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## Dry Eye: an Inflammatory Ocular Disease

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### Abstract

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Keratoconjunctivitis sicca, or dry eye, is a common ocular disease prompting millions of individuals to seek ophthalmological care. Regardless of the underlying etiology, dry eye has been shown to be associated with abnormalities in the pre-corneal tear film and subsequent inflammatory changes in the entire ocular surface including the adnexa, conjunctiva and cornea. Since the recognition of the role of inflammation in dry eye, a number of novel treatments have been investigated designed to inhibit various inflammatory pathways. Current medications that are used, including cyclosporine A, corticosteroids, tacrolimus, tetracycline derivatives and autologous serum, have been effective for management of dry eye and lead to measurable clinical improvement.

**Keywords:** Keratoconjunctivitis Sicca, Sjögren’s Syndrome, Dry Eye, Inflammation, Treatment

### OVERVIEW

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Although often disregarded as a minor problem, keratoconjunctivitis sicca, commonly referred to as dry eye, is a growing public health concern affecting as many as 17% of women and 11.1% of men in the United States.<sup>1</sup> This is likely an underestimate if one also considers self-treating patients and milder/periodic cases with intermittent symptomatology.

A recent international Dry Eye Workshop (DEWS) defined dry eye as 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 which is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.”<sup>2</sup> Identification of inflammation as a major factor in dry eye helped make a tremendous step forward in the description and treatment of this condition.

The DEWS also recognized two subgroups of dry eye based on etiopathogenesis: aqueous deficient and evaporative. Among the aqueous deficient group, there are two major subclasses: Sjögren’s syndrome (SS) dry eye and non-SS dry eye. Diagnosis of SS is generally made based on the American-European Consensus Group 2002 revised classification criteria, requiring at least four out of six criteria, or three out of the four objective criteria, to be present. The six criteria include: subjective and objective ocular

dryness; subjective and objective oral dryness; presence of Sjögren-specific antibody A (SSA)/Ro and/or Sjögren-specific antibody B (SSB)/La; and positive minor salivary gland biopsy.<sup>3</sup> However, in 2012, a new classification criteria for SS was endorsed by The American College of Rheumatology that requires at least 2 of the following 3 criteria: 1) positive serum anti-SSA and/or anti-SSB or rheumatoid factor or antinuclear antibody (titer >1:320), 2) total ocular surface staining score >3, and 3) presence of focal lymphocytic sialadenitis with a focus score >1/4 mm<sup>2</sup> in labial salivary gland biopsy samples.<sup>4</sup>

According to the classification criteria from the European-American collaboration, secondary SS (sSS) consists of features of primary SS (pSS) together with features of an overt autoimmune connective tissue disease, the most common of which is rheumatoid arthritis. There is a well-known association of several systemic diseases with dry eye syndrome such as SS, rheumatoid arthritis, scleroderma, polymyositis, lymphoma, amyloidosis, hemochromatosis, sarcoidosis, and systemic lupus erythematosus.<sup>5</sup> Although the rate of dry eye in various inflammatory diseases is known, the frequency of associated systemic rheumatic conditions in patients with dry eye is currently unknown. A previous retrospective study from a single tertiary eye care center determined that pSS is underdiagnosed and should be the focus of diagnostic evaluations in individuals with clinically significant aqueous deficient dry eye. Only 33.3% of patients with pSS carried the diagnosis at the time of presentation and 50% were diagnosed as a result of the initial evaluation.<sup>6</sup> A more recent multicenter prospective study confirmed these findings in a group of more than 300 patients with clinically significant dry eye and found the rate of SS to be 11.6%.<sup>7</sup> The difference in the rate of SS between these two studies could perhaps be attributed to the fact that the prospective study was limited in regards to the diagnostic tests performed: minor salivary gland biopsy or tests for objective dry mouth findings were not utilized. Nonetheless, both studies concluded that ophthalmologists managing patients with clinically significant dry eye should have a high index of suspicion for underlying SS and a low threshold for diagnostic work-up.

