Ocular Surface Diseases –
A Perspective of Clinical Practice
Between Present and Future

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Dry eye disease (DED) is an important problem for patients and their eye care providers because it can affect daily function, quality of life, vision, and the outcomes of cataract and refractive surgery. It is also significant because it is a common condition in populations around the world.

Dry eye disease seems to be increasing in response to local alterations already present in the eye, systemic diseases and external factors like poor air quality, high pollution and, even, changes in climate. This affects quality of life causing a disruption of a healthy microenvironment at the ocular surface.

Studies investigating the epidemiology of DED report a wide range of prevalence rates, which may be explained in part by the use of different definitions. According to available data, however, as many as 33% to 40% of adults have dry eye symptoms. Importantly, findings of studies evaluating signs of DED (eg., tear film breakup time and tear volume) and the effects of tear hyperosmolarity.

The vicious circle model of DED pathogenesis is consistent with the modern definition of DED, which states, “Dry eye disease is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.”

The schema of the vicious circle (Figure 1) presents the many factors that can cause or increase the risk for DED and how they act as triggers at different points in the pathophysiological pathway. The pathophysiological pathway itself is depicted by a stepwise series of interacting events. Each step drives the next, perpetuating the vicious circle in a process that manifests clinically as DED progression.

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Dry Eye Disease is a Multifactorial Disease of the Tears and Ocular Surface

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CHOOSING TREATMENT FOR DED

Offering practical guidance on therapeutic decisions for patients with DED, Dr Baudouin said that the severity-based treatment algorithm proposed by the first Dry Eye WorkShop seems to offer a simple and convenient tool. Its application can be challenging, however, in situations where there is not concordance in the severity of a patient’s DED signs and symptoms. Consider a patient who reports severe symptoms and yet has no or minimal corneal or tear signs of DED, Dr Baudouin said.

He explained, “This example raises the question of how to grade DED severity in order to select treatment. Should the grading be based on the signs, the symptoms, or both?” The mechanistic approach to treatment suggested by Dr Baudouin recognizes that different interventions act at different points in the vicious circle of DED pathogenesis (Figure 2).

He proposed that compared with other artificial tears, a new product formulated with two lubricant polymers—carboxymethylcellulose (CMC) and hyaluronic acid (HA)—plus osmoprotectant excipient ingredients may work better because it addresses multiple mechanisms of DED pathogenesis. Like other artificial tears, the novel formulation stabilises the tear film, but this effect is enhanced by synergism of its dual-polymer system. In addition, the new artificial tear targets another central mechanism in DED pathogenesis as it protects ocular surface epithelial cells from hyperosmotic-associated damage.

Summarising data from clinical trials, Dr Baudouin reported that the new artificial tear demonstrated advantages when compared with other marketed products containing only CMC or HA. One multicenter clinical trial enrolling 80 patients met its primary endpoint, demonstrating the new artificial tear was non-inferior to an HA-only product for improving ocular surface staining after 35 days.7 However, a significantly greater number of patients considered the dual-polymer artificial tear with osmoprotectants easier to use (P=.0002).

In another head-to-head comparison study, both the dual-polymer osmoprotectant formulation and a CMC-only artificial tear produced rapid and sustained improvements in symptom severity and tear film breakup time.8 Results of subgroup analyses, however, showed the new artificial tear product was significantly superior to the CMC product for improving symptoms in patients with severe ocular surface staining at baseline.

“Symptoms are often what brings patients to seek treatment for their DED, and so it is important that a product used in the management of DED provide effective symptom relief,” Dr Baudouin said.

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Are There Any Differences Amongst Artificial Tears?

Peter A. Simmons, PhD, USA

Artificial tears are a mainstay of treatment for dry eye disease (DED), regardless of the level of severity. When recommending a product to patients, however, physicians need to know that the clinical performance of an artificial tear is affected by all of the formulation’s ingredients, said Peter A. Simmons, PhD, USA.

“Artificial tear products with similar active ingredients may be very different because it is not just the lubricant polymers listed as active ingredients on the product label that are important,” he said.

