# TREATMENTS FOR LACRIMAL INSUFFICIENCY IN THE DRY EYE SYNDROME

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***Abstract:*** *Along with a better understanding of the dry eye pathophysiology, the treatment of this disease has passed from the simple administration of artificial tears with the role of hydration and lubrication of the eye surface, to true therapeutic strategies that result in increased natural production of tear constituents, integrity of the epithelium of the ocular surface, or inhibition of the synthesis of mediators of inflammation. New therapeutic approaches have allowed a significant improvement in the quality of life for many patients with dry eye syndrome. Therapeutic recommendations should take into account the etiology and the degree of severity of the disease.*

**1. Tear replacement approaches**. Eye lubricants replacement. The products are called "artificial tears", which try to replace and/or supplement the natural tear film. These products are not concerned with the basic pathophysiology of Dry Eye Disease (DED).(1)

1.1. *Tear substitutes.* Artificial tear substitutes target one or more layers of the tear film. The side effects are: blurred vision, "eye discomfort" and strange body sensation. Although artificial tears can be effective for treating DED, there has still been a need for research in the future to allow solid conclusions.(2)

1.1.1. *Aqueous supplementation.* Although the eye lubricant formulations may vary depending on osmolarity, viscosity and pH, most have the same major component: aqueous base.(3)

1.1.1.1. *Viscosity-increasing agents.* The viscosity enhancing agents used in the lacrimal supplement formulations include: Carboxymethyl cellulose (CMC), Hydroxypropyl methylcellulose (HPMC), Hyaluronic acid (HA), Combinations between CMC and HA, Hydroxypropyl guar (HP-guar) and HP-guarA containing propylene glycol and polyethylene glycol and a double combination of HA and HPguar polymers (Systane® ULTRA HYDRATION; Alcon, Ft Worth, TX, USA), Hydroxypropyl Cellulose (LACRISERT). Viscosity increasing agents are considered beneficial to the ocular surface of the DED through a number of mechanisms. These include increasing the thickness of the tear layer, protecting against desiccation, promoting lacrimal retention on the ocular surface, protecting the ocular surface, maintaining physiological corneal thickness, improving cell density and relieving dry eye symptoms. Very viscous eye drops are usually recommended for the night, and low viscosity droplets are used during the day.(2)

1.1.1.2. *Osmotic agents.* The original Tear Film Ocular Surface Dry Eye Workshop (TFOS DEWS) reports the importance of lacrimal osmolarity, demonstrating that tear osmolarity is associated with DED. The authors conclude that measuring changes in levels of inocytin and lacrimal osmolarity could objectively assess the anti-inflammatory effects of topical methylprednisolone applied in the treatment of patients with moderate to severe dry eye syndrome. Osmolarity has also been demonstrated when patients use topical cyclosporine, osmo-patch drops and PEG/HP-Guar drops.(3)

1.1.1.3. *Optoprotectors* (e.g., L-carnitine and betaine) are a group of compatible solvents that protect the cells from extreme osmotic stress by balancing the osmotic pressure without disrupting cellular metabolism. The osmoprotective effect depends on the amount of drug absorption and its retention time.(2)

1.1.1.4. *Antioxidants*. The presence of free radicals in the tears of patients with DED has led to the exploration of the potential application of antioxidants for the treatment of DED. One study has shown that many antioxidants can be useful if they are incorporated into topical eye lubricants. Quercetin, n-propyl galactate and gallic acid have good bioavailability and can be effective in protecting the corneal epithelium from oxidative damage. Visomitin is the first drug to have antioxidant properties. SelP tear is a key molecule that protects the eye surface against environmental oxidative stress.(2)

1.1.1.5. *Preservatives.* Multidose artificial lubricants typically require a preservative to prevent microbial growth, while unit-dose vials that are discarded after a single use, do not. Benzalkonium chloride (BAK) is the most commonly used preservative in ophthalmic drops. There is sufficient evidence to confirm that patients with DED requiring frequent dosing with lubricants or using ocular medicines in combination with other topical chronic therapies, such as glaucoma medicines, should avoid using BAK-preserved eye lubricants. New variants of preservatives designed to have a lower impact on the eye surface, including oxidizing preservatives (sodium chlorite, Purite® and OcuPure ™ and sodium perborate, GenAqua ™), polyquaternium-1®) and Sof-Zia™. "Preservatives that disappear" may have some negative effects on the eye surface. Therefore, preservative drops may be a better choice for patients with preexisting ocular conditions and/or frequent eye drops.(3)

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1.1.1.6. *Inactive agents:* swabs, excipients, electrolytes.

