

Tear Substitutions and Science

Recent advancements in the realm of tear substitutes.

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The annual conference of the Association for Research in Vision and Ophthalmology (ARVO) inevitably unveils exciting innovations in the ongoing evolution of tear substitutes, and this year's meeting yielded even more varied research on the topic than usual. From the introduction of novel artificial tear formulations to the success of new implementations of existent products, ARVO provided ample evidence that dry eye management is becoming ever more science-driven and efficacious.

Results of studies for several drops in development were presented, generating interest in further testing of these formulations. Cationorm (Novagali), a cationic oil-in-water emulsion, was tested at two different concentrations in moderate dry eye patients and appeared safe and tolerable to patients while improving such clinical signs as Schirmer scores, tear film break-up time (TFBUT) and lissamine green staining relative to baseline.¹ In a basic science study, Cationorm achieved positive results with regard to surface wettability in rabbit cornea and conjunctiva, and showed an ability to spread quickly and fully in the tear film.²

Another experimental formulation undergoing animal testing—Clarity (Alimera)—focused on controlling tear film dehydration. This lubricant eye drop exhibited superior deturgescence (ocular hydration control) compared to Refresh Tears (Allergan) in damaged rabbit cornea.³

I-Drop (Bioscia) is a visco-adaptive wetting solution that was tested in a small group of post-LASIK patients (n=20), and was generally preferred by patients due to less blurring and greater comfort relative to comparable

marketed artificial tears.⁴ While inconclusive due to the small sample size, the data suggests that further investigation into this formulation is warranted.

The most developed of the investigational dry eye products at ARVO this year was diquafosol tetrasodium 2%. A six-week study measured tear film thickness and found that diquafosol-treated subjects had thicker tear film measurements between blinks and overall at six weeks.⁵

While many of the experimental tear substitutes discussed at ARVO seem promising, researchers are also continuing to investigate products already on the market. For example, GenTeal (Novartis) and Tears Naturale Single-Dose Units (Alcon) were compared for safety and efficacy in 37 dry eye patients. Over the course of the four-week study, the number of GenTeal-treated subjects with clinical signs indicative of dry eye was significantly reduced compared to the Tears Naturale group. Patient tolerability and convenience of use were comparable for the two treatments, and the lack of adverse events suggests that the GenTeal preservative GenAqua is non-irritating.⁶

A study of the more viscous GenTeal Gel, which contains a carbopol-type gel, was also presented this year. The outcomes suggest that tear substitutes may have important alternate uses: in 10 cases of small-gauge cataract surgery, GenTeal Gel effectively served as a long-lasting wetting agent capable of maintaining corneal clarity.⁷

A recent trial compared Refresh Tears and Systane (Alcon) for comfort and tolerability in a population of early-stage dry eye patients (n=55). Refresh contains the viscosity agent

carboxymethylcellulose (CMC) while Systane uses the gelling agent HP-Guar to deliver the demulcents polyethylene glycol (PEG) and propylene glycol (PG). For this study, patients instilled Refresh in one eye and Systane in the other and rated each drop on blurring, stickiness and soothing, immediately and at a one-week follow-up visit. Subjects reported less blurring and stickiness with the CMC-based drop, and 53 percent of patients indicated a preference for the CMC drop at the follow-up visit.⁸ While these results are interesting, previous studies comparing Systane and Refresh Tears have demonstrated a reduction in clinical signs of dry eye (staining and TF-BUT) in favor of Systane.^{9,10}

Refresh Tears were also tested against Restasis (cyclosporine, Allergan), the only prescription product currently indicated for dry eye. This study looked at treatment effects on goblet cell density—goblet cells are responsible for ocular mucin production and are therefore vital to the maintenance of a healthy tear film. As CMC is intended to improve the mucin component of the tear film, this seemed a logical parameter. A small group of six severe dry eye sufferers was treated for four weeks with Refresh Tears and for 12 weeks with Restasis. Restasis treatment resulted in significant increases in goblet cell density compared to both baseline and Refresh treatment after six weeks, though not at 12 weeks (despite higher values, the data was not

significant). Refresh Tears treatment did not result in any notable changes in goblet cell density.¹¹

