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Canine keratoconjunctivitis sicca therapeutics: literature review*

Terapêutica da ceratoconjuntivite seca canina: revisão bibliográfica

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Resumo

A ceratoconjuntivite seca (CCS) é uma doença comumente observada em cães caracterizada pela ausência ou redução das secreções lacrimais. Pode ser classificada como qualitativa ou quantitativa, sendo que ambas as categorias são capazes de desencadear inflamação da conjuntiva e da córnea, dor ocular, doença corneana progressiva e redução da visão. O tratamento desta doença é contínuo e se baseia no restabelecimento e manutenção da homeostase do sistema da superfície ocular. Os pacientes podem se beneficiar de diferentes protocolos terapêuticos, tais como o uso de lacrimomiméticos, que aumentam a estabilidade lacrimal ajudando na retenção da umidade ocular; lacrimoestimulantes para a promoção de secreção de lágrimas; ácidos graxos, que desempenham papel na síntese de meibum e bloqueiam a expressão gênica de citocinas pró-inflamatórias; produtos derivados do sangue, baseando-se nos fatores de crescimento de promoção epitelial; e células tronco, devido à sua capacidade de auto renovação. Em casos estáveis, o uso de anti-inflamatórios esteroidais ou não esteroidais pode ser benéfico no controle de sinais clínicos. Casos refratários ao tratamento podem eventualmente se beneficiar de terapias cirúrgicas, que incluem as técnicas de transposição de ducto parotídeo, transplantes glandulares e oclusão da puncta lacrimal.

Palavras-chave: cão, oftalmologia, superfície ocular.

Abstract

keratoconjunctivitis sicca (KCS) is a disease commonly seen in dogs that is characterized by the reduction or absence of lacrimal secretions. It can be classified as qualitative or quantitative, and both categories are able to elicit conjunctival and corneal inflammation, ocular pain, progressive corneal disease, and vision impairment. This disease's treatment is based on reestablishing and maintaining ocular surface homeostasis. Patients may benefit from different therapeutic protocols, such as the use of lacrimomimetics, that increase lacrimal stability, helping to retain ocular humidity; lacrimostimulants, that promote lacrimal secretion; fatty acids, which play a role on meibum synthesis and block pro-inflammatory cytokine genic expression; blood products, based on promotion of epithelial growth factors; and stem cells, due to their self-renewing capabilities. Stable cases may benefit from the use of steroidal or non-steroidal anti-inflammatory agents on the control of clinical signs. Refractory cases may eventually benefit from surgical therapies, which include techniques for parotid duct transposition, gland transplants, and lacrimal puncta occlusion.

Keywords: dog, ocular surface, ophthalmology.

Introduction

Keratoconjunctivitis sicca (KCS) is a disease commonly described in dogs, characterized by the absence or diminishing of lacrimal secretions. Desiccation and inflammation of the conjunctiva and cornea are commonly seen, leading to ocular pain, progressive corneal disease, and compromised vision (ELIZABETH, 20210). Because it is one of the main ocular morbidity causes in humans, researches are constantly conducted; dogs are seen as excellent animal models for the understanding of this disease (SEBBAG and MOCHEL, 2020).

The most common causes of KCS in both dogs and humans are immunomodulated reactions that affect lacrimal glands, meibomian glands, and conjunctival goblet cells, leading to ocular surface inflammation (SGRIGNOLI et al., 2019). Other causes described in dogs include infectious diseases (e.g., canine distemper virus, toxoplasmosis, leishmaniosis), drugs (e.g., sulfonamides, atropine), breed predisposition (e.g., acinar hypoplasia and ichthyosiform dermatoses in Cavalier King Charles Spaniels), third eyelid gland protrusion, orbital trauma, orbital inflammatory diseases, loss of lacrimal glands' parasympathetic innervation, and loss of the ocular surface's sensorial innervation. It can also occur secondarily to systemic metabolic diseases such as hypothyroidism, diabetes mellitus and Cushing syndrome (ELIZABETH, 2021). The main elements that may contribute to KCS's pathophysiological process are tear film instability, hyperosmolarity, inflammation, and ocular surface damage (CRAIG et al., 2017).

The treatment for immunomodulated keratoconjunctivitis sicca must be continuous. Besides, the treatment based in artificial tears, ointments, and sustained release pellets are only palliatives, and may have limited efficacy (STERN et al., 2002).

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Therefore, the search for new therapeutics is constant. Patients may benefit of different therapeutic options; however, KCS treatment must be guided towards reestablishing and maintain ocular surface homeostasis, which was interrupted due to the disease's vicious cycle (BAEYENS et al., 2012).

This literature review aims to describe the most common treatment options for this disease, as well as the most current advances in the subject.