Previously unrecognized autoimmune thyroid disease has also been shown to be a cause of inflammatory ocular surface disease with dry eye symptomatology and should be considered when evaluating patients with dry eye. A retrospective, observational case series of 539 patients referred for dry eye evaluation has confirmed this correlation; of the 32 patients who underwent standardized orbital echography with a clinical suspicion, 21 (66%) were diagnosed with occult thyroid eye disease.<sup>8</sup>

On the other hand, based on multiple epidemiological studies, older age and female sex are widely recognized as the two most common risk factors for dry eye.<sup>9,10</sup> Peri- and postmenopausal females seem to be particularly at a higher risk. This perhaps suggests that dry eye is an involuntal disorder. In addition, hormonal studies demonstrate that sex hormones influence ocular surface conditions through their effects on aqueous tear secretion, meibomian gland function, and conjunctival goblet cell density.<sup>11,12</sup> Thus, an altered hormonal state (e.g., following menopause) may be blamed to cause dry eye. Several other external factors are also known to precipitate and exacerbate dry eye, such as long-term contact lens wear, refractive laser surgery, smoking, and extended visual tasks like computer use, watching television and prolonged reading.<sup>13-15</sup> Worsening of dry eye may also be attributed to low relative humidity conditions that are common in office environments, air-conditioned cars, airplane cabins, and extreme hot or cold weather.<sup>16</sup> Dry eye may be caused by systemic medications with anticholinergic effects (e.g. antihistamines, antidepressants, antipsychotics) as well as diuretics.<sup>17</sup> Frequent instillation (>4-6 times daily) of preserved eye drops, particularly with benzalkonium chloride for example for glaucoma, may also contribute to dry eye because of their well-established ocular surface toxicity.<sup>17</sup>

Irrespective of the presence of any identifiable underlying local or systemic inflammatory disorder, dry eye seems to be invariably associated with chronic inflammation of the ocular surface, as detailed below, although it is not known whether the local inflammation is causative or simply occurs as a

consequence of ocular dryness. Nevertheless, recognition of the role of inflammation in dry eye has been a crucial factor in facilitating dry eye treatment.

## **PATHOPHYSIOLOGY**

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There is growing evidence from the past decade indicating that dry eye-related ocular surface inflammation is mediated by lymphocytes.<sup>18</sup> Based on earlier immuno-histopathological evaluations, patients with both SS-related as well as non-SS dry eye have identical conjunctival inflammation manifested by T cell infiltrates and upregulation of CD3, CD4, and CD8 as well as lymphocyte activation markers CD11a and HLA-DR.<sup>19</sup> These results suggested that clinical symptoms of dry eye may be dependent on T-cell activation and resultant autoimmune inflammation. Multiple other studies followed and demonstrated the role of pro-inflammatory cytokines and matrix metalloproteinases (MMPs) in the pathogenesis of dry eye. Interleukin (IL)-1 is one of the most widely studied cytokines accompanying dry eye. An increase in the pro-inflammatory forms of IL-1 (IL-1 $\alpha$  and mature IL-1 $\beta$ ) and a decrease in the biologically inactive precursor IL-1 $\beta$  have been found in the tear film of dry eye patients.<sup>20</sup> The source of increased levels of IL-1 was thought to be the conjunctival epithelium based on immunohistochemical studies.<sup>20</sup> More recently, reactive nitrogen species expressed by conjunctival epithelium have been recognized in the pathogenesis or self-propagation of SS-related dry eye.<sup>21</sup> In the same study, IL-1 $\beta$ , IL-6, IL-8 and tumor necrosis factor (TNF)  $\alpha$  were also investigated and found to play a significant role in SS-related dry eye as compared to normal eyes.

The response of cells to extracellular stimuli such as ocular surface stress, including changes in the composition of tear film or hyperosmolarity and ultraviolet light exposure, is mediated in part by a number of intracellular kinase and phosphatase enzymes.<sup>22</sup> Mitogen-activated protein (MAP) kinases are integral components of parallel MAP kinase cascades activated in response to a number of cellular stresses including inflammatory cytokines (e.g. IL-1 and TNF- $\alpha$ ), heat shock protein, bacterial endotoxin and ischemia. Activation of these MAP kinase homologues mediates the transduction of extracellular signals to the nucleus and is pivotal in regulation of the transcription events that determine functional outcomes in response to such stresses. These stress-activated protein kinases have been identified in the tear film of patients with dry eye. It has been documented that activation of these stress pathways results in transcription of stress-related genes, including MMPs, mainly MMP-9.<sup>23</sup> In another study, MAP kinases were found to stimulate the production of inflammatory cytokines including IL- $\beta$ , TNF- $\alpha$ , and MMP-9 and thereby cause ocular surface damage.<sup>24</sup>

As previously mentioned, hyperosmolarity is one of the factors contributing to ocular surface inflammation. Hyperosmolarity induces inflammation in human limbal epithelial cells by increasing expression and production of pro-inflammatory cytokines and chemokines such as IL-1 $\beta$ , TNF- $\alpha$ , and the C-X-C chemokine IL-8.<sup>25</sup> This process appears to be mediated through activation of the c-Jun N-terminal kinases and MAPK signaling pathways.

