Accessed: Sep. 07, 2021. doi: 10.1155/2018/2475047.

NAKAJIMA, S. et al. Novel pathogenesis of atopic dermatitis from the view of cytokines in mice and humans. **Cytokine**, v.148, p.1-9, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/34388479/>. Accessed: Nov. 12, 2021. doi: 10.1016/j.cyto.2021.155664.

NETO, S. A. et al. Eficácia da Ciclosporina no controle da dermatite atópica em cães. **Pesquisa Veterinaria Brasileira**, v.37, p.729-733, 2017. Available from: <https://www.scielo.br/j/pvb/a/sSmyXVGMVQDG9ctCBTdsBnG/?lang=pt>. Accessed: Nov. 12, 2021. doi: 10.1590/S0100-736X2017000700013.

NOMURA, T. et al. Endophenotypic variations of atopic dermatitis by age, race and ethnicity. **Journal of Allergy and Clinical Immunology in Practice**, v.8, p.1840-1852, 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/32499033/>. Accessed: Oct. 15, 2021. doi: 10.1016/j.jaip.2020.02.022.

NUTTALL, T. et al. Life-long diseases need life-long treatment: Long-term safety of ciclosporin in canine atopic dermatitis. **Veterinary Record**, v.174, p.3-12, 2014. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995266/>. Accessed: Oct. 15, 2021. doi: 10.1136/vr.102471.

OLIVRY, T.; BANOVIC, F. Treatment of canine atopic dermatitis: time to revise our strategy? **Veterinary Dermatology**, v.30, p.87-90, 2019. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/vde.12740>. Accessed: Sept. 07, 2021. doi: 10.1111/vde.12740.

OLIVRY, T. et al. Toward a canine model of atopic dermatitis: amplification of cytokine-gene transcripts in the skin of atopic dogs. **Experimental Dermatology**, v.8, p.204-211, 1999. Available from: <https://pubmed.ncbi.nlm.nih.gov/10389638/>. Accessed: Nov. 15, 2021. doi: 10.1111/j.1600-0625.1999.tb00372.x.

OLIVRY, T. et al. Treatment of canine atopic dermatitis: update guidelines from the international committee on Allergic Diseases of Animals. **BMC Veterinary Research**, v.16, p.210, 2015. Available from: <https://pubmed.ncbi.nlm.nih.gov/26276051/>. Accessed: Sept. 07, 2021. doi: 10.1186/s12917-015-0514-6.

OLIVRY, T. et al. Early activation of Th2/Th22 Inflammatory and Pruritogenic Pathways in Acute Canine Atopic Dermatitis Skin Lesions. **Journal of Investigative Dermatology**, v.136, p.1961-1969, 2016. Available from: <https://pubmed.ncbi.nlm.nih.gov/27342734/>. Accessed: Jun. 24, 2022. doi: 10.1016/j.jid.2016.05.117.

ORAY, M. et al. Long-term side effects of glucocorticoids. **Expert Opinion on Drug Safety**, v.14, p.457-465, 2016. Available from: <https://pubmed.ncbi.nlm.nih.gov/26789102/>. Accessed: Nov. 15, 2021. doi: 10.1517/14740338.2016.1140743.

PESCITELLI, L. et al. Novel Therapeutic Approaches and Targets for the treatment of atopic dermatitis. **Current Pharmaceutical Biotechnology**, v.22, p.73-84, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/32525769/>. Accessed: Nov. 15, 2021. doi: 10.2174/1389201021666200611112755.

PETERSON, A. L. et al. Frequency of urinary tract infection in dogs with inflammatory skin disorders treated with ciclosporin alone or in combination with glucocorticoid therapy: a retrospective study. **Veterinary Dermatology**, v.23, p.201-e43, 2012. Available from: <https://pubmed.ncbi.nlm.nih.gov/22409401/>. Accessed: Sept. 07, 2021. doi: 10.1111/j.1365-3164.2012.01044.x.

PUCHEU-HASTON, C. M. et al. Review: Lymphocytes, cytokines, chemokines and the T-helper 1-T-helper 2 balance in canine atopic

dermatitis. **Veterinary Dermatology**, v.26, p.124-e32, 2015. Available from: <https://pubmed.ncbi.nlm.nih.gov/25808535/>. Accessed: Nov. 15, 2021. doi: 10.1111/vde.12205.

RATMAN, D. et al. How glucocorticoid receptors modulate the activity of other transcription factors: a scope beyond tethering. **Molecular and Cellular Endocrinology**, v.380, p.41-54, 2013. Available from: <https://pubmed.ncbi.nlm.nih.gov/23267834/>. Accessed: Oct. 12, 2021. doi: 10.1016/j.mce.2012.12.014.

SALANT, H. et al. Systemic toxoplasmosis in a cat under cyclosporine therapy. **Veterinary Parasitology: Regional Studies and Reports**, v.23, p.1-5, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33678395/>. Accessed: Nov. 15, 2021. doi: 10.1016/j.vprsr.2021.100542.

SANTORO, D. Therapies in canine atopic dermatitis: an update. **The Veterinary Clinics of North America. Small Animal Practice**, v.49, p.9-26, 2019. Available from: <https://pubmed.ncbi.nlm.nih.gov/30262146/>. Accessed: Oct. 15, 2021. doi: 10.1016/j.cvsm.2018.08.002.

SCHACKE, H. et al. Mechanisms involved in the side effects of glucocorticoids. **Pharmacology and Therapeutics**, v.96, p.23-43, 2002. Available from: <https://www.sciencedirect.com/science/article/pii/S0163725802002978?via%3Dihub>. Accessed: Jun. 08, 2022. doi: 10.1016/S0163-7258(02)00297-8.