Keraconjunctivitis sicca therapeutics

1. Lacrimomimetics

Lacrimomimetics, or ocular lubricants, increase the tear film stability in order to decrease the loss by evaporation and help retaining ocular humidity (NASSIRI et al., 2017), aiming towards an improvement of the ocular surface's physiological condition, providing symptomatic relief (WALSH and JONES, 2019). They do not treat the cause.

However, there are limitations to the use of these artificial tears. The complex composition of natural tears cannot be completely substituted, and the integrity of the lipidic, aqueous and mucous structure is not totally replicated by these artificial components (DOGRU et al., 2013). The chronic nature of keratoconjunctivitis sicca may demand the use of multiple doses during a long period, and any drops administered in a multidose format must have some sort of mechanism to maintain the content sterile during the period of intended use. For this end, topical formulations may contain preservatives, and there are evidences showing the adverse effects of these substances on the ocular surface (WALSH and JONES, 2019). Ideally the better solutions are conservative free, but they usually are more expensive also. Before choosing the ideal lacrimomimetic, it is important to consider if the benefits of their use will improve or worsen a damaged ocular surface.

Lacrimomimetics are formulated from a hypotonic or isotonic buffering solution which contains additives such as electrolytes, surfactants, and viscosity agents in order to increase or substitute the tear film. Viscosity agents found in artificial tears include carboxymethyl cellulose, polyvinyl alcohol, polyethylene glycol, propylene glycol, and hydroxypropyl guar. Lipid additives, such as mineral oil, aim to diminish lacrimal film's evaporation (NASSIRI et al., 2017).

Sodium carboxymethyl cellulose is an anionic polymer, water soluble, that once attached to the cellular surface allows for reduced water losses and promotes epithelial cell growth to provide osmoprotection (GARRETT et al., 2007). Associating sodium carboxymethyl cellulose with glycerol (Optive®) may lead to increased comfort and diminish KCS' clinical signs, besides significantly improving all stages of the disease (mild, moderate, and severe) (KAERCHER et al., 2009).

Hydroxypropyl guar is used in combination with polyethylene glycol 400, propylene glycol, and sorbitol and borate (ARAÚJO and GALERA, 2016). These ophthalmic formulations may be prepared at a neutral pH and remain liquid within their flask, which helps application. Once applied, it turns into a gel, due to the eye's pH (around 7-8); this helps providing better lubrification and longer retention in the ocular surface (PETRICEK et al., 2008). When compared to carboxymethyl cellulose with glycerol, hydroxypropyl guar/ polyethylene glycol/propylene glycol combination have been shown to have similar effects, lowering scores of ocular surface pigmentation with fluorescein and Lissamine green, indicating improvement in KCS' clinical signs (LABETOULLE et al., 2017).

Synthetic polymer lubricants commonly used include carbomer (polyacrylic acid) and povidone (polyvinylpyrrolidone). Povidones are linear polymers with mucinemimetic properties with a good retention time (ARAÚJO and GALERA, 2016).

Sodium hyaluronate is a glycosaminoglycan present in natural tears that possesses anti-inflammatory properties and promotes corneal epithelial wounds healing by promoting cellular migration, adhesion, and proliferation, and these properties should also be considered in a damaged cornea, and not only the lubrification effect. Sodium hyaluronate also has a relatively long staying time on the ocular surface (SCHMIDL et al., 2015). Besides, it improves comfort and demands lower application frequencies when compared to carbomer (BAEYENS et al., 2012).

Since the role of osmolarity has been established in the pathogenesis of dry eye disease in humans, it is possible that hypotonic tear replacements may correct hyperosmolarity. In clinical contexts, hypotonic sodium hyaluronate 0,1% eye drops seem to have a better therapeutic effect when compared to isotonic drops of the same agent. However, hypotonic products tend to have shorter persistence times on the eye, and it is expected that osmoprotectors are more beneficial to the patients (LEE et al., 2014), since it can be verified that conjunctival hyperemia is improved when using carboxymethyl cellulose associated to osmoprotectors (GUILLON et al., 2010).

Organic osmolytes, also known as compatible solutes, may be classified as amino acids (glycine, betaine, proline, taurine), polyols (glycerol, erythritol, inositol, sorbitol), small carbohydrates (trehalose), methylamines (L-carnitine), methylsulfonium solutes or urea (BAUDOUIN et al., 2013). L-carnitine and erythritol protect corneal cells from osmotic stress. Betaine suppresses metalloproteinase's expression, production, and activation, which are all enhanced in a hyperosmotic environment (ARAÚJO and GALERA, 2016).

The utilization of different compositions of artificial tears is efficacious at relieving clinical signs, which can be observed though the improvement of the three tests for evaluation of dry eye: lacrimal osmolarity, Schirmer tear test (STT), and tear film break-up time (TFBUT) (ÇÖMEZ et al., 2013). However, it is paramount to emphasize that lacrimomimetics are prescribed only as adjuvants until normal lacrimal production is achieved (ARAÚJO and GALERA, 2016).