All of these inflammatory mediators and pathways should not only be considered important as they relate to the pathogenesis of dry eye; they should also be kept in mind when discussing treatment strategies.

## **TREATMENT**

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As it is widely recognized that inflammation has a significant role in the etiopathogenesis of dry eye, promoting ocular surface disruption and symptoms of irritation, a number of anti-inflammatory treatments are currently in use for its management. Many more anti-inflammatory medications are in development or clinical trial phases. These agents inhibit the expression of inflammatory mediators on the ocular surface, thereby restoring the secretion of a healthy tear film and reducing signs and symptoms.

## Cyclosporine A

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The immunomodulating effects of cyclosporine A are achieved through binding with cyclophilins, which are a group of proteins. Cyclophilin A which is found in the cytosol, and the cyclosporin e-cyclophilin A complex inhibits a calcium/calmodulin-dependent phosphatase, calcineurin, the inhibition of which is thought to halt the production of the transcription of T-cell activation by inhibiting IL-2.<sup>26</sup> Cyclophilin D is located in the matrix of mitochondria. Cyclosporine A-cyclophilin D complex modulates the mitochondrial permeability transition pore thereby inducing mitochondrial dysfunction and cell death.<sup>27</sup> The reduction in inflammation, via inhibition of T-cell activation and down-regulation of inflammatory cytokines in the conjunctiva and lacrimal gland,<sup>28,29</sup> is thus thought to enhance tear production.<sup>30-32</sup> Topical cyclosporine also increases goblet cell density and decreases epithelial cell apoptosis.<sup>33</sup> Commercially available topical cyclosporine 0.05% (Restasis, Allergan, Irvine, CA, USA) or 1% compounded preparations are frequently utilized for treatment of various inflammatory ocular surface disorders.<sup>34</sup> Dosing topical cyclosporine at a frequency greater than twice a day may be more effective for patients who do not demonstrate improvement of severe dry eye disease with the twice-daily regimen.<sup>8,35</sup>

## Tacrolimus

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This topical anti-inflammatory agent (previously known as FK506) is a macrolide antibiotic isolated from *Streptomyces tsukubaensis* fermentation.<sup>36</sup> Although the mechanism of action of tacrolimus is similar to cyclosporine A, its potency in vitro has been shown to be significantly greater, exhibiting similar effects at 100 times lower concentrations.<sup>37</sup> Only when bound to immunophilin does it become biologically active, thus effectively inhibiting calcineurin, and inhibiting T and B lymphocyte activation via reduction in IL-2 synthesis.<sup>38-44</sup> Tacrolimus suppresses the immune response by inhibiting the release of other inflammatory cytokines as well (e.g., IL-3, IL-4, IL-5, IL-8, interferon-gamma, and TNF-alpha).<sup>45-48</sup> Systemic tacrolimus has been reported to be effective for improving dry eye associated with graft versus host disease; however, there are potential adverse reactions to be aware of when administering long-term systemic therapy.<sup>49</sup> Topical tacrolimus, available as 0.03% and 0.1% ointments as well as compounded eye drops, is promising for the treatment of dry eye in the setting of chronic graft versus host disease and SS.<sup>50-52</sup>

## Corticosteroids

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Topical steroids, through several mechanisms of action, help reduce ocular inflammation. Corticosteroids function via suppression of cellular infiltration, capillary dilation, proliferation of fibroblasts, and collagen deposition. They stabilize intracellular and extracellular membranes. Corticosteroids increase the synthesis of lipocortins that block phospholipase A2 and inhibit histamine synthesis in mast cells.<sup>53</sup> Inhibition of phospholipase A2, an essential step in the inflammatory cascade, prevents the conversion of phospholipids to arachidonic acid. Corticosteroids also interfere with transcription factor NF-kB, which regulates the synthesis of a number of pro-inflammatory molecules, thereby stimulating lymphocyte apoptosis. Corticosteroids mediate their anti-inflammatory effects primarily through modulation of the cytosolic glucocorticoid receptor at the genomic level.<sup>54,55</sup> After corticosteroids bind to the glucocorticoid receptor in the cytoplasm, the activated corticosteroid-glucocorticoid receptor complex migrates to the nucleus, where it up-regulates the expression of anti-inflammatory proteins and represses the expression of pro-inflammatory proteins. However, recent work suggests that the activated corticosteroid-glucocorticoid receptor complex also elicits non-genomic effects, such as inhibition of vasodilation, vascular permeability and migration of leukocytes.<sup>54,56</sup>

