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REVIEW

Managing Sjögren's Syndrome and non-Sjögren Syndrome dry eye with anti-inflammatory therapy

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Abstract: Dry eye from Sjögren's syndrome is a multifactorial disease that results in dysfunction of the lacrimal functional unit. Studies have shown changes in tear composition, including inflammatory cytokines, chemokines, and metalloproteinase. T-lymphocytes have been shown to increase in the conjunctiva and lacrimal glands in patient and animal models. This inflammation is in part responsible for the pathogenesis of the disease, which results in symptoms of eye irritation, ocular surface epithelial disease, and loss of corneal barrier function. There are a number of anti-inflammatory approaches for treating this disease. The current study reviews details of immune response and anti–inflammatory therapies used to control this disease.

Keywords: keratoconjunctivitis sicca, SS, cyclosporin A, steroids, dry eye, Sjögren's Syndrome

Introduction

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disorder that primarily affects exocrine glands such as salivary and lacrimal glands (LG). These glands show significant infiltration of lymphocytes that result in the destruction of the gland with variable degrees of acinar loss and fibrosis. Histologically, the infiltrating cells are a mix of T-cells, B-cells, dendritic, and natural killer cells.[1] These cells have been shown to have a strong predilection for females and an increased prevalence around the fourth to fifth decades of life.[2]

The pathogenesis of SS is not completely understood. It is unclear what triggers lead to glandular impairment and destruction, so the question remains: does lymphocytic infiltration precede or follow the glandular insult? Conflicting results in animal models have kept the "chicken or the egg" question unresolved.[3,4] Increased type I interferon signature in the LG and submandibular salivary glands of SS models suggest a strong response due to glandular apoptosis and toll-like receptor activation.[5,6] Some studies have postulated that infections with Epstein-Barr, Cocksakie B, cytomegalovirus, and other viruses could be an initiating event for autoimmunity. These hypotheses are based on findings that showed high antibody titers against viral infections in patients with SS compared to normal controls.[7] Acinar apoptosis and production of autoantibodies such as anti-muscarinic 3 receptor, anti-SSA, and anti-SSB are frequent events.[2,8,9]

Increased lymphocytic infiltration leads to secondary B-cell activation and generation of autoantibodies both in situ (salivary and LG) and in lymphoid organs.[9] Although infrequent, 5%–10% of SS patients will develop B-cell lymphoma, demonstrating that clonal activation of B-cells favors the development of malignancies over time.[10] The risk of developing non–Hodgkin's lymphoma, which is equivalent in both primary and secondary SS patients, has been estimated to be 44 times greater than that observed in a comparable normal population.[11]

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Diagnosis of SS was based on criteria established by the American and European Consensus Group for SS. The clinical presentation of SS can present alone as a primary condition (primary SS) or can be associated with other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis (secondary SS).[12] Classification of SS involves positive answers to questions regarding ocular symptoms such as persistent dry eye, scratchy sensation, and use of artificial tears, as well as oral symptoms such as dry mouth, swollen salivary glands, and use of liquids to aid in swallowing. Objective criteria include clinical tests for ocular signs such as decreased amount of tears by Schirmer's test, increased vital dye staining and tear break-up time, and salivary gland dysfunction as shown by decreased salivary flow, parotid sialography showing presence of diffuse sialectasias, and salivary scintigraphy showing delayed uptake. Histopathology of the salivary glands showing lymphocytic infiltration and acinar loss and presence of autoantibodies were used as diagnostic tools. Secondary SS was identified at the moment when the presence of these signs and symptoms was associated with other well-defined connective tissue diseases.[13]