2. Lacrimostimulants

As KCS is most often developed by immune-mediators mechanisms, lacrimostimulants are used to treat the main cause. Lacrimostimulants include two categories of therapeutic agents: cholinergics and immunomodulators (ELIZABETH, 2021). Given the role of inflammation in KCS' pathogenesis, modulating underlying immune responses is more efficacious in the treatment than using artificial tears (KUNERT, 2000).

Ciclosporin A is extracted from the fungus *Tolypocladium inflatum*, and acts as an immunosuppressant and, when administered topically, acts as an immunomodulant (DREW et

al., 2018). Its immunosuppressant mechanisms are related to binding to specific nuclear proteins which are needed for the beginning of T-cell activation; as a consequence, inflammatory cytokines are not produced, interrupting immunomodulated processes (MOORE et al., 2001). As such, cyclosporin A affects T-cell activity, blocking calcineurin activity and interleukin 2 (IL-2) production (NASSIRI et al., 2017). Besides, ciclosporin A quantitatively increases tear film production, and its ability to do so is well documented in dogs (NASSIRI et al., 2017; ELIZABETH, 2021).

In dogs, it has been demonstrated that ciclosporin A diminishes lymphocytic infiltrates in conjunctival and lacrimal glands, and some additional benefits of its topical use have also been observed, such as the decrease of mucopurulent conjunctivitis, faster healing of refractive corneal ulcers, and the decrease in the dependence of frequent topical KCS treatments (KASWAN et al., 1989).

Given this, one of the most commonly used lacrimal stimulants in dogs with KCS is ciclosporin A, topically administered in concentrations of 0,2%, 1%, or 2% (in these cases, in an oil-based solution). However, some patients present topical irritation and fail to produce tears in normal levels again, which is a limiting factor on the efficacy levels of this drug (BERDOULAY et al., 2005). The choice by the initial concentration finds controversies among veterinarians. Some begin with higher concentrations reducing it with the improvement of the clinical parameters, and those who start with 0,2% and use the higher dose in dogs that do not respond to the medication. It is important to keep in mind that tears improvement takes more than two weeks of treatment with the use of lacrimostimulants. During this initial period, the clinician can associate (but it is not mandatory) anti-inflammatories medicaments to relieve the clinical signs.

Tacrolimus is a macrolide antibiotic isolated from *Streptomyces tsukubaensis* that has effects similar to those of ciclosporin A, and include a combination of local immunosuppression, goblet cell proliferation, lacrimal cell apoptosis suppression, and anti-inflammatory action (BERDOULAY et al., 2005; HENDRIX et al., 2011; MOSKOVICI et al., 2015). Several studies have showed tacrolimus' efficacy both in dogs and humans, either systemically or topically at 0,03%, in improving dry eye clinical signs and symptoms (BERDOULAY et al., 2005; HENDRIX et al., 2011; MOSKOVICI et al., 2015; NASSIRI et al., 2017), particularly in Sjögren syndrome in humans (MOSKOVICI et al., 2015).

Dogs with KCS have been successfully treated upon topical application of tacrolimus 0,02% (BERDOULAY et al., 2005). The use of 0,03% tacrolimus eye drops diluted in linseed oil and olive oil was also proven to be effective, with the only significant difference between the two vehicles being that the linseed oil eye drop showed a decrease in neutrophil count on palpebral conjunctival cytological examination (ZULIM et al., 2018).

When comparing topical instillation of tacrolimus and ciclosporin in dogs, there are no differences regarding STT results for increase of lacrimal production (HENDRIX et al., 2011). However, tacrolimus has been shown to be 10 to 100 times more potent than ciclosporin A in inhibiting cytotoxic T-cells, and *in vitro* production of IL-2, IL-3, and gamma IFN. It has also been shown, *in vitro*, that tacrolimus penetrates skin better than ciclosporin, likely due to its smaller molecular size and lipophilic nature (BERDOULAY et al., 2005). In practice, dogs that respond well to medication respond to both, with cyclosporine or tacrolimus being the veterinarian's choice.

Pimecrolimus belongs to the ascomycin class of macrolactam immunosuppressives, and selectively interferes in T-cell activation, as well as inhibits the production of inflammatory cytokines through calcineurin inhibition, the same molecular action mechanism as ciclosporin A. Its 1% formulation is highly efficacious in relieving KCS' clinical signs in dogs, such as lacrimal secretion and ocular surface inflammation (OFRI et al., 2009). Pimecrolimus is not currently used as the CsA or tacrolimus.

However, prolonging the time it stays in contact with the ocular surface must be an applicable strategy for KCS's treatment due to its high hydrophobic characteristics. A new polymer can be used for forming nano-sized polymeric micelles. These micelles, through endocytosis, increase the drug's permeability. Given that the corneal epithelial barrier limits absorption and drug delivery, how it is formulated is a crucial factor in influencing pimecrolimus' tolerability, availability, and elimination profile (YINGFANG et al., 2016).

