



THE ROLE OF INFLAMMATION AND IMMUNE RESPONSE IN DRY EYE



Counteract flareups
with appropriate management.

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The dry eye space is ripe in opportunity for eye care practitioners who wish to provide medical eye care, while also improving their patients' daily quality of life. In fact, one of the most common problems we encounter as eye care practitioners is dry eye. It is estimated that approximately 33% of eye care patients will present with

complaints of dry eye, with some reports indicating that nearly half of all US adults will experience signs and symptoms of dry eye.^{1,2}

To treat dry eye properly, we need to know its etiology. No definition has stood the test of time greater than the Tear Film and Ocular Surface Society's Dry Eye Workshop II definition: "Dry eye is a multifactorial disease of the

ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play an etiological role."³ In this article, we explain the role that ocular surface inflammation plays in dry eye.

THE INFLAMMATORY PROCESS

Inflammation manifests in two primary forms: acute and chronic. Factors such as trauma, microbial invasion, and exposure to toxic compounds, culminating in immediate tissue damage, trigger acute inflammation. On the flip side, chronic inflammation is characterized by a prolonged and gradual onset, persisting for months to years. Regarded as the greatest threat to human health, chronic inflammation exerts its influence across every organ, including the eyes and the ocular surface.^{4,5}

This sustained inflammatory state may arise from constant low-level exposure to irritants or it can be associated with autoimmune disorders, such as lupus, rheumatoid arthritis, rosacea, and Sjögren syndrome.⁴ Common health conditions, including diabetes, arthritis, seasonal allergies, obesity, cancer, and chronic obstructive pulmonary disease, are often linked

to chronic inflammation. Moreover, various risk factors contribute to the perpetuation of this inflammatory state, including advancing age leading to the accumulation of free radicals, obesity amplifying proinflammatory cytokines, diets rich in saturated fats and refined sugars, smoking, sleep disorders, and stress.^{4,6} Each of these factors has the potential to induce and sustain low-level chronic inflammation, thereby subjecting the body, including the eyes, to significant physiological stress.⁴ These factors, in addition to age-related changes, can induce inflammation not only on the corneal surface, but also in the conjunctiva, lacrimal gland, and meibomian glands.⁷ The collective effect of this inflammation disrupts the balance of the tear film, ultimately leading to a loss of homeostasis and resulting in inflamed dry eyes.⁵

An elevation in tear film osmolarity prompts a direct response from the corneal epithelial cells, initiating the release of matrix metalloproteinases. These enzymes play a pivotal role in kickstarting the inflammatory cascade by inducing the release of inflammatory mediators, such as chemokines, interleukins, and tumor necrosis factor. These mediators attract inflammatory cells, including dendritic

cells, monocytes, and macrophages. This cascade further activates sensory nerves, intensifying sensations of burning and irritation commonly reported by patients with dry eyes.⁸

The released cytokines and inflammatory cells, in turn, activate the adaptive immune response by triggering various T-cells, which release additional proinflammatory cytokines, perpetuating the inflammatory process. In cases of chronic inflammation, this cascade takes a toll on corneal and conjunctival epithelial cells, inhibiting goblet cells and resulting in an even greater imbalance in the tear film, which then exacerbates the inflammatory cascade, creating the vicious cycle of dry eye disease.⁶⁻⁸

TREATMENT

Antiinflammatory therapies include corticosteroids (prednisolone, fluorometholone, dexamethasone, and loteprednol), immunomodulators (lifitegrast and various iterations of cyclosporine), and oral tetracyclines (doxycycline). Recently, we've also had substantial success using perfluorohexyloctane ophthalmic solution (Miebo, Bausch + Lomb) to help prevent inflammation from reoccurring. If a patient presents with

significant inflammation, we will use a corticosteroid for 2 to 4 weeks and then prescribe perfluorohexyloctane to help avoid the desiccation stress of the ocular surface, which will result in tissue damage and lead to inflammation.

Yet another new treatment that has allowed us to reduce ocular surface inflammation is lotilaner ophthalmic solution 0.25% (Xdemvy, Tarsus Pharmaceuticals), which reduces the *Demodex* mite load found in *Demodex* blepharitis.^{9,10} Ocular *Demodex* infestation has been found to cause various ocular surface diseases. This chronic inflammatory disease is caused by an infestation of *Demodex* mites, which affects the lid margin and ocular surface in up to 70% of the worldwide population. *Demodex* mite infestation can also lead to dryness.^{11,12}

We have also successfully used the OTC drop polyvinyl alcohol and povidone (Freshkote, Harrow) in-clinic to mitigate and alleviate inflammation.¹³ Another new entrant into the dry eye space is a product that we, along with other dry eye specialists, created called the Dry Eye Drink (Bruder). This proprietary, sugar-free drink mixture contains electrolytes, antiinflammatory ingredients (green tea extract, turmeric, taurine, and DHA omega-3 from algae), and vitamins designed explicitly for the ocular surface. In much the same way, ingesting the various omega-3 supplements available on the market has also yielded a substantial reduction in our patients' ocular surface inflammation.

LOOKING AHEAD

The dry eye space has seen substantial innovation in the past year, and we can look forward to more in the coming years to help treat ocular surface inflammation. A development we are excited about is AZR-MD-001 0.5% (Azura Ophthalmics), which is a selenium sulfide (keratolytic) ophthalmic ointment. It aims to reduce the

AT A GLANCE

- Chronic inflammation is considered the greatest threat to human health and affects every organ, including the eyes and the ocular surface.
- Various risk factors contribute to the perpetuation of this inflammatory state, which subjects the body to significant physiological stress and can induce inflammation on the corneal surface and in the conjunctiva, lacrimal gland, and meibomian glands.
- Cases of chronic inflammation take a toll on corneal and conjunctival epithelial cells, inhibiting goblet cells and resulting in an even greater imbalance in the tear film, which then exacerbates the inflammatory cascade, creating the vicious cycle of dry eye disease.

hyperkeratinization of the meibomian glands by breaking down the bonds between abnormal keratin, which softens the meibomian gland blockage, therefore allowing the patient's own meibum to protect the ocular surface from the stress that typically causes inflammation.¹⁴

A drop making headlines is novel, small-molecule drug candidate topical ocular reproxalap 0.25% (Aldeyra Therapeutics), which is specifically designed to reduce ocular inflammation in dry eye disease by inhibiting reactive aldehyde species, which are elevated in various inflammatory diseases, notably dry eye and allergic conjunctivitis.^{15,16} In November, it was announced that Aldeyra had entered into an exclusive option agreement with AbbVie for the license to develop and commercialize the drug. Later that month, Aldeyra received a complete response letter from the FDA stating that an additional trial is required to demonstrate a positive effect on ocular symptoms of

dry eye, thus pushing the possible arrival of this drop until 2025 at the earliest.

BE PROACTIVE, NOT REACTIVE

As we spend more time in front of electronic devices, and as our diets include more proinflammatory foods, inflammatory-based dry eye will continue to plague our patient base. This is where we come in, to offer effective patient education and management for the best long-term results. ■

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