1.1.2. *Lipid supplementation.* The lipid layer of the lacrimal film has an important role in preventing tear evaporation. A variety of oils, such as mineral oils and phospholipids, have been incorporated into eye lubricating formulations to help restoring the lipid layer of the tear film. Drops containing lipids are formulated under the form of emulsions. Emulsions are defined as insoluble liquids that are finely dispersed in another liquid, such as oil and water. Emulsions can generally be classified into three types, based on droplet size. Macroemulsions contain droplets larger than 100 nm (nm), nanoemulsions are droplets of 10 to 100 nm and microemulsions have drops <10 nm. New approaches use cationic substrate oil in emulsion oil indicated for the treatment of DED. The cationic excipient is acetalconium chloride, a BAK alkyl derivative that is lipophilic. Some studies have shown that Cationorm is well tolerated by human corneal epithelial cells in culture. However, another in vitro study has shown epithelial losses and alteration of the superficial corneal layer in corneas treated with Cationorm.(3)

1.2. *Biological tear substituents*

1.2.1. *Autologous serum*. Other treatments that have been successfully used in the treatment of severe dry eye are dilute solutions of hyaluronic acid and autologous serum drops (which require a special formula). The composition of the diluted autologous serum is somewhat similar to that of normal tears, especially regarding the growth factors; several benefits are due to the tropical function of these substances. Serum is the fluid component of the blood that remains after clotting. The advantage of the autologous serum is that many of its biochemical features, including pH, nutrient content, vitamins, fibronectin, growth factors such as epithelial growth factor (EGF) or nerve growth factor (NGF), are similar to those of the people. Autologous serum contains specific epitheliotrophic factors, such as EGF, NGF, in addition to a high protein concentration such as albumin and fibronectin. Autologous serum directly supports the proliferation and migration of epithelial cells or indirectly enhances epithelial viability by binding and neutralizing inflammatory cytokines. The majority of clinical trials and the series of autologous serum studies indicate that it may be effective in the treatment of eye pain sufferance secondary to DED, probably due to its anti-inflammatory, epithelial and neurotrophic functions, significantly improving the signs and symptoms over time. While treatment is intense, it has few complications, but eye pain may occur after discontinuation.(3)

1.2.2. *Allogeneic serum*. Allogeneic serum may be an alternative when patients have active systemic inflammation or in infants, elderly and those with chronic anemia. Because it can be prepared from previously stored blood, it is potentially more convenient.

1.2.3. *Umbilical cord serum* has similar benefits to allogeneic serum because it can be prepared in large quantities (up to 250 ml) from a single donor and can be used for many patients. Moreover, it is useful in patients with systemic inflammation, anemia or chronic diseases who cannot be ideal candidates for autologous serum drops. Umbilical cord serum is taken from the umbilical cord veins after delivery. After centrifugation, the serum is diluted to a concentration of 20% and administered 4 times a day. Umbilical cord serum has a higher concentration of tear components such as EGF, NGF and transforming growth factor (TGF) - compared to the peripheral blood serum. Symptoms scores, TBUT tests, corneal fluorescence and cytology have shown to improve significantly after application of eye drops in patients with DED resistant to conventional treatment.(2)

1.3. *Other agents*

1.3.1. *Mucolytics* are a group of substances that decompose mucin and which include ambroxol (Mucosolvan® Boehringer Ingelheim, Ingelheim am Rhein, Germany). A small clinical trial in subjects with Sjogren's syndrome has shown that oral ambroxol has improved symptoms. Acetylcysteine, which also has antioxidant properties, has been reported to have a better effect in reducing the subjective symptoms of DED than artificial tears. Acetylcysteine 10% packed in a dropping bottle can be used as a mucolytic agent and is useful in relieving these symptoms.(4)

1.3.2. *TRPV1 Receptor Antagonist.* Topical administration of SYL1001, a short-term RNA targeting TRPV1 (at a dose of 1,125% once a day), produced a significant decrease in the symptom score in patients with DED. Selective inhibition of the production of the TRPV1 receptor may reduce the symptoms of the dry eye and provide a new therapeutic opportunity for relieving the dry eye effect.(5)

**2. Tear preservation approach**.

2.1. **The punctal occlusion.** The concept of temporary or permanent occlusion of one or both points is to retain the tears on the ocular surface by blocking their drainage.

*Indications and contraindications:* Sjogren's syndrome, autoimmune diseases, dry eyes associated with a rapid TBUT, systemic drugs that produce film production reduction, upper limb keratoconjunctivitis, any corneal irregularities or scarring that affect tear stability, toxic epitheliopathy, Use of punctal occlusion in the presence of ocular inflammation of the surface is controversial.

*Plug occlusion*. The plug may be located at the level of the punctal opening or deeper opening in the canal.(3)

There are a variety of models: Freeman; Herrick plug is an intracanalicular-silicone connector; Cylindrical SmartPlug ™ is an intracanalicular closure made from anthermolable polymer that changes size and shape when inserted; FORM FIT® (Oasis Medical, Glendora, CA, USA) is made from an injectable hydrogel that hydrates in situ for 10 minutes and extends to conform to the shape of the canal. In addition to devices, certain types of cyanoacrylate adhesives can be used for temporary punctal occlusion. For permanent occlusion, there are a variety of surgical options.(3) Regarding complications, the most common complication of punctal occlusion is spontaneous exclusion of the plug, infection, canal migration of the swab, piogenic granuloma, tumors.