Sirolimus is a macrocyclic lactone isolated from *Streptomyces hygroscopicus*, and is structurally similar to tacrolimus, able to bond to the same intracellular immunophilin (FKPB12). It does not, however, lead to calcineurin inhibition; instead, sirolimus bonds to the mammalian target of rapamycin (mTOR) intracellular protein kinase serine/threonine. When inhibited, the mTOR pathway leads to a decrease of T and B cells function, as well as to the negative regulation of associated cytokines and cell growth factors needed for immune system cells to be activated and to proliferate (SPATOLA et al., 2018).

Sirolimus' usage is limited due to its physicochemical properties: it is basically insoluble in water, produces high liposolubility, does not have ionizable groups, and is unstable in ionic mediums. Besides, it hardly permeates the cornea, and seems promising only for conditions of the ocular surface (LINARES-ALBA et al., 2016). Despite positive preliminary results shown regarding topical use of an aqueous solution of sirolimus 0,02%, more studies are needed to understand its role as a potential therapeutic option (SPATOLA et al., 2018).

On the other hand, pharmaceutical nanocarriers such as liposomes, micelles, nanoemulsions, polymeric nanoparticles, and many others, should allow for drug bioavailability with a specific release profile. Subconjunctival injections of liposomes containing 1 mg/ml of sirolimus improve lacrimal production, as well as tear film stability, with a clinical improvement of conjunctival secretion, congestion, and vascularization (LINARES-ALBA et al., 2016).

In cases of neurogenic keratoconjunctivitis, immunomodulatory therapy is unlikely to elicit a response; therefore, pilocarpine is the drug of election. Pilocarpine is a parasympathomimetic capable of unspecific stimulation of the parasympathetic nervous system, including lacrimal glands (MATHEIS et al., 2012). By increasing the amount of goblet cells, oral pilocarpine increases mucous secretion, improving conjunctival epithelial function, regardless of the aqueous layer of the lacrimal film (NASSIRI et al., 2017). The route through which pilocarpine is administered depends on the patient's tolerance; alternatively, it can be diluted and topically applied on the eyes. There may be some side effects such as

blepharospasm, conjunctival hyperemia, and miosis. The irritant effects can be controlled with topical anti-inflammatory agents, either steroidal or non-steroidal (ELIZABETH, 2021).

3. Anti-inflammatory therapeutics

Anti-inflammatories may be valuable adjuvants for KCS' clinical treatment and improvement of clinical signs. Usually, topical steroids are used to alleviate conjunctivitis, diminish discomfort, and reduce opacity correlated to chronic keratitis. However, for patients with corneal lesions and fluorescein retention, the use of topical steroids may severely compromise the healing process; therefore, it is not recommended in these cases. (ELIZABETH, 2021) Its use is also limited due to its potential to significantly increase intraocular pressure (IOP) and form cataracts (NASSIRI et al., 2017).

Prednisolone is a synthetic analogue of hydrocortisone. Methylprednisolone 1% was the first corticosteroid proven useful for the treatment of KCS' patients, showing improvement of the clinical signs; however, when compared to current compounds is the one most likely to increase IOP. Other topical corticosteroids have been studied and used successfully on the treatment of dry eye disease, and the extent of side effects may vary significantly depending on the molecule used, the posology, and the patient's susceptibility (CUTOLO et al., 2017).

Loteprednol etabonate is currently the most studied compound for the treatment of dry eye disease in humans and belongs to a corticosteroid class in which the ketone group has been substituted by methyl ester chlorine; the absence of this ketone may be the reason why this drug is less likely to cause cataracts (CUTOLO et al., 2017).

Non-steroidal anti-inflammatory drugs (NSAIDs) are amply used on ophthalmology. They inhibit cyclooxygenase by blocking prostaglandin synthesis, an important inflammation mediator. Even though their use is no associated with elevated IOP and cataracts, they are associated to corneal perforation in patients with pre-existing corneal epithelium damage. Besides, NSAIDs have a proved anesthetic effect, and chronic use may worsen corneal hypoesthesia in grave KCS cases (CUTOLO et al., 2017). Studies on the role of NSAIDs in the treatment of KCS are lacking; therefore, its use is not usually recommended specifically for KCS (NASSIRI et al., 2017).

4. Blood products

Tears are composed of water, proteins, carbohydrates, lypids, and electrolytes, similarly to serum. The total protein concentration is 10% lower in the tears than in serum. Lactoferrin that is present in tears is responsible for carrying iron is absent in serum; however, transferrin is present and has similar function to lactoferrin. Most growth factors' concentrations are equivalent in both tears and serum. Vitamin A, vitamin C and glutathione are present in both, but in different concentrations. Sodium ions are equivalent in both; on the other hand, potassium concentration is higher in tears, while calcium and phosphate are higher in serum (TSUBOTA and HIGUCHI, 2000).

