Dry-eye disease is well-recognized as a complex, chronic disease that needs chronic therapy. Superimposed on the intricate landscape of oxidative processes, immunological priming, autoimmunity and inflammatory responses are bouts of acute distress brought on by a constellation of extrinsic and intrinsic factors. Dry-eye-associated discomfort typically waxes and wanes, based on behavior and environment, as well as diurnal and seasonal biorhythms. Dry-eye subjects also use behavioral modification to optimize comfort and visual function. Nevertheless, a few times a year, dry-eye subjects can fall off the wagon: an extended stay in the sauna; cleaning the attic; painting the house; an airplane trip; or hiking, skating or mountain biking on a dry, windy day. This is reckless behavior for a dry-eye subject who, like a Flying Wallenda, has to climb gingerly back up on the high wire after falling off.

Non-environmental factors can also bring about an acute attack of dry eye. We need to ask questions: Did the patient have a recent bout of the flu, a gastrointestinal virus, a fever or episodes of vomiting that may have led to dehydration? Alternatively, is the patient experiencing the onset of menopause, which may have exacerbated a previously milder type disease? The introduction of new medications, such as an antihistamine, or a new antidepressant or antihypertensive therapy may also be responsible for acute worsening of dry eye. These acute episodes require not only stepping up the maintenance therapy, but also additional pulses of more robust therapeutic options to bring the patient back from the precipice. This month we’ll speak to the acute versus chronic presentations of dry eye and discuss how to recognize and treat them, as well as how to educate the patient in recognizing and pre-empting the downward cycle of ocular surface discomfort and damage.

Clinical Presentation

When a dry-eye patient presents with an abrupt worsening of her disease, what she’s feeling is acute, severe discomfort. Innate protective blink mechanisms are overwhelmed by these acute challenges, and normal blink patterns are therefore altered, resulting in compromised visual function that is perceptible to the patient. To the clinician, the eyes are very red, with prominent horizontal vessels in the interpalpebral fissure as well as under the lid. These are signs that the discomfort is not only environmental, but also endogenous in origin. There is occasionally scleritis, and there is profuse rose bengal and fluorescein staining.

What has occurred is acute damage juxtaposed on the baseline chronic inflammatory state of dry eye. The body responds to this damage with a wound-healing process that is remarkably the same in all tissues: mounting of an inflammatory response; clearing away of the dead cells and tissues; and gradual mitotic renewal of the epithelial surface. This reparative process is impaired in the dry-eye patient due to a dysfunctional tear film in which the balance of tear constituents such as mucins and lipids is disrupted, a situation that can prolong the reparative process and delay the biological cleanup to the point that it lasts weeks in the dry-eye patient instead of hours or days as in a normal subject.
Most research in the past decade on dry-eye disease points to inflammatory processes at its origin. Even if we limit our discussion to non-systemic, non-Sjögren’s activation of dry eye, local inflammation plays a significant role. As with all inflammation, there are chronic and acute pathways that converge and diverge with different signals, but all must begin with an initiating, immunologically priming event. The most challenging aspect of dry-eye research has been to pull apart these threads and try to identify which cell or pathway may be the initial instigating player. By the time the patient is bothered enough to go to the doctor, his or her clinical dry-eye disease is usually in its chronic stages and the continuous cycles of tear film instability are causing mounting inflammation. However, in the case of a dry-eye attack or exacerbation, the clinician has a chance to observe the disease in its acute, early stage. Understanding what happens at the inception of dry eye can give us greater insight on how best to manage acute exacerbations of the disease.