Dry eye affects subjects with and without SS and it is a frequent cause of patients seeking eye care in the US. Patients with SS often have a moderate to severe aqueous-deficient form of dry eye as a result of a destructive autoimmune response in the lacrimal gland. A cohort of 1,200 subjects, showed that 85% (1,020) reported dry eye-related symptoms and 920 of them had at least one of the following criteria associated with SS: a positive biopsy of minor salivary glands with a focus score >1, an abnormal ocular surface score ≥ 3, a positive serologic result for anti-SS A or B antibodies, or a combination thereof. In this cohort, 28% (228) had all three characteristics and 28% (228) had only dry eye signs and symptoms. It was also observed that only SS patients had the highest ocular surface score compared to non SS subjects.[14]

Clinically, autoimmune dry eye (either SS or non-SS) is a multifaceted disease characterized by eye irritation, blurred and fluctuating vision, tear film instability, increased tear osmolarity, and ocular surface epithelial disease.[15–18] By decreasing functional vision, dry eye disease have a major impact on quality of life, affecting the ability to perform simple daily activities such as reading, using a computer, or driving a vehicle.[19] Symptoms can vary daily and from patient to patient, often experienced as an exacerbation of symptoms when subjected to drafty and/or low humidity environmental conditions such as airplane cabins and air-conditioned spaces. Symptom variability presents a challenging clinical problem while attempting to accurately identify dry eye syndrome.

Studies in the past 20 years suggest that dry eye is an autoimmune inflammatory disease.[20–26] Changes in tear composition such as hyperosmolarity caused by dysfunction of the tear secretory glands can stimulate the production of inflammatory mediators on the ocular surface.[20] In turn, inflammation causes dysfunction or loss of cells responsible for tear secretion and retention.[21] Inflammation can also be initiated by chronic irritation such as contact lenses and systemic inflammatory/autoimmune diseases such as rheumatoid arthritis. Regardless of the initiating cause, an uncontrolled cycle of inflammation can develop on the ocular surface of the dry eye and lead to ocular surface disease. Because clinical management of different types of dry eye disease involves anti-inflammatory therapy, the current study will focus on ocular therapeutic approaches based on the fact that it is often used as an adjunct to systemic management.

Pathogenesis of dry eye disease

Understanding of the pathology of dry eye disease has significantly improved over the last decade. Although not completely understood, the discovery of molecular and cellular processes responsible for dry eye have revealed that dry eye is the result of inflammation. There are many cellular and molecular processes involved in the pathogenesis of dry eye, including increased inflammatory cytokines, tear film osmolarity, metalloproteinases, chemokines and their receptors, inflammatory cascades, and activation of immune cells.

Increased inflammatory cytokines

Increased production and activation of pro-inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α have been reported in dry eye.[22–24] Increased concentrations of pro-inflammatory cytokines and chemokines in the tear fluid, such as IL-6, IL-1, and TNF-α have been extensively reported.[21,25–32] Significantly, increased levels of IL-1α, IL-6, IL-8, TNF-α, and transforming growth factor (TGF)-β1 RNA transcripts have been found in the conjunctival epithelium of SS patients compared to controls.[26] However, the exact role of these cytokines in the occurrence of dry eye disease has not been fully elucidated. Substantial evidence from animal and patient models suggests that the T helper associated cytokines interferon-gamma (IFN)-γ and IL-17 are of significant importance in the pathogenesis of dry eye while IL-13 might have a protective role.

IFN-γ

IFN-γ has been shown to be involved in goblet cell loss and epithelial apoptosis. It has been proposed as a biomarker for dry eye disease and SS, since elevated levels have been observed in protein and/or RNA in tears, saliva, conjunctiva, submandibular glands, blood,[31,33–39] conjunctiva,[39–42] saliva,[43,44] lacrimal,[4,45–50] submandibular glands,[37,45,51–53] and blood.[54,55]

IL-17

IL-17 has been shown to play a role in corneal barrier disruption and stimulation of matrix metalloproteinase (MMP)-3 and -9 in murine models.[56,57] Increased levels of IL-17 were detected in tears and increased levels of IL-17, IL-23, and IL-6 were found in the saliva and salivary gland biopsies of patients with the severe autoimmune dry eye condition associated with Sjögren syndrome.[58–60]

