

Drops To Biologics: Where It All Fits
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Course Abstract:

Addressing meibomian gland dysfunction and blepharitis in general is the key to suppressing the inflammatory nature of dry eye disease (DED). However, artificial tears (AT) still play a pivotal role in the management of the condition. The amount of eye drops available can make selection overwhelming for a doctor (let alone a patient). This lecture will help optometrists choose appropriate artificial drops based on the key properties. We will also simplify when it makes sense to turn to biological drops in the management of DED.

Learning Objectives:

1. Explore key properties in artificial tears that makes them appropriate for dry eye treatment
2. Indications and clinical pearls on how and when to use blood biologics to manage DED

COURSE OUTLINE

This Just Dropped - Eltis

Artificial Tears (AT) - Overwhelming Choice

- Addressing MGD and blepharitis in general is the key to suppressing the inflammatory nature of dry eye disease (DED).
- ATs play a pivotal role in managing DED.
- AT are particularly effective at providing symptomatic relief to patients especially during flare ups.
- Advise DED patients to use tears regularly “like a lip balm” and not wait until their ocular surface is compromised and symptomatic.
- AT can reduce inflammation and help prevent epithelial cell death.
- When chosen carefully, drops can play a significant role in the management of dryness.
- The amount of eye drops available can make selection overwhelming for a doctor (let alone a patient).
- Let's explore some favorites and clarify when they are most appropriate.

Preservatives - The Necessary Evil

- Important in preventing bacterial contamination in a multidose bottle
- However, they are counterproductive to treating the condition.
- This is because an irritant is being introduced to an already compromised tear film and ocular surface.
- Preservative free formulations are always superior but should be highly recommended for those using drops more than 4 times a day.
- BAK and thimerosal formulations should be avoided at all costs.

- Studies show corneal toxicity and nerve damage at the 7 day mark with BAK use

Selecting An AT Drop:

- Tear osmolarity can be used as a guideline for selecting AT viscosity.
- Moderate to severe DED often necessitates a thicker drop.
- As viscosity increases the duration of effect of the drop increases—but so does the potential for blurred vision.

Systane Ultra Hydration (Alcon)

- A relatively inexpensive and effective option for mild to moderate DED.
- It's a moderately viscous drop with the coating power of hyaluronate.
- HP-Guar interacts with the blinking motion prolonging the contact time
- HP-guar molecules bind preferentially to dried or compromised hydrophobic areas of the cornea, containing further damage while epithelial cells regenerate.
- It forms a gel layer (acting as a mucomimetic), compensating for a compromised tear layer and reducing friction during blinks.

Hylo Dual Intense (Candorvision):

- Multi-dose preservative-free option for more advanced dry eye.
- It combines ectoine (a natural anti-allergy and anti-inflammatory agent) with a higher viscosity level (produced by a high concentration of heavier molecular weight sodium hyaluronate) that does not blur vision.
- Ectoine is effective in patients suffering from DED and allergic conjunctivitis and accelerate wound healing post-op.

Thealoz Duo Gel (Labtacian-Thea)

- Trehalose is an osmoprotectant designed to guard dried epithelial cells and stabilize their membranes.
- Single use gel, great for night time protection
- Trehalose protects against the destructive inflammatory cascade of DED.
- Sodium hyaluronate (as a glycosaminoglycan) enhances viscosity.
- Carbomer (a water-soluble polymeric resin) increases viscosity and maintains the hyaluronic acid and trehalose together in contact with the ocular surface for six hours without being sticky.

Calmo spray (CandorVision)

- A unique product for MGD and preservative free.
- It is used with the eyes closed which allows it to seep into the eye slowly replicating meibomian gland secretions.
- Excellent option for people who hate putting drops into their eyes.
- Contains liposomes to replicate the oil deficient layer in MGD sufferers (to prevent tear evaporation) and dexpanthenol (pro-vitamin B5), which moisturizes the eye and surrounding skin.

Optase Hylo Night (Scope):

- A nighttime ointment using vitamin A to speed up epithelial healing.
- It is preservative free and good for mild to moderate dry eye.
- It is also phosphate free and good for 6 months once opened.

Refresh Lacrilube ointment (Allergan)

- The go-to for very thick overnight coverage.
- Uses mineral oil as an ointment base that allows melting at body temperature and white petroleum which serves as a lubricant.
- Patients need to be warned that the ointment will blur them out for a sustained duration. Ideally, they should already be sitting in bed when inserting it for safety.

The Liposec (Bausch and Lomb):

- Has been a reasonably priced option for decades.
- While patients with MGD don't always respond best to oil replenishment drops, this particular product has endured in both drop and ointment form (for nighttime use).
- The drops contain carbomer, sorbitol, medium chain triglycerides (Myritol 318) and cetrimide as a preservative.
- Liposec gel has sodium hydroxide, which closely mirrors the PH of tears at 7.4, and attempts to replicate all three tear layers.