**Initial Steps in Acute Cases**

One of the earliest players in dry-eye disease is interleukin 17 (IL-17), found in a subset of T cells called CD4+ T cells because they express the CD4 glycoprotein on their surface. CD4+ T cells mature along four distinct paths determined by the pattern of signals they receive during antigen presentation; these are defined as Th1, Th2, Th17 and regulatory T or Treg cells. This nomenclature is based on the primary cytokine secreted by each cell population: Th1 cells secrete interferon-gamma (IFN-γ); Th2 cells secrete interleukin-4, IL-5 and IL-13; and Th17 cells secrete IL-17. CD4+ T cells are responsible for surveillance of the ocular surface for infectious or noxious stimuli and, in systemic disease, are most notorious for their role in the pathophysiology of HIV infection, many neoplasms and autoimmune diseases such as diabetes. IL-13 and Treg are the good guys of this family because of their anti-inflammatory activity and the latter cells’ essential role in immune tolerance, both of which are dysfunctional in dry-eye disease.

Several mouse models of CD4+ T cell biology have been key to understanding the role of these cells in the induction of dry eye. In one of these, mice were kept in an adverse desiccating environment for 14 hours, and then watched for the next four months under normal environmental conditions. Their dry-eye disease peaked at 14 days, and then slowly improved. However, even after 126 days, the corneal staining never returned to normal, demonstrating that chronic inflammation continued even months after the initial 14-day exposure trigger. In this study the acute phase of dry-eye disease was characterized by predominance of interferon-gamma (IFN-γ) and IL-17. After the adverse exposure had ceased, only IL-17 remained elevated. This IL-17 response was associated with lymphangiogenesis, or the growth of lymph vessels in and around the cornea, a key event to priming the region for more antigen presenting cells and a richer immune response. Even more suggestive, when naïve mice receive Th17 cells, isolated from chronic dry-eye animals they developed disease much more quickly, peaking at day six versus day 14; their symptoms were also more severe than normal mice. If instead, T cells from mice in the acute phase were transferred, only slightly more severe disease was seen compared to normals. In both cornea and conjunctiva, chronic dry-eye mice were found to have the highest quantity of effector memory T cells, which contain twice the amount of IL-17 as in other T cells. What these fascinating experiments tell us is that the acute phase of dry eye is a function of both IL-17 and IFN-γ-containing Th1 cells and Th17 cells but that, in the chronic phase, Th17 cells predominate, propagating and priming the reaction by revving up lymphangiogenesis. These effector memory T cells are called this exactly because they are the immune system’s permanent memory of a particular disease response, the
results. These include lacrimal and meibomian glands, goblet cells, the cornea and conjunctiva the lids, and the sensory and motor nerves that communicate among all of these elements. A breakdown in any of these will lead to altered rheological properties and hyperosmolarity of tears, decreased corneal sensitivity and alterations in blink, and imperfectly anchored or dissolved mucins, all of which culminate in either aqueous-deficient or evaporative dry-eye disease.13

Second Step: How to Treat

First, it’s possible that an evaporative dry-eye patient who changes his medication regimen can present with aqueous-deficient dry eye. Conversely, a classic case of aqueous deficiency may be complicated by the onset of meibomian gland dysfunction. If the patient is only on tear supplementation, stepping up tear production with continuous Restasis therapy (cyclosporine emulsion 0.05%) is certainly advisable, coupled with adding an ointment at night such as Systane Ultra Nighttime Ointment (Alcon), and perhaps changing the tear substitute to a more viscous, retentive gel such as GenTeal Gel, Systane Ultra (Alcon) or Refresh Celluvisc (Allergan). However, addition of a single pulse of steroid therapy for squelching these acute inflammatory episodes of dry eye might be the single best indication for steroid therapy for this disease. The discrete nature of these episodes, brought on by an identified intrinsic or extrinsic source, allows for an appropriate use of a drug that we all know to not use indiscriminately. Of course, if the exacerbated dry eye is due to a medication change, alternatives should be discussed with the patient and decided upon in collaboration with the patient and his primary-care physician.

