Ocular surface: what's new?

Highlights from Laboratoires Théa's Satellite Education Program, "Ocular Surface: What's New?" held on October 8, 2015, at the 7th EVER Congress, Nice, France.

Dry eye disease (DED) is a particular burden for both doctor and patient alike. There are three principal reasons behind this: high prevalence (up to 100 million people worldwide are thought to be affected by DED to some degree), many causes (autoimmune, environmental, drug adverse events, and ocular and systemic disease) with multiple forms (principally aqueous-deficient and evaporative). From the ophthalmologist's perspective, the presence of DED precludes patients from receiving surgery, complicates recovery after surgical procedures, and can present with symptoms of discomfort, visual disturbance, and tear film instability – leading to patients who are constantly unhappy with how their eyes feel.

DED is frequently characterized by increased osmolarity of the tear film and inflammation of the ocular surface, which without intervention, can ultimately result in permanent damage. Poor eyelid hygiene or impaired function of the meibomian glands can also cause or exacerbate inflammation and ocular surface damage. Because of DED's many and multifactorial etiologies, there's a wide range of therapeutic options in use – from lubricants to immunomodulators, and treatment needs to be individualized to each patient. However, it's clear that DED-induced perturbations in tear film – no matter what the cause – lead to increased inflammation and visual disturbances. This supplement aims to document the issues involved in DED; its causes, its effect on the tear film – and vision – and how this situation can be improved with topical eyedrops containing a bioprotectant like trehalose. (see page 2).

A new paradigm in dry eye disease

Christophe Baudouin, Professor and Chairman of the Department of Ophthalmology, Quinze-Vingts National Ophthalmology Hospital, Paris, France.

Inflammation is a ubiquitous mechanism in ocular surface diseases, but sometimes it can be difficult to identify, even in situations where it plays a key role. For example, in many cases of DED, there are no signs of clinical inflammation – no redness or swelling can be observed, and often no pain is felt – just a sensation of dryness or grittiness. Nevertheless, subclinical inflammation as evidenced by cytokine and lymphocyte presence, is one of the four key mechanisms of DED and a significant contributor to its pathophysiology, along with tear hyperosmolarity, apoptosis and tear film insufficiency and instability. These mechanisms form the basis of the "vicious circle" hypothesis (see Figure 1).

Tear hyperosmolarity is a significant contributor to inflammatory activation in DED. Hyperosmolarity induces inflammatory cytokines such as CCL2 and IL-8; in a mouse model of DED, an antagonist to CCR2 – the CCL2 receptor – decreased monocyte infiltration into the cornea. Damaged or dysfunctional corneal nerve signaling (which can result from corneal surgery, congenital factors, and even from dry eye itself), can also contribute to the pain and inflammation patients with DED experience. Once established, this inflammation can lead to the keratinization of the meibomian gland orifices, leading to blockage, dropout, and ultimately meibomian gland dysfunction (MGD). We now know that DED is not restricted to the ocular surface – with the involvement of nerves, mucosa and even the immune system, there's much more going on behind the scenes – and it's time to begin addressing those aspects of the disease.

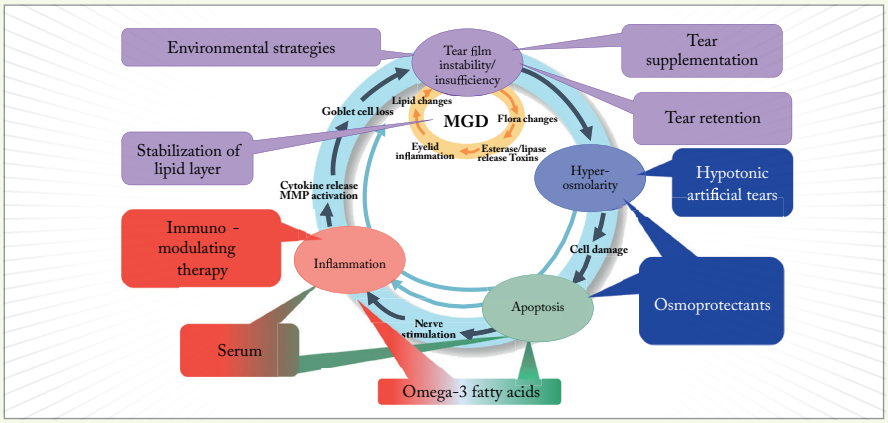


Figure 1. The four target areas contributing to the pathophysiology of DED are tear film instability, tear hyperosmolarity, apoptosis and inflammation. The "vicious circle" is primarily driven by hyperosmolarity and tear film instability, but can be entered at any point (1). LPS, lipopolysaccharide; MGD, meibomian gland dysfunction; MMP, matrix metalloproteinase.