There is ample interest in the application of blood products in the treatment of dry eye, particularly because there is a wide range of therapeutic products. Natural tears are the main source of nutrition for corneal epithelium, transporting growth factors in the case of a lesions. Therefore, they are vital for normal corneal surface epithelization. Patients with severe corneal surface disturbances do not have enough tears to support epithelization. Because of that, the use of autologous blood serum as an eye drop gives the cornea the necessary growth factors that are found both in tears and in blood serum (YAMADA et al., 2008).

The topical treatment with autologous serum has been beneficial or, at least, encouraging in humans (YAMADA et al., 2008). Serum eye drops are prepared through the sampling of blood from the patient (autologous source) or from donors (heterologous source), without anticoagulant agents and left to clot for several hours before centrifuging. Besides, the serum may or may not go through a filter for sterilization and bacterial clarification. There is not a consensus on the ideal formulation and dilution factor; however, no preservatives are added to serum eye drops, so the preparation proceeding must be carefully controlled so there is no bacterial contamination (DREW et al., 2018).

The use of platelet-rich plasma has also been reported as a successful treatment for moderate to severe KCS cases. Despite serum eye drops being superior to treatments with artificial tears, they have less growth factors than platelet-rich plasma; that is because platelets, which are used as growth factors' sources, are discarded during the serum obtaining process (TANDON et al., 2010). The effect of autologous platelet-rich plasma treatment in the regeneration of the cornea of dogs with KCS showed satisfactory results for the treatment, even though this is not a vastly diffused therapy within the veterinary field, despite the knowledge that platelets play a role in tecidual regeneration (VATNIKOV et al., 2020).

In a comparative study between topical tacrolimus 0,03% (1 drop, q 12 hours, on both eyes, for six months) and injectable homologous platelet-rich plasma group (injected in the third eyelid gland, the upper and lower palpebral conjunctiva of both eyes, with variable frequency depending on the improvement of clinical signs, for a maximum of three applications). Both protocols also prescribed a topical lubricant (1 drop, q 12 hours, on both eyes, for six months). The results showed that tacrolimus was more efficient in increasing tear production and the number of goblet cells. At the same time, the platelet- rich plasma was more efficient in decreasing the number of conjunctival inflammatory cells; therefore, it can be used as an adjuvant to conventional KCS treatment (ESTANHO et al., 2023).

5. Fatty acids

It has been demonstrated in humans that essential fatty acids dietary supplements such as omega-3 and omega-6 were efficacious in improving subjective symptoms such as palpebral margin hyperemia, TFBUT, and lacrimal secretion (MACSAI, 2008; HARGAVA et al., 2013; OLEÑIK et al., 2013). Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha-linolenic acid (ALA) are the three omega-3 fatty acids that must be dietarily supplemented since they are not synthesized by the mammalian body (BHARGAVA et al., 2013)

Omega-3 plays an important role in meibum's synthesis and are related to the production of PGE_3 and leukotriene B5, both possessing anti-inflammatory properties (RONCONE et al., 2010). Fatty acids also block gene expression of pro-inflammatory cytokines (GILBARD, 2004), as well as are useful in the formation of specific factors that bond to negative regulation receptors of macrophages and mastocytes, which are hyperactive during inflammation (AMALFITANO et al., 2019).

In humans, dietary supplementation of 2000 mg of omega-3, thrice a day, lead to improvements in human patients' overall Ocular Surface Disease Index (OSDI©) score, TFBUT, and meibum score. These patients were evaluated every three months, for a year (MACSAI, 2008). In another study, the usage of a capsule containing 500 mg of omega-3 fatty acids (325 mg of EPA and 175 mg of DHA), twice a day, was able to induce changes in the ocular surface, improving conjunctival cytology impression scores, TFBUT, and rose bengal score. However, no correlation was found between symptomatic improvement and Schirmer tear test scores (BHARGAVA et al., 2013). In a third study, oral supplementation of omega-3, 1500 mg per day, showed improvement in the mean OSDI©, TFBUT, meibomian gland expression and lid margin inflammation (OLEÑIK et al., 2013).

Long term supplementation with gamma-linolenic acid and polyunsaturated omega-3 fatty acids has shown promising effects in humans, with the improvement of dry eye syndrome symptoms and a significantly smoother corneal surface. Conjunctival inflammation suppression also results from a stable expression of HLA-DR (human leukocyte antigen complex), which must increase when exposed to inflammatory cytokines such as gamma-interferon. However, this increase may not occur when this supplementation is in place, but more studies are needed to elucidate this mechanism (SHEPPARD et al., 2013).