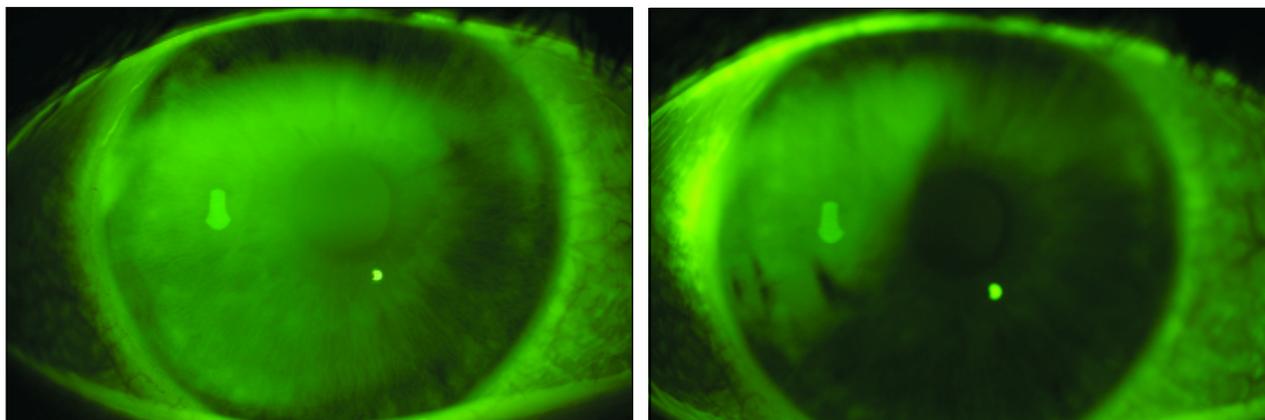
The corticosteroid loteprednol etabonate (Lotemax, Bausch & Lomb) and the oil-in-water metastable solution Soothe (Alimera) were tested for their immediate and long-term effects on lid-wiper epitheliopathy (LWE)—upper lid margin staining thought to be indicative of dry eye symptomatology. Lotemax, as a steroid, has primarily anti-inflammatory effects, while Soothe is intended to stabilize the tear film by enhancing the lipid layer and increasing ocular surface lubricity. Both treatments effectively reduced LWE findings during the five-to-10-week treatment phase of the study, and these improvements were still present throughout the one-year maintenance phase. Traditional corneal and conjunctival staining values were also recorded, and both Soothe and Lotemax reduced these overall scores by 35 percent during the treatment phase, improvements that did not revert in the course of the following year.¹²

Systane Free (Alcon), a recent introduction to the market, was the subject of several posters at ARVO. Systane Free is a liquid gel formulation that is unpreserved in the eye—instead of traditional preservatives, the drop incorporates an ionic buffer system comprising substances such as borate, sorbitol, aminomethyl propanol and zinc. These components keep the tear substitute

preserved in the bottle, but the molecules are deactivated by ions in the human tear film upon instillation. Systane Free was compared to GenTeal, which contains the preservative sodium perborate; Refresh Tears, which contains the synthetic oxychloro complex preservative; and Soothe, which is preserved with polyhexamethylene biguanide. All of the formulations were assessed for their ability to reduce three common bacterial varieties and two types of fungus (to determine adherence to USP efficacy standards). Demonstrating a four-to-five-log reduction of all bacteria and a three-to-four-log reduction of both fungi by the end of the four-week study, Systane Free's ionic buffer system met USP preservative efficacy standards as well as the more traditional preservatives used in the other marketed drops.¹³

At this year's ARVO, results of a study were presented that compared Systane Free to Refresh Tears and Refresh Plus (Allergan) in order to assess efficacy in reducing symptoms and signs of dry eye in a population of 135 dry eye subjects. While all three products reduced dry eye symptoms, Systane Free patients showed a mean improvement in corneal staining that was statistically significant relative to Refresh Tears and exhibited a statistical trend relative to Refresh Plus.¹⁴

Another study compared Refresh Liquigel (Allergan) and Systane Free to determine any differences in blurring tendencies and patient comfort and ac-



One of the primary goals of any new tear substitute or therapy for dry eye is extension of tear film break-up time. Note here the tear film prior to and during break-up. The black spots in the second image are micelles, or dry areas.

ceptability. Subjects deemed Systane Free caused less blurring than Refresh Liquigel. There was no significant difference in drop comfort between the two tear substitutes.¹⁴

One study measured tear film thickness and meniscus properties using OCT to examine the effects of Refresh Liquigel, Refresh Tears and Systane on the tear film. The result was a determination that tear viscosity heavily influenced tear film thickness and the properties of the lower tear meniscus (Liquigel is the most viscous, followed by Systane), whereas Systane had the most distinct influence on the properties of the upper tear meniscus.¹⁵