Even now, there's no shortage of targets for blocking inflammation: we use steroids, antibiotics, essential fatty acids, and even topical cyclosporine. But in the race to do so as effectively as possible and with as few side effects as possible, treatment options like trehalose – a bioprotectant that acts at multiple points of dry eye's vicious circle – could be a good alternative.

The MEIBUM survey: a closer look at the eyelids

David Díaz-Valle, Section Chief, Ocular Surface Unit, San Carlos Clinic Hospital; Madrid, Spain.

One significant cause of DED is MGD, which can result in tear film alteration, symptoms of eye irritation, inflammation, and ocular surface disease. It's the main cause of evaporative DED (which comprises 49–58 percent of all dry eye) and is typically diagnosed by examining a patient's symptoms, clinical signs, meibography (see Figure 1), and gland expression.

To better understand the management of MGD, a study known as MEIBUM (Management of Eyelid DIsorders By Ophthalmologists in Usual Medical Practice) was conducted at clinics across nine countries in Europe. In the first three countries completed (Poland, Spain and Germany), a total of 4,884 patients (mean age 57.5, 63 percent female, 80 percent with pre-existing eye disorders) have been surveyed thus far. Of those patients, 92 percent presented with at least one DED-related symptom, and 78.7 percent showed evidence of eyelid disease. Ultimately, 55 percent of patients were diagnosed with MGD and 64 percent with DED.

The fact that over half of non-selected patients have MGD with negative impact on their daily vision- or contact lens-related activities shows that it's a significant concern in the clinic. It impacts on patients' quality of life, their professional and personal activities, and even on their perceived visual acuity and overall satisfaction. There's also a significant correlation ($p<0.001$) between MGD and dry eye – which is unsurprising, as MGD is the main risk factor for DED. It's therefore vital to evaluate the eyelids and free margin in every patient, as many exhibit some degree of MGD and would benefit from treatment by eyelid hygiene and artificial tears.

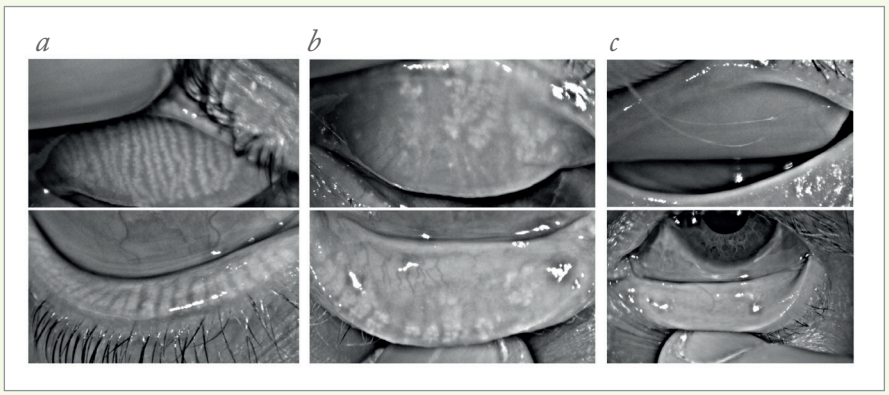
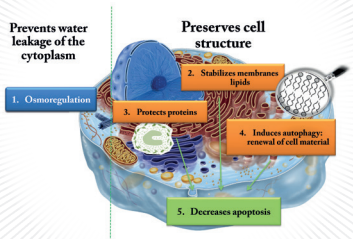


Figure 1. Meibography in a. normal eyes, b. moderate-to-severe MGD with some loss of gland tissue, and c. severe MGD with complete loss of gland tissue (3).

What is trehalose?