Several clinical studies have demonstrated the effectiveness of topical steroids for treatment of dry eye. In a retrospective clinical series, topical administration of a 1% solution of non-preserved methylprednisolone, given three or four times daily for several weeks to patients with SS related dry eye, provided moderate to complete relief of symptoms in all patients.<sup>57</sup> In addition, there was a decrease in corneal fluorescein staining score ( $2.6 \pm 0.5$  on a 12-point scale) and complete resolution of filamentary keratitis. This therapy was effective even for patients suffering from severe dry eye who had no improvement from maximum aqueous tear enhancement/replacement therapies.

A pilot study on 64 patients was conducted evaluating the efficacy of loteprednol etabonate (LE) 0.5% ophthalmic suspension 4 times a day versus placebo for treatment of the inflammatory component of dry eye associated with aqueous tear deficiency and delayed tear clearance.<sup>58</sup> After 2 weeks of therapy in the subset of patients with moderate to severe clinical inflammation, a significant difference was observed between LE-treated group and vehicle-treated group in central corneal staining, nasal bulbar conjunctival hyperemia, and lid margin injection. None of the patients experienced a clinically significant increase in intraocular pressure following one month of therapy. Patients treated with topical corticosteroids should be monitored closely for known risks of cataract formation, glaucoma, corneal thinning and infectious keratitis.<sup>59</sup>

## Tetracycline Derivatives

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Tetracycline derivatives uniquely possess antibacterial as well as anti-inflammatory properties. Doxycycline has been shown to inhibit c-Jun N-terminal kinase and extracellular signal-related kinase mitogen-activated protein kinase signaling in epithelial cells of the ocular surface exposed to hyperosmolar stress, down-regulating the expression of CXCL8 and pro-inflammatory cytokines IL-1 $\beta$  and TNF.<sup>60</sup> Doxycycline inhibits MMP-9 activity and supports ocular surface integrity.<sup>61,62</sup> Additionally studies demonstrated that minocycline inhibits the expression of cell-associated pro-inflammatory molecules, including major histocompatibility complex class II.<sup>63</sup> Doxycycline has been reported to be effective in patients with ocular rosacea by reducing irritation symptoms, improving tear film stability, and decreasing the severity of ocular surface disease.<sup>64-66</sup> In addition, doxycycline has been useful in the treatment of corneal erosions.<sup>67,68</sup>

## Autologous Serum

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Serum contains several anti-inflammatory factors that have the capability to inhibit soluble mediators of the ocular surface inflammatory cascade associated with dry eye. These include inhibitors of inflammatory cytokines (e.g., IL-1 RA and soluble TNF-receptors) and MMP inhibitors (e.g., TIMPs).<sup>69-71</sup> Clinical trials have shown that autologous serum drops improve ocular irritation symptoms, and conjunctival and corneal dye staining in dry eye that occurs in the setting of SS.<sup>72-74</sup> Conversely, there is greater risk of microbial growth as autologous serum drops, in addition to antimicrobial agents, contain high protein content and are generally non-preserved.<sup>75</sup>

Recent studies have investigated cord serum drops (prepared from donor umbilical cord serum) as well as allogenic serum drops (from a related donor). A clinical trial included 17 patients with GVHD- and 13 patients with SS-associated dry eye treated for 1 month with cord blood serum. Patients received cord blood once a day (containing 0.15 ng epithelial growth factor per drop). Patients reported a decrease in discomfort symptoms as measured with the Ocular Surface Disease Index score (OSDI) ( $22.3 \pm 10.3$  vs.  $39.3 \pm 16.9$ ). Also clinical findings such as impression cytology score ( $3.8 \pm 1.2$  vs.  $6.6 \pm 2.1$ ), tear osmolarity ( $312.5 \pm 7$  vs.  $322 \pm 9.1$  mOsm/L), and corneal sensation (measured with Cochet-Bonnet esthesiometer) ( $48.2 \pm 2.1$  vs.  $49.7 \pm 2.1$  nylon/mm/length) improved significantly.<sup>76</sup> Another study involving 12 patients with chronic GVHD-associated severe dry eye treated with cord blood serum for a period of 6 months reported statistically significant improvement ( $P < 0.01$ ) in

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