Dr Simmons reviewed properties of specific compounds within three categories of ingredients used in artificial tears—lubricant polymers, excipients used as toxicity agents, and preservatives—and explained how by optimising ingredient selection, formulation researchers created a new artificial tear to provide enhanced lubrication and ocular surface protection. The advanced product contains two water-soluble polymers that in combination exhibit synergistic viscoelastic behavior; excipients that help protect the ocular surface from the stress associated with a hyperosmolar tear film; and a proprietary gentle preservative (Figure 1).
LUBRICANT POLYMERS

Lubricant polymers in artificial tears enable drop retention and act to hydrate and lubricate the ocular surface. The new artificial tear uniquely combines carboxymethylcellulose (CMC) and hyaluronic acid (HA).

CMC is a well-established lubricant polymer ingredient in artificial tears, and findings from in vitro and animal studies also show that CMC binds to corneal epithelial cells and promotes epithelial wound healing.1,2

HA is a natural component of the tear film and another leading ophthalmic lubricant polymer that is found in viscoelastic products used in ophthalmic surgery in addition to artificial tears. Dr Simmons pointed out that the properties of lubricant polymers, including HA, can vary depending on their purity, method of manufacture, and chain length (molecular weight).

“Originally, HA used in ophthalmic products was derived from animal sources, but the HA in the new artificial tear is a highly purified form obtained through a bacterial biofermentation process,” he said.

“In addition, this HA is a very high molecular weight molecule. Compared with low and medium molecular weight HA, high molecular weight HA is less likely to be proinflammatory, and it has higher viscosity, which results in longer residence time on the ocular surface.”

HA has other benefits that make it attractive as a lubricant polymer in artificial tears. Like CMC, it binds to epithelial cells on the ocular surface, although at different sites, and it displays high shear thinning behavior so that it provides excellent lubrication between the ocular surface and the blinking lid.

When CMC and HA are combined in the same formulation, they form a flexible bridged matrix in which CMC is entangled within the HA. In this structure, CMC and HA each retain the ability to interact with their specific epithelial cell binding sites. However, results of laboratory studies indicate that when the two polymers are combined, they act synergistically for enhanced viscoelastic behavior.

Under low-shear conditions, which characterize the tear film between blinks, the viscosity of the combination is about 60% greater than the sum of the viscosities of the individual polymers.3

Then, in response to increasing shear that corresponds to the effect of the blinking lid, the combination exhibits reduced viscosity.

“The viscoelastic properties of the polymer combination are consistent with enhanced retention, tear film stabilisation, ocular surface hydration, and lubrication, and indicate that the new artificial tear should provide comfortable protection of the ocular surface,” Dr Simmons said.

TONICITY AGENTS

Dr Simmons noted that the choice of excipients used to adjust the tonicity of artificial tears is important to a product’s clinical performance because specific ingredients either

promote hyperosmotic stress-induced epithelial cell damage or provide protection against it.

“When formulating the advanced artificial tear product, the tonicity agents were carefully selected, favouring beneficial solutes as a means to minimise the addition of sodium that causes hyperosmotic stress,” he said.

Dr Simmons explained that when exposed to the hyperosmotic environment of the altered tear film present in dry eye, ocular surface epithelial cells initially lose water and shrink. As a defensive mechanism to re-establish osmotic equilibrium and restore volume, the cells take up whatever solutes are available in the environment. If this regulatory process results in uptake of sodium ions, an intracellular electrolyte imbalance occurs that initiates a pathway of cellular changes ultimately leading to apoptosis and triggering an inflammatory response. Uptake from the environment of other electrolytes and non-ionic compounds allows safe restoration of cell volume.

“These latter ‘compatible solutes’ that allow cells to retain water while avoiding damage from hyperosmotic stress are referred to as osmoprotectants,” Dr Simmons said.

He added, “Osmoprotection is a well-established mechanism in human physiology as cells in various internal organs accumulate compatible solutes in order to protect themselves from the deleterious effects of changing osmolarity. Its application to formulate an artificial tear that can prevent damage to ocular surface cells from hyperosmotic stress is a new concept.”