SCHLOTTER, Y. M. et al. Lesional skin in atopic dogs shows a mixed type-1 and type-2 immune responsiveness. **Veterinary Immunology and Immunopathology**, v.143, p.20-26, 2011. Available from: <https://pubmed.ncbi.nlm.nih.gov/21684616/>. Accessed: Nov. 12, 2021. doi: 10.1016/j.vetimm.2011.05.025.

SCHWARTZ, D. M. et al. JAK Inhibition as a therapeutic strategy for immune and inflammatory diseases. **Nature Reviews: Drug Discovery**, v.16, p.843-862, 2017. Available from: <https://pubmed.ncbi.nlm.nih.gov/29104284/>. Accessed: Nov. 15, 2021. doi: 10.1038/nrd.2017.201.

SHIOMITSU, S. et al. Evaluation of the cutaneous expression of IL-17, IL-22, IL-31, and their receptors in canine atopic dermatitis. **Research in Veterinary Science**, v.136, p.74-80, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33588097/>. Accessed: Sept. 07, 2021. doi: 10.1016/j.rvsc.2020.12.015.

SIMON, D. et al. Eosinophils and atopic dermatitis. **Allergy**, v.59, p.561-570, 2004. Available from: <https://pubmed.ncbi.nlm.nih.gov/15147438/>. Accessed: Oct. 12, 2021. doi: 10.1111/j.1398-9995.2004.00476.x.

SIMPSON, A. C. et al. The frequency of urinary tract infection and subclinical bacteriuria in dogs with allergic dermatitis treated with oclacitinib: a prospective study. **Veterinary Dermatology**, v.28, p.485-e113, 2017. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/vde.12450>. Accessed: Oct. 15, 2021. doi: 10.1111/vde.12450.

SOUZA, C. P. et al. 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. **Veterinary Dermatology**, v.29, p.489-e164, 2018. Available from: <https://pubmed.ncbi.nlm.nih.gov/30141223/>. Accessed: Nov. 12, 2021. doi: 10.1111/vde.12682.

STEFANOVIC, N. et al. The role of environment and exposome in atopic dermatitis. **Current Treatment Options in Allergy**, s/v, p.1-20, 2021. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8139547/>. Accessed: Nov. 15, 2021. doi: 10.1007/s40521-021-00289-9.

TAKATSU, K. Interleukin-5 and IL-5 receptor in health and diseases. **Proceedings of the Japan Academy, Series B Physical and Biological Sciences**, v.87, p.463-485, 2011. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3313690/>. Accessed: Jun. 08, 2022. doi: 10.2183/pjab.87.463.

TAMAMOTO-MOCHIZUKI, C. et al. Proactive maintenance therapy of canine atopic dermatitis with the anti-IL-31 lokivetmab. Can a monoclonal antibody blocking a single cytokine prevent allergy flares? **Veterinary Dermatology**, v.30, p.98-e26, 2019. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/vde.12715>. Accessed: Nov. 12, 2021. doi: 10.1111/vde.12715.

TASZKUN, I. The evaluation of Canine Atopic Dermatitis Extent and Severity Index (CADESI) test in dogs with atopic dermatitis (AD) treated with cyclosporine or prednisone. **Polish Journal of Veterinary Sciences**, v.13, p.681-688, 2010. Available from: <https://pubmed.ncbi.nlm.nih.gov/21370747/>. Accessed: Oct. 15, 2021. doi: 10.2478/v10181-010-0005-4.

TAWADA, C. et al. Interferon-g decreases ceramides with long-chain fatty acids: possible involvement in atopic dermatitis and psoriasis. **Journal of Investigative Dermatology**, v.134, p.712-718, 2014. Available from: <https://pubmed.ncbi.nlm.nih.gov/24008422/>. Accessed: Sept. 07, 2021. doi: 10.1038/jid.2013.364.

TENERO, L. et al. Anti-IL-5 in pediatric allergic diseases. **Pediatric Allergy and Immunology**, v.31, p.14-16, 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/33236428/>. Accessed: Nov. 12, 2021. doi: 10.1111/pai.13374.

TOKURA, Y.; HAYANO, S. Subtypes of atopic dermatitis: from phenotype to endotype. **Allergology International**, s/v, p.1-11, 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/34344611/>. Accessed: Nov. 12, 2021. doi: 10.1016/j.alit.2021.07.003.

VANDEWALLE, J. et al. Therapeutic mechanisms of glucocorticoids. **Trends in Endocrinology and Metabolism**, v.29, p.42-54, 2018. Available from: <https://pubmed.ncbi.nlm.nih.gov/29162310/>. Accessed: Nov. 12, 2021. doi: 10.1016/j.tem.2017.10.010.

VINH, L. B. et al. Ginsenosides from Korean red ginseng modulate T cell function via the regulation of NF-AT-mediated IL-2 production. **Food Science and Biotechnology**, v.28, p.237-242, 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6365338/>. Accessed: Oct. 12, 2021. doi: 10.1007/s10068-018-0428-8.

WILHEM, S. et al. Breed-associated phenotypes in canine atopic dermatitis. **Veterinary Dermatology**, v.22, p.143-149, 2011. Available from: <https://pubmed.ncbi.nlm.nih.gov/20887404/>. Accessed: Jun. 08, 2022. doi: 10.1111/j.1365-3164.2010.00925.x.

YAWALKAR, N., et al. Down-regulation of IL-12 by topical corticosteroids in chronic atopic dermatitis. **Journal of Allergy and Clinical Immunology**, v.106, p.941-947, 2000. Available from: <https://pubmed.ncbi.nlm.nih.gov/11080718/>. Accessed: Jun. 08, 2022. doi: 10.1067/mai.2000.109825.