Trehalose is a naturally occurring bioprotective disaccharide molecule present in organisms from bacteria to crustaceans – but not in mammals (5). It acts as a protector against environmental stress (6), chiefly through osmoregulation (preventing water leakage from the cytoplasm). It also preserves cell integrity by stabilizing membrane lipids, protecting proteins, inducing autophagy (to renew cell material), and decreasing apoptosis and inflammation.

Trehalose: a natural bioprotector



Trehalose is able to suppress structural changes due to dehydration – likely by hydrogen bonding with protein surfaces to maintain their conformation and activity (7), and now its bioprotective effects are being applied to DED. It can protect corneal cells from desiccation (9), apoptosis (10), accelerate their healing (11) and restore and maintain the osmotic balance of the ocular surface (12,13). The availability of eyedrops containing both sodium hyaluronate and trehalose, capitalizing on the components' lubricant and bioprotectant properties, are clearly an advance in the treatment of DED.

Visual function impairment in dry eye disease

Pierre-Jean Pisella, Professor, University François Rabelais; Hospital practitioner, Hôpital Bretonneau, Tours, France.

In DED, there is often a discordance between clinical signs and functional ones like dryness or the sensation of itching, burning or foreign bodies (see Table 1). In moderate DED, for instance, there may be weak or absent corneal staining and moderate tear-film breakup time (TBUT), but many subjective and difficult-to-quantify visual complaints due to tear film instability.

The most powerful refractive surface of the eye is the interface between air and tears – so the state of the lacrimal tear film can clearly affect the eye's refractive index. In DED, when the tear film thickness decreases in an irregular manner, the result can be a significant impact on patients' optical quality as determined by scattering and aberrations (see Figure 1). An irregular alteration of the tear film, as seen in DED, dramatically changes the refractive power of the cornea and can lead to visual acuity decreases of greater than 1.0 D, as well as significant increases in higher-order aberrations.

Of note, the tests most commonly used to diagnose DED – fluorescein staining and TBUT – are subjective, in that no strict correlation exists between their results and optical quality in DED. What's needed, then, are tests that can dynamically visualize corneal tear film quality, like the Ocular Quality Analysis System (OQAS), a "double pass" aberrometer that also generates an ocular scattering index (OSI) by screening a projected point source on the retina after two passes through the eye.

Because tear film irregularity has such a significant impact on optical quality, tear film substitutes can decrease the mean OSI (and the variability of it) and improve contrast sensitivity, visual quality and tear film stability. This is why it's important to evaluate DED using both eye and visual symptoms, use both classical and new tools to examine the impact of the disease, and consider tear film substitutes with a long residence time as a treatment to improve optical quality.

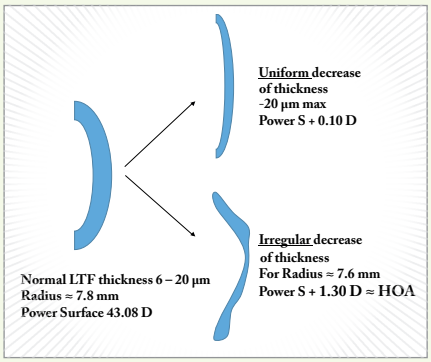


Figure 1. The effect of the lacrimal tear film on refractive index. In DED, an irregular decrease in tear film thickness (bottom right) affects the eye's optical quality and can affect aberration measurement (2).

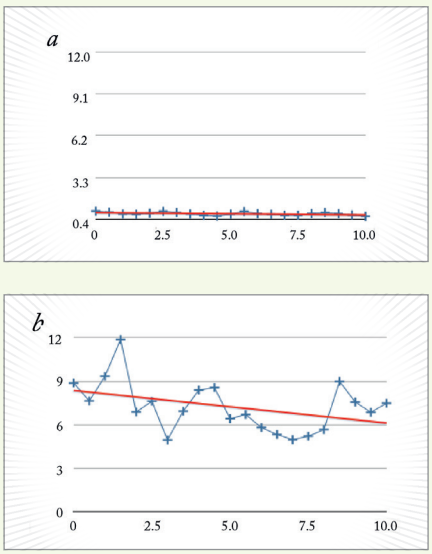


Figure 2. OSI is measured at half-second intervals to plot ocular scatter over time in a. normal eyes and b. severe DED. Variation in OSI indicates a patient's disease severity (2).