PRESERVATIVE PROTECTION

Multi-dose artificial tears must contain a preservative to protect against microbial contamination, but some preservatives have known cytotoxic potential.

The preservative contained in the new advanced artificial tear, stabilized oxychloro complex, is a proprietary mild agent. It provides antimicrobial efficacy in the bottle through oxidative activity, but on contact with the ocular surface it quickly breaks
down into harmless components—sodium and chloride ions, oxygen, and water. Dr Simmons presented results from animal studies showing repeated dosing with the proprietary oxidative preservative did not adversely affect corneal cell morphology or survival 4 (Figure 2).

“Exposure to other ophthalmic preservatives, however, resulted in progressive damage and cell death,” he reported. “Even with exposure to a level 10-fold greater than that found in the advanced artificial tear, this oxidative preservative is not toxic to ocular surface cells. Therefore, it is gentle enough to use frequently.”

**PROOF OF PRINCIPLES**

Results from preclinical and clinical studies investigating the advanced artificial tear support its benefits as an option for managing dry eye disease, Dr Simmons said.

He cited a published study that investigated the efficacy of different artificial tears for either preventing or treating environmentally-induced dry eye in mice.5 Animals were randomised into five groups to receive the new artificial tear combining CMC and HA, a product containing CMC or HA alone, saline, or no treatment.5 In both the prevention and treatment experiments, animals in all three artificial tear groups had significantly less corneal staining compared with both control groups. However, the effect of the CMC + HA product was significantly better than the effect of using CMC or HA alone.

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**How to Manage the Real Patient – Case Studies**

Maurizio Rolando, MD, Italy

**CASE 1**

A 54-year-old woman presents complaining about a 4-year history of foreign body sensation and eye burning that worsens in the afternoon and evening. She is using artificial tears on as needed basis, but says her symptoms are limiting her social activities. She has no ocular or medical comorbidities.

**DIAGNOSIS:** Discussing this case, Maurizio Rolando, MD, Italy, emphasised the need for an accurate diagnosis to guide specific management (Figure 1).

“The assessment requires recognition that dry eye is not just a disease of the tears or the cornea. Rather it is a disease of the ocular surface system, and the examination must also consider the conjunctiva, the lids with the periocular skin, and the nerves,” he said.

On clinical examination, the patient had increased blink frequency and seemed to avoid direct gazing. She had “slightly dirty” film deposits along her eyelashes, indicating meibomian gland dysfunction (MGD); severe staining of the bulbar conjunctiva with lissamine green, showing inflammation; and staining of the limbal region under the superior lid.

“Always stain the conjunctiva, and don’t forget to look under the upper lid because staining in this area can suggest a diagnosis of Sjögren syndrome or thyroid eye disease,” Dr Rolando said.

Tear breakup time was shortened and staining of the inferior tear meniscus persisted 10 minutes after lissamine green instillation, which Dr Rolando pointed out demonstrated slow tear turnover. Tear osmolarity was 325 mOsm/L in the worst eye, indicating hyperosmotic stress.

**MANAGEMENT:** Dr Rolando said treatment for this patient will include an artificial tear, but it must be used on a regular basis rather than as needed in order to promote tear turnover and clear the ocular surface of pro-inflammatory mediators.

“The selected product should provide epithelial protection, prevent hyperosmotic stress, and have good viscoelastic behavior that will provide lubrication during blinking in order to relieve lid friction,” he said.

The patient was also advised about lid hygiene for management of MGD.

**CASE 2**

A 66-year-old man presents with complaints of persistent eye redness and discomfort. He reports feeling burning and a foreign body sensation for the past 2 years. His symptoms are occasionally worse in the evening, and he has some intermittent blurring that sometimes improves with blinking. The patient was diagnosed with type 2 diabetes 20 years earlier. He takes an oral medication for glycaemic control and antihypertensive medication. His history is negative for allergy, ocular surgery, and ocular trauma. He is not using any topical treatments for his symptoms.

