The acceleration of research focused on dry eye over the past several decades has led to an increase in knowledge regarding the pathophysiology of the disease. The dry eye pipeline is now brimming with innovation, from investigational therapies to pioneering clinical models, study designs, and technologies.

Several new dry eye drug candidates are currently under evaluation and show great potential. SAR1118 (SARCode) is a selective small-molecule LFA-1 antagonist, inhibiting T-cell migration, proliferation, adhesion, and cytokine release thus preventing T-cell mediated chronic inflammation. A phase III study evaluating the efficacy of SAR 1118 (5.0%) compared with placebo in the treatment of dry eye is currently ongoing.

Mimetogen has developed a family of small-molecule tyrosine kinase receptor agonists that are powerful mucin secretagogues that have been shown to stimulate MUC 5AC secretion from conjunctival goblet cells. MIM-D3 is a small-molecule mimic of nerve growth factor (NGF) and has completed a phase II study designed to compare the safety and efficacy of 1% MIM-D3 and 5% MIM-D3 with placebo for the treatment of the signs and symptoms of dry eye.

RX-10045 (Resolvyx) is a synthetic resolvin analog formulated for topical application to treat diseases of the eye and is being investigated for the treatment of dry eye. In a phase II trial, RX-10045 produced dose-dependent improvement in both the signs and symptoms of dry eye, and was generally shown to be safe and well tolerated.

Last year, Resolvyx and Celtic Therapeutics announced that they would be entering into a final agreement under which Celtic had acquired and licensed rights to RX-10045.

Also on the docket and of obvious interest is Allergan’s Restasis X, a new variation of cyclosporine, which is listed in phase II.

New knowledge
At Ora, we have studied more than 10,000 patients across 150 dry eye trials. One core concept we’ve learned is that dry eye symptoms fluctuate as the seasons come and go, with many patients experiencing a worsening of signs and symptoms during heightened dry eye seasons. For example, patients living in the Northeast region of the United States may find the winter months especially challenging, because the air is drier and the humidity is decreased both indoors and outdoors. Tradi-
tionally, environmental studies investigating dry eye therapies have been conducted across many seasons, some continuing for many years. In order to minimize the environmental influences, a clinical trial is best conducted during a single season to reduce the unpredictability of environmental factors. Trying to control for environmental factors is also challenged by numerous situational factors that may further exacerbate dry eye, such as prolonged visual tasking, ocular surgery, aging, and certain medications that cause ocular drying.

By reducing the variability caused by environmental and situational factors using an environmental model like the Controlled Adverse Environment (CAE), which was designed to exacerbate the signs and symptoms of dry eye by regulating humidity, temperature, airflow, lighting conditions, and visual tasking, we are able to study dry eye in a more controlled manner. The CAD model has been shown to be a valuable tool for screening and enriching patient populations in environmental trials, measuring the impact of therapeutic regimens on various subjective and objective endpoints before and after CAD exposure, and understanding of dry eye.

Using established technologies to select and diagnose patients properly can also yield better-controlled dry eye studies. These technologies have been revised and improved upon as the understanding of dry eye has increased.

The work of Lemp in the 1970s brought about one of the most widely used clinical tests used to measure properties of the tear film, tear-film breakup time (TFBUT). Subsequent studies have identified improvements to the measurement of tear film stability. While the standards developed for TFBUT were >10 seconds for normal subjects and <10 seconds for subjects with dry eye, reducing the quantity of fluorescein used led to a modification of reference values to a more accurate threshold of 5 seconds. A TFBUT value less than 5 seconds is generally agreed to constitute tear-film stability consistent with dry eye.

Next, because both the lids and the tear film are responsible for providing protection to the ocular surface, it became evident that TFBUT alone does not provide a complete picture of ocular health. In light of this, the ocular protection index (OPI) was developed to evaluate the interaction between blinking and TFBUT. Most recently, the development of the OPI 2.0 System allows for a measure of tear film stability under a natural blink pattern and normal visual conditions. By capturing the natural dynamics of the tear film with automated methods, studies of the interaction between blinking and TFBUT are enhanced by adding an additional component for analysis, that of tear film breakup area. The measure of the amount of ocular surface exposure provides a more complete picture of ocular surface health and has been previously studied. Because of the ability to automate the analysis of the tear film, the role of blink patterns has also evolved. Aspects such as blink frequency, microsleeps, and fissure width will also play a pivotal role in our understanding of dry eye. Automated analysis has become useful in other diagnostic tools as well. While numerical scales...
Dry eye comes in a variety of guises and, once diagnosed, may require various therapeutic options. Some patients can experience symptomatic relief with simple instillation of a tear supplement daily, while others may require several medications. Two specialists in treating dry eye, Barry A. Schechter, MD, and David A. Goldman, MD, described how they approach the management and treatment of patients with this common and often problematic disorder.

Tailor treatment for dry eye

Individualized therapy is paramount for different levels, degrees, variable responses

By Lynda Charters
Reviewed by David A. Goldman, MD, and Barry A. Schechter, MD

It is of utmost importance that we continue to learn more about the pathological processes at work and strive to develop novel methods and models to understand the disease better.

Take-Home Message

A number of therapies to treat dry eye are available and can provide relief based on the severity of the disease. A hydroxypropyl cellulose ophthalmic insert (Lacriseert, Valeant Ophthalmics), designed to be placed in the inferior cul-de-sac of the eye, provides relief for patients with the most severe dry eye.

Individualized treatment is paramount for Dr. Schechter, director of cornea and external disease, Florida Eye Microsurgical Institute, Boynton Beach, FL.

“There are different levels and degrees of dry eye, and it is sometimes difficult to treat because patients have variable responses,” Dr. Schechter said. “Some may have terrible symptoms that exceed their clinical signs and vice versa. Treatment really must be individualized to patients based on their pathology, their symptoms, and how dry eye affects their lives.”

Management is sometimes guided by the results of an FDA-approved questionnaire, the Ocular Surface Disease Index (OSDI), which evaluates how dry eye affects a patient’s lifestyle.

“Based on the information from the OSDI, I gain an idea of the severity of the dry eye symptoms and can tailor treatment,” he explained.

Patients who have mild dry eye usually begin treatment with instillation of preservative-free tears titrating up to three to four times daily. Dr. Schechter asks patients to report their prog-

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Dry eye is quite suitable for automated detection of redness and may be useful as a supplement to clinician grading. New technologies in ocular imaging techniques have also been improved. While once a challenge for ophthalmic clinicians and researchers, microscopic evaluation of ocular structures has been facilitated by the use of confocal microscopy. This technology allows in vivo examination of the human cornea and conjunctiva at a cellular level.

Last but not least, research to discover pertinent and clinically relevant biomarkers for dry eye, including cytokines, mucin gene expression levels, and tear osmolarity, is also of interest to the industry. These biomarkers may serve as important determinants of disease risk, prognosis, or even response to a treatment.

Conclusion

As we wait with bated breath for the approval of additional options for the treatment of dry eye, it is of utmost importance that we continue to learn more about the pathological processes at work and strive to develop novel methods and models to understand the disease better.

References


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