	Minimal DED	*Moderate DED*	*Severe DED*
Functional signs	+	+/++	+++
Visual signs	–	+	++
*Staining**	–	+	++
Tear film break-up time	*>10 seconds*	*<10 seconds*	*<5 seconds*

Table 1. Clinical evaluation of minimal, moderate and severe DED. *Corneal or conjunctival.

New treatment to improve tear film thickness in dry eye disease

Leopold Schmetterer, Section Head, Department of Clinical Pharmacology, Center for Medical Physics and Biomedical Engineering, Medical University of Vienna; Vienna, Austria.

The eye clinic at the Medical University of Vienna's Department of Clinical Pharmacology has a custom-built optical coherence tomography (OCT) imaging system prototype that is capable of detecting tear film changes on the order of 50 nanometers – a threshold that is far more sensitive than any commercially available system. That system has been used to compare the thicknesses of the tear films of patients with and without DED and evaluate the impact of topical artificial tear application to these eyes.

In a randomized, double-masked, controlled parallel group study, 60 DED patients received a single dose of either preservative-free sodium chloride 0.9% (Hydrabak®), preservative-free sodium hyaluronate (HA) 0.15% (Hyabak®), or preservative-free HA 0.15% + trehalose 3% mg/mL (Thealoz Duo®). HA

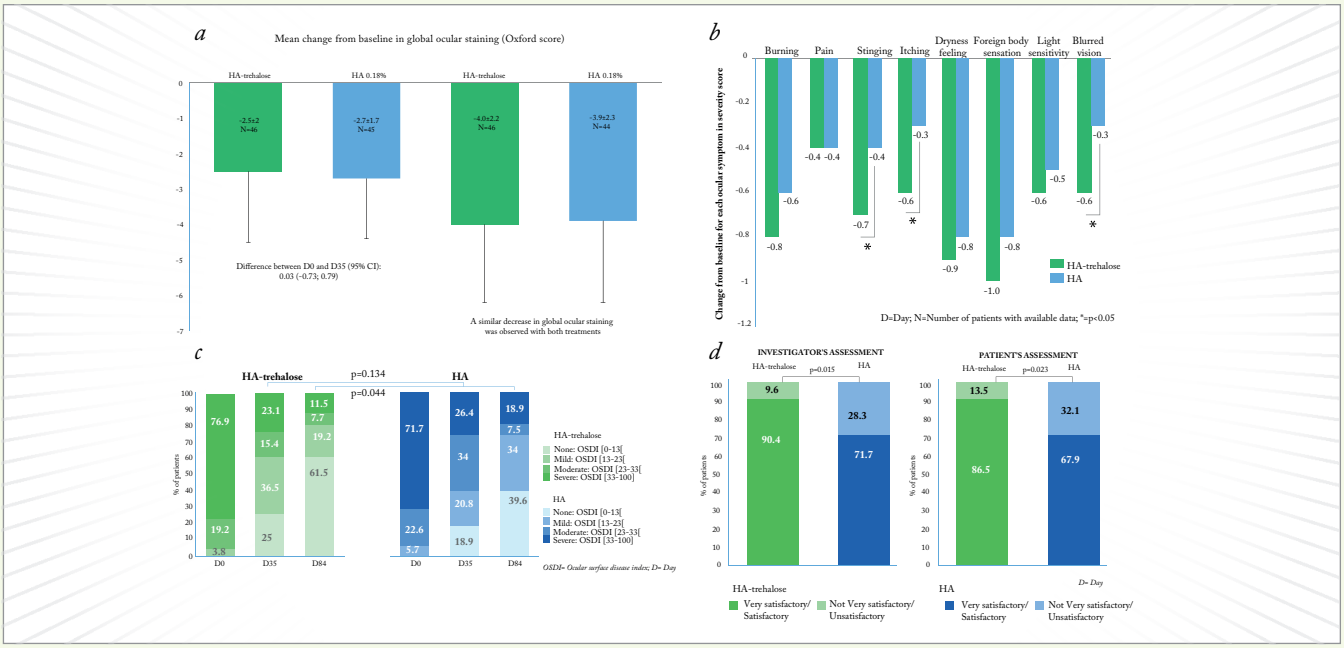


Figure 1. Study outcomes comparing the safety and efficacy of Thealoz Duo® and HA. a. Change in Oxford scheme grades at months one and three, b. Change in severity of ocular symptoms at month one, c. Change in OSDI score at month three, and d. Investigator and patient satisfaction scores at month three (5).

drops increased tear film thickness as compared to sodium chloride over a four-hour period, and combining HA with trehalose was even more effective (4).