Findings of the ophthalmic examination are as follows:

- Mild bulbar hyperaemia OU; reduced lower tear meniscus OU; Schirmer I test 7 mm/5min OD; 8 mm/5 min OS; TBUT 12/11 sec OD/OS; mild staining of lower nasal conjunctiva and lower corneal epithelium OU; reduced corneal sensitivity (cotton thread testing); tear surface irregularities on topography a few seconds after blinking; tear film osmolarity 321/324 mOsm/L OD/OS; normal lid and periocular skin.

**DIAGNOSIS:** Dr Rolando commented that the patient’s complaints of blurred vision could be explained by irregularity and instability of the tear film. He said the findings of the examination...
correspond with a diagnosis of non-Sjögren aqueous-deficient dry eye disease, and the presence of reduced corneal sensitivity is consistent with the hypothesis that sensory neuropathy is an underlying mechanism, triggering the vicious circle of dry eye pathogenesis by disrupting the reflex arc for tear stimulation. Tear film hyperosmolarity arises from the reduced tear secretion and drives the vicious circle, he explained.

“Although this patient had no other signs of diabetic neuropathy, we are learning that neuropathy in the cornea can occur very early in diabetes. Therefore, it is important to assess corneal sensitivity when checking for effects of diabetes on ocular health,” Dr Rolando said.

**MANAGEMENT**

The approach to management of this patient aimed to provide symptomatic relief and interrupt the vicious circle of DED pathogenesis by addressing the tear film instability, epithelial damage, and inflammation.

“The ocular surface disease in this patient was not very severe, but it is important to intervene to prevent it from worsening,” Dr Rolando said.

Treatment for controlling ocular inflammation was initiated, including oral unsaturated omega-3 fatty acid supplementation, topical cyclosporine A, and a short-tapering course of a well-tolerated topical corticosteroid as induction therapy with the cyclosporine A. The patient was also given an artificial tear product with a formula optimised to protect the epithelium from both shear stress imparted during blinking and a hyperosmotic environment.

“Once the ocular surface inflammatory response has been controlled, it may be possible to discontinue the cyclosporine and maintain the patient on a regularly administered tear substitute that is formulated to provide lubrication and osmoprotection,” Dr Rolando said.

**What are the Future Trends in the Management of Dry Eye Disease?**

José AP Gomes, MD, PhD, Brazil

A look at ongoing research suggests the future will bring promising new modalities for the management of dry eye disease, said José AP Gomes, MD, PhD, Brazil.

“The high and rising prevalence of dry eye has captured the attention of scientists, ophthalmologists, and industry,” he said.

“Now we are seeing developments in medical management, device-based approaches, and surgery.”

**MEDICAL MANAGEMENT**

Lifitegrast is an investigational pharmacotherapy in late stage clinical development. This small molecule integrin antagonist acts by interfering with the immunological synapse, blocking binding of lymphocyte function-associated antigen-1 to intercellular adhesion molecule-1 and thereby preventing T-cell activation, inflammatory cell migration, and release of pro-inflammatory cytokines.

Phase 3 studies comparing lifitegrast 5% with placebo have been completed. Published results from one of those trials showed statistically significant improvement in dry eye-related symptoms, but not in ocular surface staining. 1 Dr Gomes said.

Diquafosol, another new molecule for management of dry eye, has been available in Japan for more than 5 years and is in Phase 3 development in the United States. Acting as an agonist of the P2Y2 cell receptor, diquafosol stimulates secretion of ocular mucins.

Results of a study evaluating diquafosol 3% and sodium hyaluronate 0.1% used alone or together showed diquafosol was more effective than sodium hyaluronate for improving signs and symptoms of DED, and the combination was significantly more effective than diquafosol monotherapy. 2 Rebamipide, which has been available for decades in Japan as a treatment for gastric ulcer prevention and treatment of gastritis, also increases mucin production and has anti-inflammatory activity. As a 2% preparation, it was shown in a Phase 3 study to be significantly superior to 0.1% sodium hyaluronate for improving ocular surface staining and patient symptoms. 3