Corticosteroids and Dry Eye

Corticosteroids mediate their anti-inflammatory effects primarily through modulation of the cytosolic glucocorticoid receptor at the genomic level.14 In the eye, we have fluorometholone, prednisolone acetate and dexamethasone to choose from, as well as the newer additions such as loteprednol etabonate. Different from conventional synthetic corticosteroids, loteprednol etabonate 0.5% suspension is designed as a site-active corticosteroid that undergoes relatively rapid metabolism to inactive metabolite, thus improving its safety profile relative to traditional steroids.15

Studies have investigated various topical steroids in dry eye.16-19 Loteprednol was first investigated versus placebo in 64 patients with four weeks of treatment. While primary endpoints were not met, in the subset of patients with at least moderate clinical inflammation there was significant improvement with loteprednol.14

A more recent trial evaluated the effect of the addition of loteprednol two weeks prior to initiation of cyclosporine treatment. In 118 patients, loteprednol was found to provide a more rapid relief of dry-eye signs and symptoms, with greater efficacy than cyclosporine or artifi-
cial tears alone. In a Korean study, 32 patients with moderate to severe dry eye were treated for eight weeks with 1% methylprednisolone q.i.d. in addition to artificial tears. Corneal and conjunctival staining and tear-film breakup time were significantly improved from baseline, tear osmolality decreased, and IL-1, IL-8 and monocyte chemo-attractant protein-1 were all significantly decreased at eight weeks compared to baseline. Thus, short-term steroid treatment was shown to improve all signs of dry eye in tandem with a lowering of tear

In another study of 100 patients, the difference between preserved and non-preserved therapies was assessed using active therapies and tear supplementation. Half of the patients were treated with preservative-free sodium hyaluronate and 0.1% fluorometholone eye drops in the first month, continuing with the tears and Restasis for the second and third months. The other 50 patients were treated with identical preserved therapies. Researchers found that non-preserved therapies were more effective than their preserved counterparts in improving the following: symptoms; TFBUT; Schirmer’s I scores; impression cytology; IL-1β; IL-6; IL-12; and TNF-α. Non-preserved therapies also increased tears’ antioxidant contents. The authors speculate that benzalkonium chloride from the active and tear therapies causes significant oxidative/inflammatory damage that exacerbates dry-eye disease. While this study did not have a no-steroid arm, it was clear that all signs, symptoms and markers improved with treatment compared to baseline.

In mouse models, various non-steroidal, anti-inflammatory drugs, corticosteroids and doxycycline were evaluated in a botulinum toxin B-induced mouse model of dry eye. While tear substitutes did not improve any sign of dry eye, fluorometholone, nepafenac and doxycycline all significantly improved corneal staining within two weeks. Topical ketorolac, diclofenac and bromfenac were less effective and slower to show any effect. Aqueous tear production started to return to baseline within two weeks, although not significantly; however, all other groups still had reduced tear production even as far out as four weeks. In a similar animal model, only topical fluorometholone was shown to improve tear production and signs, and NSAIDs were ineffective.

Dexamethasone was investigated preclinically in a rabbit model of dry eye involving lacrimal gland inflammation initiated by injection of the T cell mitogen, concanavalin A (ConA) followed by exposure to an adverse-environment chamber. This mitogen induces lymphocytic infiltration, necrosis and fibroplasia of lacrimal glands. Clinical manifestations of reduced TFBUT, tear clearance and corneal staining were all inhibited by topical pre-treatment with dexamethasone 0.1% q.i.d. Post-exposure therapeutic efficacy was also shown when dexamethasone was administered two days following injection of ConA.

The anti-inflammatory properties of dexamethasone and other synthetic glucocorticoids are not the only properties that can profoundly affect the status of dry-eye disease. Dexamethasone in particular is known to modify a wide variety of immune functions by promoting a tolerogenic immune response. It has been shown to alter the phenotype and function of dendritic cells, attenuating their priming responses. In a groundbreaking study, dexamethasone was used as an adjuvant to peptide antigens to induce expansion of antigen specific CD4+ Fox3+ T regs, the “good-guy” regulatory T cells that dampen immune responses through heightened tolerogenesis. Myeloid-derived suppressor cells also suppress T cell proliferation and function while promoting the good T regs. All of these immune-modifying properties of dexamethasone can benefit the dry-eye patient, not only by inhibiting the inflammation that has already occurred as a result of the initiated immunological priming, but also by preventing those initiating immune responses from recurring by rendering actively primed cells antigen-tolerant.