The question is: how do these results on tear film thickness relate to what is seen in the clinic? To answer that, a multicenter, randomized, investigator-masked, parallel group Phase III clinical trial was conducted to demonstrate the noninferiority of Thealoz Duo® (HA 0.15% + trehalose 3%) to VISMED® (HA 0.18%) in treatment of DED (5). 105 patients with moderate-to-severe DED (OSDI ≥18) and at least one eligible eye (global ocular staining grade 4–9 on the Oxford scheme and at least one of: Schirmer test 3–9 mm wetting of paper after 5 minutes, or sum of three TBUT measurements ≤30 seconds). Patients were given one week of Hydrabak® treatment, then assigned to receive one drop per eye of either Thealoz Duo® or HA three to six times daily over three months. Eleven males and 41 females (mean age 60.0±12.2) received Thealoz Duo®, and eight males and 45 females (mean age 58.5±13.4) received HA. The primary efficacy criterion was global ocular staining according to the Oxford grading scheme (fluorescein in the cornea and lissamine green in nasal and temporal conjunctiva); secondary criteria included change in OSDI score, change in DED symptoms, and global efficacy assessments by investigators and patients.

At the one- and three-month marks, both drugs showed similar improvements in Oxford grades (see Figure 1a). Thealoz Duo® showed a significantly greater improvement both in the severity of ocular symptoms at the one-month mark (see Figure 1b) and in the OSDI score at three months (see Figure 1c). At the conclusion of treatment, Thealoz Duo® also yielded significantly better investigator and patient satisfaction reduces inflammation and apoptosis and induces autophagy (7).

Why does adding trehalose increase efficacy? One likely reason is because trehalose is a bioprotectant that not only provides osmoregulation, but also stabilizes the membrane lipid bilayer, protects proteins, reduces inflammation and induces autophagy.

Ultra-high-resolution OCT provides a new and effective method of determining tear film thickness in DED patients and has allowed ophthalmologists to verify that preservative-free HA 0.15% + trehalose 3% offers a longer residence time on the ocular surface. The clinical study that compared Thealoz Duo® with HA has also shown that both drugs yield similar improvements in ocular staining, but that Thealoz Duo® offers significantly greater improvements in OSDI score, symptom severity, and patient and investigator satisfaction. Some or all of these may be related to trehalose's mechanisms of action – in particular, its natural bioprotection.

References

1. *C Baudouin, J Fr Ophtalmol, 30, 239–246 (2007).*
2. *T Habay, et al., J Fr Ophthalmol, 37, 188–194.*
3. *D Díaz-Valle, "MGD MEIBUM study". Presented at the 7th EVER Congress; October 8, 2015; Nice, France.*
4. *D Schmidl, et al., Cornea, 34, 421–426 (2015).*
5. *S Doan, et al., Acta Ophthalmologica, 93, S255 (2015). Available at: bit.ly/thealozduo.*
6. *NK Jain, I Roy, Protein Sci, 18, 24–36 (2009).*
7. *S Sarkar, et al., J Biol Chem, 282, 5641–5652 (2007).*
8. *X Zhang, et al., Autophagy, 10, 588–602 (2014).*
9. *K Uchida, et al., J Toxicol Pathol, 27, 153–158 (2014).*
10. *T Matsuo, Br J Ophthalmol, 85, 610–612 (2001).*
11. *W Chen, et al., Exp Eye Res, 89, 311–318 (2009).*
12. *J Cejková, et al., Histol Histopathol, 27, 1029–1040 (2012).*
13. *M Hovakimyan, et al., Curr Eye Res, 37, 982–989 (2012).*
14. *J Li, et al., Mol Vis, 18, 317–329 (2012).*