An *in vitro* study showed the usefulness of using fluorescein to stain the concentrated active component from an artificial tear and thereby assess epithelial wound healing. The research looked specifically at CMC and demonstrated that it bound to corneal cells with a primary residence time of 1 to 2.5 hours, and that it appeared to stimulate wound closure. The wound-healing testing procedure could be especially applicable to a tear substitute's efficacy in post-LASIK patients.¹⁶ While wound healing was confirmed as a reasonable post-LASIK efficacy parameter, other researchers tried to determine if aqueous tear evaporation could be influenced by tear substitute use. Five products were tested for their ability to modulate the evaporative rate of the tear film: two lipid emulsions, a demulcent tear, an *in situ* gelling formulation and a lipid preparation applied externally. Interestingly, at the 15-minute time point, not one of the formulations exhibited a significant influence on the aqueous tear evaporation rate. However, some of the drops did exhibit statistical trends, either in decreasing or in increasing the evaporative rate, suggesting that this merits further study—ideally including observations at more extended time points.¹⁷

In addition to the introduction of novel parameters and new methods of measuring and interpreting existent pa-

rameters, newly conceived formulations and newly discovered substances are being studied in the hopes that they might be able to satisfy the ever-changing parameters and prove useful to dry eye sufferers. The lacrimal gland, it was recently found, produces an extra-cellular glycoprotein called lacritin that is present in the tear film. Lacritin was hypothesized to be important for ocular surface maintenance, and this theory received an initial confirmation with the results of an animal study in which lacritin-treated rabbits experienced statistically significant increases in tear flow (as measured by Schirmer strips) over a four-week period.¹⁸ Although rabbits likely have lower natural lacritin production than humans, the results of this trial still suggest that the substance has potential as a dry eye therapy and should be tested further.¹⁹

A preservative-free suspension of phosphatidylcholine derivatives and cholesterol in trehalose solution that is currently in the basic science phases of testing represents a potential tear substitute with a more traditional mechanism of action. Trehalose is a dehydration-resistant carbohydrate, and in combination with the lipid-layer-enhancing suspended components, it is hoped it can help effect a drop that increases tear film retention time and promotes ocular epithelial health.²⁰

Another experimental drop looking to achieve similar endpoints and display therapeutic benefit in doing so is Moli1901. This Type B lantibiotic is thought to stimulate water and chloride secretion in the ocular epithelium, effectually hydrating the eye. Moli1901 significantly increased tear production in rabbits at relatively high concentrations, and was found to be safe and tolerable in humans over the course of a four-week study at concentrations up to 0.1%, although 80 percent of subjects experienced non-serious treatment-related adverse events.^{21,22}

Another study looked at the wound-healing capabilities in patients recovering from photorefractive keratectomy

(PRK) of Xan-hyal, a non-preserved ophthalmic gel containing xanthan gum, a gelling agent and sodium hyaluronate—a naturally occurring lubricant. Xan-hyal was not only well-tolerated, but showed exceptional efficacy in promoting corneal wound healing in the post-PRK patients, with a median healing time of three days.²³ While not yet tested for dry eye, the wound-healing ability and composition of Xan-hyal suggest it has potential as an investigational dry eye treatment.

Once again, ARVO provides a bevy of studies with information to help practitioners better treat dry eye as well as learn more about innovative tear substitute and dry eye therapy research. Recent research has served to refine our understanding of currently marketed drops, determine the strengths of newly marketed ones, develop new tests and parameters for helping us compare and comprehend tear substitutes and introduce promising new potential therapies in the early stages of development. All of this research, highlighted by new science-driven treatment formulations, makes the future for dry eye sufferers look considerably less bleak.

REFERENCES

1. Binlich F, Baudouin C, Pisella PJ, Garcher C, Nicolas-Oprea L. A Novel Cationic Emulsion, Cationorm, for Treatment of Patients With Bilateral Moderate Dry Eye Syndrome. ARVO 2006; 254/B432.
2. Abdulrazik M, Rabinovich-Guillat L, Lambert G, Benita S. Study of Formulation Parameters Effect on Interafacial Interactions of Topically Instilled Eye Drops With the Ocular Surface by Dynamic and Static Methods: Implication for Tear Substitutes Wettability. ARVO 2006; 5089/B487.
3. McCarey BE, Kane FE, Green KE. *In vivo* Corneal Deturgescence With a New Lubricant Eye Drop. ARVO 2006; 2992/B92.
4. Hofmann I, Gould HL. Postoperative Management of Dry Eye Conditions Following LASIK: A Subjective Pilot Study Comparing Viscous Eye Drops (Systane) and Viscoadaptive Eye Drops (I-Drop). ARVO 2006; 272/B450.
5. Nichols KK, Nichols JJ, King-Smith PE, Kelleman DJ. Tear Film Thickness and Thinning Rate Following a Six-Week Trial of 2% Diquafosol Tetrasodium vs. Placebo in Dry Eye Patients. ARVO 2006; 271/B449.
6. Ciiment AO. Comparison of GenAqua-Preserved Genteal in Multidose Bottles vs Preservative-Free Tears Naturale® in Single Dose Units in Patients With Moderate to Severe Dry Eye. ARVO 2006; 261/B439.
7. Pruzon J, Guo S, Frieman B. An Excellent Alternative Corneal Wetting Agent For Cataract Surgery - GenTeal Gel. ARVO 2006; 722/B643.