Exploring different formulations of corticosteroids, or different platforms for their delivery, might be the ideal choice for treating acute episodes of dry-eye disease without worrying about steroid abuse or toxic effects with chronic use. One exciting new prospect in ophthalmic steroid development is the resorbable polyethylene glycol-based hydrogel punctal plug depot delivery system (Ocular Therapeutics). Inserted non-invasively through the inferior punctum, the plug resides within the canaliculus, delivering a four-week release of the corticosteroid to the ocular surface. The hydrogel is conjugated with fluorescein to provide confirmation of the product’s presence. This delivery system for dexamethasone contains approximately 0.4 mg active drug and is designed to provide a sustained and tapered release of therapeutic levels for up to 30 days. Over time, and through hydrolysis, the depot-drug softens, liquefies and is cleared through the nasolacrimal duct. A product such as this could be inserted at the time of the visit, providing the dry-eye patient with one month of complete coverage, allowing for ideal treatment compliance in a discrete period, while eliminating potential washout of the supplemental tear substitute and/or other active therapy such as Restasis. This drug-eluting plug is already entering Phase III clinical trials for postoperative inflammation, and has shown significant clinical efficacy compared with placebo, with

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pigment epithelium, which are often subtle and self-resolving. Visual field testing often demonstrates scotomas that correlate with retinal findings or an enlarged blind spot, and fluorescein angiography demonstrates early punctate hyperfluorescence in a wreath-like pattern and late staining of the white dots.\(^3,4\) Fundus autofluorescence has been proven to be a valuable tool in highlighting RPE changes, even in the absence of clear white dots on fundus examination.\(^5\) The exact pathophysiology of the pigmentary alterations remains unknown, although recent reports speculate that photoreceptor loss, as demonstrated on SD-OCT, may unmask the underlying RPE autofluorescence.\(^5,6\)

The cause of MEWDS is not entirely clear, although it is theorized to be preceded by a viral illness such as influenza in the majority of cases. It has also been reported in association with influenza, hepatitis B and hepatitis C vaccinations.\(^7,8,9\) The clinical course of MEWDS is self-limited and resolves in a majority of cases without any need for treatment. However, scotomata, photopsias and dyschromatopsia may persist.\(^3,4\) \textbf{REVIEW}


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100-percent retention through day 14, and 97 percent through day 30. In this study, no long-term spikes in IOP were encountered, and the placebo subjects were prescribed significantly more rescue medication (\textit{ocucom.com/ pipeline/dexamethasone- punctum-plug}). This concept might be ideal for a dry-eye drug treating a spike of acute inflammation for several reasons: A constant, slow release of the active drug ensures effective concentrations; the choice of a local steroid allows for anti-inflammatory and anti-immune effects, altering the course of future localized autoimmune responses to noxious stimuli; and the unique pharmacokinetics improve the safety profile of the corticosteroid.

To conclude, IL-1- and IL-17-rich CD4+ T cells appear to be at the origin of the immune response brought on by an acute environmental challenge; however, IL-17 T cells then sustain the memory of the disease long after the acute environmental onslaught has finished. Choosing a steroid like dexamethasone during these acute overays of dry eye might benefit the patient not only in the short term by quenching the inflammatory reaction, but also might dampen responses to future environmental exposures, promoting a non-pathological response to adverse stimuli. We look forward to more studies into this fascinating area of dry-eye research and hope to be able to use key pieces of this new information to better the treatment and lives of our patients. \textbf{REVIEW}

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17. Sheppard JD, Donnfeldt ED, Holland EJ et al. Effect of loteprednol etabonate 0.5% on initiation of dry eye treatment with topical cyclosporine 0.05%. Eye & Contact Lens 2014;40:289-296.

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