On the other hand, a large-scale prospective double-masked study, with 109 initial subjects, showed a different perspective. The treatment group received a total daily dose of 2000 mg of EPA and 1000 mg of DHA, for 12 months, while the placebo group received 5000 mg of olive oil. Despite the improvement observed in clinical signs, the results showed no significant difference between the treatment and placebo groups (HUSSAIN et al., 2020).

In dogs, topical applications of a fatty acid peri-ophthalmic cream (palmitic acid, oleic acid, stearic acid, linoleic acid) associated to an isotonic hialuronate eye drop lead to an improvement in Schirmer tear test results and ocular discomfort control (AMALFITANO et al., 2019). Moreover, good results were obtained from the association of fatty acids to other therapies, such as the association to tacrolimus 0,03% in the treatment of aqueous deficiency dry eye in dogs (SILVA et al., 2018).

In humans, a recent study has tested the efficacy of omega-3 fatty acids in eye drop form, aiming for supplementation directly in the tear film. The results showed, in 33 patients, over 8 weeks of treatment, clinically and statistically significant improvements in total corneal staining, TFBUT, meibomian gland dysfunction score, as well as in symptoms measured by OSDI©. However, no control group was used (JACOBI et al., 2022).

Nonetheless, balance must be reached, since results aren't as favorable when the proportion omega-3/omega-6 decreases. There is competition between conversions from linoleic acid (omega-6) into arachidonic acid (omega-6) and from ALA into EPA and DHA. This means that excessive consumption of linoleic acid leads to an excess of arachidonic acid in relation to EPA and DHA (RONCONE, et al., 2010).

6. Stem cells

Because dry eye syndrome is an autoimmune local disease, which involves both innate and adaptative immune responses in its development and progression, therapeutic methods that inhibit immune response are encouraged (BARABINO et al., 2012), such as the use of mesenchymal stem cells. The tecidual repair mechanisms these cells possess are attributed to their immunomodulant effects (LEE et al., 2015).

Mesenchymal stem cell biological activities are related to two action mechanisms. The first one is related to their auto-renewal capabilities, by differentiating into different cell types. The second is based on their ability to influence and stimulate actions of other cells, in other tissues, exerting a strong paracrinous activity due to the secretion of several bioactive molecules that have antiapoptotic, angiogenic, antifibrotic, anti-inflammatory, and immunomodulating properties, besides stimulating and recruiting stem cells from other tissues, allowing for an endogenous restorative effect (SGRIGNOLI et al., 2019).

In a study with mesenchymal stem cells in mice, a marked reduction in CD3+ and CD4+ cells infiltration was observed, and the intraorbitary gland structure was preserved, suppressing inflammation in experimentally induced dry eye, restoring lacrimal production and conjunctival goblet cells (LEE et al., 2015). Similar results were observed in dogs, with reduction of CD4+ T cells, interleukins and TNFα (SGRIGNOLI et al., 2019).

It has been reported that mesenchymal stem cell treatment is safe and efficacious, particularly for mild to moderate KCS in dogs, and does not require lifelong medical care, nor constant monitoring. The main advantage for this method would be that a single intervention would wield long term results (BITTENCOURT et al., 2016). In humans, a trial study reported that a single injection of transconjunctival allogenic adipose-derived mesenchymal stem cells showed significant improvement in patients with severe aqueous deficient dry eye disease. This suggests that the treatment would be a safe and feasible option (MØLLER-HANSEN et al., 2021).

A technique has been described for aseptic implantation of allogenic adipose-derived mesenchymal stem cells into the lacrimal gland and third eyelid gland of dogs. The patients were evaluated for 9 months, and the therapy was shown to be safe and effective, with prolonged clinical effects; this may be explained by the persistence of cell populations around periorbital tissues and lacrimal gland area for over 4 weeks, with no signs of regression of worsening throughout the follow-up period (VILLATORO et al., 2015).

The use of limbal derived mesenchymal stem cells applied via contact lenses in dogs was recently described, with results showing that this technique provided results comparable to the traditional treatment with topical cyclosporine A, artificial tears, and antibiotic eye drops. The main advantage of this technique was reported to be a single application, compared to eye drops thrice a day, for four weeks. This suggests that the use of stem cells produced on contact lenses is promising (OZGERMEN et al., 2021).

7. Surgical approaches

When KCS is refractory to drug treatments, surgical parotid duct transposition may be considered as an option to improve ocular surface lubrification and comfort (SPATOLA et al., 2018). This technique consists of transposing the salivary duct to the ventral conjunctival sac and this is based on the fact that both saliva and tears are ultrafiltrates of plasma (WILLIAMS, 2018).