Refresh Optive Mega 3 (Allergan):

- A single dose preservative-free drop.
- Contains omega 3 from flaxseed oil.
- Studies show that eye drops using emollients can increase the lipid layer thickness (LLT) of the tear film for a short duration.
- Omega-3 fatty acids are actually found in the normal tear film. Refresh Optive Mega 3 is formulated to minimize blur and does not require shaking.
- It is designed to replenish all three tear layers and is targeted towards MGD patients (like Systane complete and Retane). Its lubricants include glycerin 1%, carboxymethylcellulose sodium 0.5% and polysorbate 80 (0.5%).
- These drops may be most helpful for patients with prolonged screen time (a lifestyle that decreases blinking and meibum secretion).⁸

Summary:

There are many other excellent products on the market for DED. There is no magic formula or perfect drop for every patient. A careful case history and an understanding (by both doctor and patient) that there will be some trial and error in finding the right combination of products is key.

Blood Biologics To The Rescue - Madan

Case Example 1: 64 YOF, Sjogren's Syndrome DED

- Referred for dry eye evaluation.

- Dry eye symptoms range in severity of pain. Patient is emotionally exhausted, using eye drops constantly
- Presenting treatment: Hylo gel Q2h, Xiidra BID, Omega 3, hot compresses, moisture goggles.

What is Autologous Serum (AS) and Platelet Rich Plasma (PRP)? And Why does it Make Sense?

- PRP is blood product having a large concentration of platelets suspended in plasma
- Why platelets? Platelets are the powerhouse for healing. They carry growth factors that play a key role in tissue repair.
- Why Plasma? Plasma makes up 55% of blood. Carries over 600 active molecules that support cellular healing
- PRP contains a similar composition of vitamins, growth factors and electrolytes to natural tears. These factors play a key role in wound healing as they support proliferation and migration of epithelial cells
- Which is something no eye drop on the market has been able to accomplish

Evidence for use of in DED:

- A study by Alio et al. found that PRP promoted healing of dormant corneal ulcers and was accompanied by reduction in pain and inflammation.
- Hartwig et al. reported a superior effect on cell growth in platelet rich plasma than in serum owing to its high content of growth factors and concluded platelet rich plasma could be a novel treatment option for ocular surface defects.
- Fea AM et al. looked at confocal microscopy of corneal nerves and found evidence that PRP significantly increases corneal subbasal nerve plexus density, suggesting a possible pathway to managing

Benefits of blood biologics

- Tissue repair
- Anti-inflammatory
- Repair osmolarity
- Natural analgesic action
- Resemble biological tears

Autologous Serum (AS) vs Platelet Rich Plasma (PRP)

- Different preparation for both
- AS is growth factor poor as platelets are eliminated in the process of making it.
- AS contains TGF-Beta and is often diluted with saline before dispensing.
- PRP does not have inflammatory cytokines that are present in AS
- PRP protects the ocular surface from scar formation more than AS
- PRP is superior to AS as PRP contains higher concentration of all the essential agents compared to AS.

- Furthermore, there are many inconsistencies in the ASED's methods of preparation, dilution and storage as well as uncertainty regarding their optimal concentration

Who can benefit from blood biologics?

- Mild/moderate/severe dry eyes
- Aqueous/evaporative or autoimmune dry eye
- LASIK induced dry eye
- Neuropathic dry eyes
- Non healing corneal surface or corneal ulcers
- Patients who have tried everything
- Patients who want natural options

Amniotic Fluid

- If drawing the patient's blood is not an option,
- consider utilizing biological eye drops derived from donor human amniotic fluid or placenta.
- Lubricants that are from natural sources.
- A study by Liang L. et al found that topical application of amniotic membrane extract eye drops reduced pain and inflammation and promoted reepithelialization in ocular chemical burns.
- Options include StimulEyes (M2 Biologics) and Regener-Eyes (Regener-Eyes)
- Cytokines, chemokines and growth factors aid in the healing of the ocular surface.

Grow The Nerves:

- When neurotrophic keratitis (NK) is suspected, cenegermin eye drops may also be used.
- Cenegermin is a recombinant nerve growth factor (rhNGF), produced in Escherichia Coli, can promote corneal healing in a neurotrophic cornea. Approved 2018
- Oxervate (cenegermin-bkbj ophthalmic solution 0.002%, Dompé) is a sterile, preservative free eye drop. It is available in 7 multi-dose vials (1.0ml) intended to be used 6 times a day for eight weeks. (See Figure 4).
- With persistent corneal staining or non healing epithelial defects are present and corneal sensitivity is reduced, neurotrophic keratitis should be suspected.
- In the current clinical studies, significant improvement in corneal healing was noted in the cenegermin treatment group vs the placebo group (Bonini, Oxervate).
- Most common side effects include hyperemia and eye pain.
- Patients can relapse when drops are discontinued

Just like with artificial tears, biologics and advanced alternatives are not a "silver bullet". Every patient is best served through an individualized treatment plan that matches their experience in the DED spectrum. As eye care providers we must be well informed on all options available to make that proper connection between a patient condition and appropriate care.