8. Hom MM, Liu N, Kame G. Comparison of the Comfort and Tolerability of 0.5% Carboxymethylcellulose (Refresh Tears) and Propylene Glycol/Polyethylene Glycol 400 (Systane). ARVO 2006; 233/B411.
9. Christensen MT, Stein JM, Stone RP, Meadows DL. Evaluation of the Effect on Tear-Film Break-up Time Extension by Artificial Tears in Dry Eye Patients. Poster Presentation at Schepens Cornea Conference, 2003; Boston, MA.
10. Christensen MT, Cohen S, Rinehart J, et al. Clinical Evaluation of an HP-Guar Gellable Lubricant Eye Drop for the Relief of Dryness of the Eye. Current Eye Research 2004; 28:1: 55-62.
11. Pflugfelder SC, De Paiva CS, Villarreal A, Stern ME. Effects of Sequential Artificial Tear and Cyclosporin Emulsion Therapy on Conjunctival Goblet Cell Density. ARVO 2006; 243/B421.
12. Herman JP, Kleiner-Goudey S, Korb DR. Long Term Treatment of Lid Wiper Epitheliopathy With an Oil-In-Water Emulsion Lubricant Eye Drop. ARVO 2006; 275/B453.
13. Rosenthal RA, Schlech BA, Buck SL. Preservative Efficacy Of A New Lubricant Eye Drop Without Traditional Preservatives. ARVO 2006; 5586/B356.
14. Christensen MT, Meadows DL, Tudor MR, Stone RP. A Report From Clinical Evaluations of a New Liquid Gel Concept Artificial Tear. ARVO 2006; 274/B452.
15. Wang J, Aquavella J, Simmons P, Vehige J, Palakuru J, Chung S. Dynamic Distribution Of Artificial Tears Measured With Optical Coherence Tomography. ARVO 2006; 264/B442.
16. Simmons PA, Garrett Q, Xu S, Zhao Z, Vehige J, Willcox M. Interaction of Carboxymethylcellulose With Human Corneal Cells. ARVO 2006; 2759/B154
17. Aronowicz JD, Uchiyama E, Butovich IA, McCulley JP. Effect of Commercial Artificial Tears on Aqueous Tear Evaporation. ARVO (2006); 247/B425.
18. Spitze AR, Sheppard Jr., JD, Williams PB, Pelosky K, Laurie GW, McKown RL, Lattanzio Jr., FA. Extended Treatment With Lacritin, a Novel Tear Glycoprotein, Stimulates Tear Production in Rabbits. ARVO 2006; 5581/B351.
19. Nakajima T, Walkup RD, Shearer TR, Azuma M. Characterization of Lacritin in Human Tears: Comparison to Other Species. ARVO 2006; 1933/B383.
20. Herrero-Vanrell R, Vicario M, Vico E, de las Heras B, Benitez del Castillo JM, Molina-Martinez IT. Development of a New Preservative Free Formulation for the Treatment of Dry Eye Syndrome. ARVO 2006; 5585/B355.
21. Molina L, Laliberte TW, Gartner T, Vogel R, Lehman TM, Butler LH. Biological Effects and Evaluation of Preclinical Activity for Dry Eye Treatment With the Nanodecapeptide Moli1901. ARVO 2006; 5593/B363.
22. Vogel R, Walters TR, Molina L, Laliberte TW, Augello-Vaisey SJ, Butler LH, Lehman TM. Ocular Safety and Tolerability of Two Doses of Moli1901 Ophthalmic Solution in Healthy Subjects. ARVO 2006; 5595/B365.
23. Milazzo G, Russo S, Rasà D, Perri P, Ferri M, Monari P, Costagliola C, Lamberti G, Papa V, Sebastiani A. Effect of an Ophthalmic Gel Containing Xanthan Gum and Sodium Hyaluronate on Corneal Wound Healing After Photorefractive Keratectomy. ARVO 2006; 2737/B132.

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