Tavilermide (formerly MIM-D3 is a tyrosine kinase A receptor agonist that mimics nerve growth factor (NGF), which is a naturally occurring protein that maintains corneal nerves, promotes epithelial proliferation, and stimulates mucin secretion. In a Phase 2 trial, patients treated with topical tavilermide had significant improvements in both signs and symptoms of dry eye compared with placebo-treated controls, and the NGF mimetic had favorable safety, comfort, and tolerability profiles. 4 In a Phase 3 study, topical tavilermide significantly improved fluorescein corneal staining compared with control, and it was associated with improvements in patient symptoms. 5 (Figure 1)

**NON-PHARMACOLOGICAL APPROACHES**

Hemoderivative alternatives to autologous serum, including platelet-rich plasma and an albumin precursor, are also being investigated as treatments for dry eye with the aim of maintaining the benefits of autologous serum while avoiding the logistical difficulties associated with its use.

A novel non-invasive intranasal lacrimal neurostimulator is also showing promise. So far, there are positive safety and efficacy results from four clinical studies including more than 200 patients, and two pivotal trials are planned, Dr. Gomes said.

In the surgical realm, Dr Gomes and colleagues have been developing a modification of salivary gland transplantation for the management of extremely severe DED with symblepharon. He reported positive results in a series of 19 patients with more than 10 years of follow-up. 6

Finally, cell therapy is also being developed for severe DED with promising results so far.

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**AGENT**

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**Figure 1. Pharmacotherapy pipeline for DED: novel agents in late stage clinical development**
Patients undergoing cataract surgery are often prescribed topical treatment with a nonsteroidal anti-inflammatory drug (NSAID), a corticosteroid, and an antibiotic to reduce postoperative pain, inflammation, and the risk of endophthalmitis. Considering evidence in the published literature, a regimen comprised of gatifloxacin, ketorolac tromethamine, and prednisolone acetate is particularly well-suited to achieve those goals, said Fernando Pellegrino, MD, Argentina.

Even though fourth-generation fluoroquinolones are the latest topical antibiotics introduced into ophthalmology, these agents are not new and bacterial resistance is a potential issue. Results of a study measuring antimicrobial susceptibility of ophthalmic isolates, however, showed there was less resistance to gatifloxacin than to moxifloxacin among both Gram-positive and Gram-negative organisms.

Another advantage of gatifloxacin is that its commercially available formulation is preserved with benzalkonium chloride (BAK). This is an important feature considering findings of an in vitro study showing that the addition of BAK to fourth-generation fluoroquinolones enhances their activity against leading postoperative endophthalmitis pathogens and reduces their propensity to select for fluoroquinolone-resistant organisms.

“In this in vitro study, the MIC90 for gatifloxacin plus BAK against coagulase-negative staphylococci and both methicillin-sensitive and methicillin-resistant Staphylococcus aureus was ≤0.008 μg/mL,” Dr. Pellegrino said.

He added that BAK cytotoxicity is not a relevant safety concern when choosing an antimicrobial agent for endophthalmitis prophylaxis because these medications are used for only a short duration.

Dr. Pellegrino pointed out that bacteria production of biofilm is another issue to consider when selecting medications for cataract surgery patients and a reason for choosing ketorolac. He explained that production of biofilm confers increased bacterial virulence and antimicrobial resistance, and one study reported that 75% of Staphylococcus epidermidis strains from eyes with post-cataract surgery endophthalmitis were biofilm producers.

“S. epidermidis is the most common case of endophthalmitis after cataract surgery. Ketonolac 0.5% not only controls pain and inflammation after cataract surgery, but it has been shown shown in vitro to reduce S. epidermidis biofilm formation by almost 50%,” Dr. Pellegrino said.

Discussing topical corticosteroid use for controlling postoperative inflammation, Dr. Pellegrino outlined reasons for using prednisolone acetate 1%. He said it is a potent inflammatory drug (NSAID), a corticosteroid, and an antibiotic to reduce postoperative pain, inflammation, and the risk of endophthalmitis.

In a randomized, double-blind study, the fixed combination was as effective as gatifloxacin plus prednisolone used separately for controlling inflammation and preventing infection after cataract surgery,” said Dr. Pellegrino.

“However, the fixed combination is easier for patients to use and may improve treatment compliance, reduce administration mistakes, and avoid drug washout that occurs if the two medications are instilled concomitantly.”

REFERENCES

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