*Surgical punctal occlusion.* Continuous surgical closure of the point is usually reserved for patients who cannot hold or tolerate punctual stoppers. A wide range of surgical methods include total or partial thermal cauterization, punctal occlusion with a conjunctive or graft clamp, screw suturing, canal elimination and canalicular ligation. Thermal methods include cauterization, diathermy and the use of an argon laser and these can be accomplished deeply into its canal or superficially in the outer part of the point. Epiphora is a potential problem if both the upper and the lower points are permanently closed. To avoid this, incomplete occlusion of the point can be accomplished with thermal cauterisation. Occlusion can be most successful when combined with other DED treatments. The data suggest that silicone plugs can provide a symptomatic relief of the severe dry eye and that temporary collagen stoppers seem similar to short-term silicone plugs.(2)

2.2. *Moisture chamber glasses*. Glasses are specially designed to slow tear evaporation by providing a damp environment and minimizing airflow

**3. Tear stimulation approaches.** Topical pharmacological technologies that stimulate aqueous, mucin,

and/or lipid secretion are commercially available in certain markets or emerging markets. Pharmacological stimulation of tear secretion has been attempted with many components, with varying degrees of success. Cholinergic agonists - pilocarpine and cevimeline stimulate muscarinic receptors present in the salivary and lacrimal glands, increasing secretion. Although studies have shown that both are effective in treating both xerostomia and dry eye in patients with Sjögren's syndrome, they are only approved for the treatment of xerostomia. It is uncertain if these agents have long-term benefits.(6)

3.1. *Secretory substances*

a. *Aqueous secretion agents.* Diquafosol tetrasodium (Diquas®; Santen, Osaka, Japan) is approved as a 3% ophthalmic solution in Japan and South Korea for the treatment of dry cancers. It is a purinergic agonist of the P2Y2 receptor that stimulates mucin secretion in conjunctive epithelial cells, resulting in improved lacrimal film stability in dry eyes. Diquafosol has potential utility in various specific dry eye disorders, including Sjögren's syndrome, tear break-up time (TBUT) dry eye lacrimal rupture), Meibomian gland dysfunction (MGD), dry eye after LASIK and cataract surgery as well as contact lens carriers. Diquafosol is effective in promoting the healing of corneal epithelial wounds.(2)

b. *Sucretagog mucin.* There are a number of medications specifically targeting the deficiency of mucin in DED, including diquafosoltetrasodium. The ribavipid ophthalmic suspension (Mucosta®, Otsuka Pharmaceutical, Chiyoda, Japan) is currently approved in Japan for the treatment of dry eye. It is a mucin secretagogue that promotes the production of mucin-like glycoproteins in human corneal epithelial cells.(4)

3.2. *Lipid stimulation.* The growth factor similar to insulin 1 (IGF-1) has lipid stimulation effects on meibomial gland cells in vitro. Androgens have been found to regulate the genes involved in lipid metabolic pathways and to regulate those linked to keratinization, in epithelial cells in human meibomal glands in a series of laboratory studies. Results of clinical trials show that treatment of patients with MGD with local testosterone improves the quality of the secretions of the meibomian gland. Additional clinical trials on the treatment with MGD with topical testosterone are currently ongoing in Europe.(3)

3.3. *Distribution of oral secretion.* Two cholinergic agonists administered orally, pilocarpine and cevimeline are commercially available for the treatment of DED. People with Sjogren's syndrome have autoantibodies that bind to muscarinic acetylcholine receptors in exocrine glands and pilocarpine and cevimelina are aspartyl muscarinic receptor agonists (parasympatomimetics) to overcome this effect. People with Sjogren's syndrome treated with oral pilocarpine for 12 weeks had a beneficial effect on the symptoms, but an increase in tear production was not reported. Other studies have shown an improvement in symptoms, corneal staining of fluorescein, bengal staining, cell density and TBUT, but again, no improvement in lacrimal production has been demonstrated by Schirmer testing. However, oral pilocarpine was able to increase the height of the lacrimal meniscus (TMH) in patients with Sjogren's syndrome.(2)

3.4. *Neuromodulation* is a therapeutic strategy that involves the direct interface with the nervous system through electrical, electromagnetic, chemical methodologies. The goal is long-term activation, inhibition, modification and/or adjustment of neural entry to correct tissue dysfunction and management of disease symptoms. An intranasal lacrimal neurostimulator has been developed to induce normal tear production by stimulating the nasolacrimal reflex.(2)

3.5. *Different methods of lacrimal stimulation.* A variety of other new methods has been reported to stimulate tear production. These include abdominal breathing for 3 minutes, which has accentuated the increase in the volume of the lacrimal meniscus in healthy women. The stimulation of corneal thermoreceptors could increase the production of tears. Finally, caffeine, probably the most consumed psychoactive substance, seems to stimulate the secretion of tears in healthy subjects.(7)

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