However, their compositions are drastically different, particularly concerning the saliva's mineral contents, which are slightly higher than the tear's. Given that, some complications have been reported in the long term, such as corneal and conjunctival calcium deposition and continuous salivary epiphora that can lead to facial dermatitis (RHODES et al., 2012). Regarding the calcium crystals on the ocular surface, the topical application of EDTA to chelate excess calcium is an option (WILLIAMS, 2018).

Aiming to reduce the excessive humidity and salivary precipitates, which can cause inflammation and irritation after the procedure, a partial ligature of the parotid duct has been proposed. One or more ligatures may be placed proximally to the parotid gland, and the patient's anatomic conformation will dictate the number of ligatures that are needed. It has been reported that a minimum of two to three ligatures were needed for positive surgical results (SCHILKE and SAPIENZA, 2012).

Success rates vary from 63% to 80%, and surgical complications include duct trauma during the procedure, parotid duct failure, post-operative edema, and facial wound dehiscence (RHODES et al., 2012). Regardless of these results, it is important to emphasize this technique's relevance in refractory cases (WILLIAMS, 2018).

Alternatives have been studied, such as salivary gland transplantation as an alternative to lubricate the ocular surface. This was first reported in humans in 1951, and the technique for submucosal labial gland graft was described in 1998 (SOARES and FRANÇA, 2005). The saliva produced by labial glands have four times the concentration of IgA when compared to the parotid glands. This high IgA concentration is important to regulate microorganisms' levels in the oral cavity and are related to significant improvement of inflammatory and infectious processes (CASTANHO et al., 2013).

In dogs, however, there are conflicting literature reports regarding the presence or absence of minor salivary glands in labial and buccal mucosae. Older reports have described labial and buccal salivary glands of many different species, including dogs, and no glandular tissue is present in their upper lip, only on the lower lip, while the dorsal buccal glands are unified and form the zygomatic gland in carnivores (HARTIG, 1907; ELLENBERGER and BAUM, 1977).

A histological study that investigated the presence of salivary glands in different regions of the dog's oral cavity (upper and lower rostral labial mucosa at midline, upper and lower labial mucosa near the commissure, and buccal mucosa approximately 1 cm caudal to the commissure) did not find any salivary glands, nor sebaceous glands or goblet cells (CHERRY et al., 2018). This is most likely due to superficial sampling technique (GABNER et al., 2021).

Evidence of dogs' labial and buccal minor salivary glands presence, localization, arrangement and histology have been recently presented. Histology and microCT were used to demonstrate the presence of minor salivary glands in the lower lip of dogs, with larger glands located near the labial commissure. Positive correlation was found between the dog's size and number of glands, with larger dog breeds presenting a larger number of glands (GABNER et al., 2021).

It has been shown that the utilization of minor salivary glands may lead to significant improvement of clinical condition, with recovery of ocular shine, increase of Schirmer tear test scores, and decrease of ocular secretion. Nevertheless, crystalline deposit formation alongside palpebral margins and on the cornea, as well as post-prandial epiphora, have been reported to occur after the first 60 days post-operatively; therefore, long-term evaluation of animals submitted to this procedure is encouraged (ANGÉLICO et al., 2011).

Another technique for KCS cases unresponsive to usual treatments is the lacrimal puncta occlusion, which prevents lacrimal drainage. A temporary occlusion is recommended by some authors by using a plug, (DREW et al., 2018) but, for them to be effective, some lacrimal secretion is needed. These lacrimal plugs are well tolerated in both humans and dogs (ELIZABETH, 2021), and in human ophthalmology, for many years punctal plugs have been used as an auxiliary treatment for KCS. Some complications have been reported, such as distal migration of the plug, which required surgical removal (WILLIS et al., 1987).

Among the many options, silicone plugs are designed for long term occlusion, while collagen ones dissolve in up to two weeks. It is important to note that some plugs may offer only partial occlusion, and round or angular pointed plugs may be used to reduce local irritation (ELIZABETH, 2021).

The permanent occlusion through surgical obstruction is also viable (DREW et al., 2018). One of the techniques for permanent occlusal of the ventral puncta is with the usage of a thermal probe, but this technique has not been yet described in dogs (WILLIAMS, 2002).

Sustained release ocular implants have been developed for a constant delivery of a drug to the eyes, maintaining therapeutic levels, and are particularly useful for the treatment of chronic ocular conditions. These also make it easier to avoid effects of owner's noncompliance of the treatment (WEINER and GILGER, 2010). Episcleral implants deliver drugs such as cyclosporine to the cornea through sustained release below toxic levels, allowing for their use in higher concentrations than with topical therapy, without systemic side effects (KIM et al., 2005).

Good results have been reported from a study with cyclosporine A episcleral implant in dogs, such as the average concentration of the drug in the conjunctiva, the lacrimal gland and the cornea, as well as an improvement in STT scores and no recurrence of KCS' clinical signs, such as conjunctival hyperemia, corneal opacity or secretions. The required surgical procedure was well tolerated by the patients, even though two eyes out of 27 lost the device implanted during follow-up (BARACHETTI et al. 2015).

Conclusions

The causes for KCS' development are countless, and consequentially, so are the treatment options. Different tear film components' deficiencies ask for different treatments, which must be adequately chosen to replace the lacrimal component that has been lost. Each patient must be thoroughly evaluated and may benefit from different treatment regimens; however, given the continuous nature of the treatment, many challenges are found, since the patients are susceptible to relapses or may be refractory to different treatment strategies.

The search for new therapeutic options is constant in research; since dogs are considered excellent animal models for the comprehension of this condition, many human studies are based

on canine experimental models, jointly benefiting veterinary medicine. As such, many studies are conducted to understand the exact role of each therapeutic agent as a potential treatment for the dry eye syndrome.

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Table 1: Compilation of the main therapeutic options for the treatment of keratoconjunctivitis sicca in dogs.

	Active principle	Mechanism of action	Administration route	Notes
Lacrimomimetic	Sodium carboxymethyl cellulose	Allows for reduced water losses and promotes epithelial cell growth to provide osmoprotection.	Topical	In association with glycerol, may lead to increased comfort and diminish KCS' clinical signs.
	Hydroxypropyl guar	Once applied, it turns into a gel, helping to provide better lubrification and longer retention in the ocular surface.	Topical	Used in combination with polyethylene glycol 400, propylene glycol, and sorbitol and borate. Similar results to the use of carboxymethyl cellulose with glycerol.
	Synthetic polymer lubricants (carbomer, povidone)	Offer mucinemimetic properties.	Topical	Good retention time has been reported.
	Sodium hyaluronate	Promotes cellular migration, adhesion, and proliferation.	Topical	Glycosaminoglycan present in natural tears. Has a relatively long staying time on the ocular surface, demanding lower application frequencies.
Lacrimostimulant	Ciclosporin A	Immunomodulant (nuclear proteins binding, interrupting production of inflammatory cytokines, blocking calcineurin activity and interleukin 2 production).	Topical	Quantitatively increases tear film production.
	Tacrolimus	Local immunosuppression, goblet cell proliferation, lacrimal cell apoptosis suppression, and anti-inflammatory action.	Topical	In vivo, no differences regarding STT results for increase of lacrimal production when compared to ciclosporin A were found. In vitro, has been shown to penetrate skin better and to be more potent at inhibiting cytotoxic T-cells and producing IL-2, IL-3, and gamma IFN.
	Pimecrolimus	Selectively interferes in T-cell activation, inhibits the production of inflammatory cytokines through calcineurin inhibition.	Topical	1% formulation found to be highly efficacious in relieving KCS' clinical signs in dogs.
	Sirolimus	Inhibits the mTOR pathway, leading to a decrease of T and B cells function, negative regulation of associated cytokines and cell growth factors.	Topical	Usage is limited due to its physicochemical properties.
			Subconjunctival injection	Liposomes containing sirolimus (1 mg/ml) have been found to improve lacrimal production and tear film stability.
	Pilocarpine	Unspecific stimulation of the parasympathetic nervous system, including lacrimal glands.	Oral	Drug of election in cases of neurogenic keratoconjunctivitis.
			Topical	Must be diluted. May cause blepharospasm, conjunctival hyperemia, and miosis.
Blood products	Autologous or heterologous blood serum	Provides necessary growth factors that are found both in tears and in blood serum.	Topical	Similar composition to natural tears. Because no preservatives are added, preparation must be carefully controlled to avoid bacterial contamination.
	Platelet-rich plasma	Provides necessary growth factors that are found both in tears and in plasma.	Topical	Offers higher concentration of growth factors than blood serum.
			Injection in palpebral conjunctiva	Found to be effective in decreasing the number of conjunctival inflammatory cells and can be used an adjuvant in the treatment.
Fatty acids	Omega-3 (EPA, DHA, ALA)	Needed for meibum's synthesis. Related to the production of PGE3 and leukotriene B5, the blocking of gene expression of pro-inflammatory cytokines, and the formation of specific factors that bond to negative regulation receptors of macrophages and mastocytes.	Oral	Studies performed in humans and dogs show promise as an adjuvant to conventional treatment.
			Peri-ophthalmic cream	When used in association to isotonic hialuronate eye drop, lead to improvement in STT results and ocular discomfort control.
			Topical	Study performed in humans show promise as an adjuvant to conventional treatment.
Mesenchymal stem cells	Allogenic adipose derived	Capability of differentiating into different cell types, strong paracrinous activity through secretion of bioactive molecules.	Implantation into lacrimal gland and third eyelid gland	Found to be safe and efficacious, with prolonged clinical effects, particularly for mild to moderate KCS in dogs.
	Limbal derived		Application via contact lenses	Results in a study comparable to the traditional treatment, with a single application.