IL-13

IL-13 promotes goblet cell proliferation and antagonizes the effect of IFN-γ. IL-13 has been detected in human tears and found to decrease with severity of disease.[34,61–63] In one study, there was no change in tear IL-13 concentration in patients with tear dysfunction with and without meibomian gland disease.[34]

Teary film osmolarity

For decades the gold standard for the diagnosis of dry eye has been recognized to be hyperosmolarity of the tear fluid.[64] It is generally accepted that dry eye patients often present with teary film hyperosmolarity. Hyperosmolarity has also been shown to be a pro-inflammatory stimulus[65,66] that triggers events involving activation of mitogen-activated protein kinases and nuclear factor-κB (NF-κB), thereby leading to the production of inflammatory cytokines and metallopro-teinases.[20,67,68] Human corneal epithelial cell cultures with media of increasing sodium chloride concentrations result in a concentration-dependent increase in the production of pro-inflammatory factors detected in the conjunctival epithelium and tear fluid of dry eye patients such as IL-1, IL-8, TNF-α, and MMP-9.[20,67,69,70]

Increased metalloproteinases

Increased concentration and activity of MMPs in the tear fluid of dry eye patients has often been observed.[27,71,72] MMPs such as MMP-9 are enzymes that lyse substrates that are components of the corneal epithelial basement membrane and tight junction proteins such as ZO-1 and occludin that maintain a corneal epithelial barrier function.[73,74] Tear MMP-9 activity levels increase with severity of corneal disease and have also been positively correlated with corneal fluorescein staining test scores and low contrast visual acuity.[75]

Increased MMP-9 activity in dogs' keratoconjunctivitis sicca (KCS) has been associated with inoperative corneal epithelial barrier function (increased fluorescein permeability), increased corneal epithelial desquamation (punctate epithelial erosions), and corneal surface irregularities.[20,73,74] The US Food and Drug Administration (FDA) recently approved a rapid in-office test for diagnosis of dry eye disease called InflammaDry® (Rapid Pathogen Screening, Inc, Sarasota, FL, USA) that detects MMP-9.

Chemokines and chemokine receptors

Chemokines are small molecules that direct cells to specific tissues. They are very important for inflammatory response since they amplify the cascade by recruiting additional inflammatory cells. The expression of CXCL9, -10, -11, and CXCR3, which are involved in the recruitment of $CD4^+$ Th1 cells, is increased in the tear film and ocular surface of patients with dry eye syndrome, especially in those with SS.[76] There is also evidence from animal models that CCL20, the ligand binding CCR6 expression on Th17 cells, is also involved in the pathogenesis of dry eye.[77,78] CXCL13, a B-cell attractant, has been found to be elevated in murine submandibular gland and LG in humans.[79] Antibody blockade of the chemokine itself or pathway blockade improved salivary and tear flow, as well as decreased B-cell infiltration while improving ocular surface integrity.[79–81]

Inflammatory cascade and HLA-DR

Soluble and cellular inflammatory mediators were increased in the tear fluid, conjunctiva, and LG of dry eye patients. A hallmark of inflammatory cascade is expression of HLA-DR and ICAM-1. Increased expression of HLA-DR and ICAM-1 has been reported in the conjunctival epithelium of patients with dry eye disease such as ocular rosacea non-SS aqueous tear deficiency, however, the highest expression of HLA-DR was found in SS patients.[82–84] Based on detection of increased HLA-DR antigen expression by the conjunctival epithelium, it has been suggested that increased HLA-DR is a universal feature of dry eye syndrome.[82,85,86]

$CD4^+$ T-cells

SS is characterized by dry eyes, dry mouth, vasculitis, and neurologic disease. The principal manifestation of SS is dryness, which results from exocrine gland dysfunction.

Exocrine tissues, including the lacrimal gland, are heavily infiltrated with lymphocytes and monocytes.[87] Increased T-cell infiltration of the conjunctiva has been observed in both SS and non-SS KCS.[88,89]

Animal models have contributed to an increase in the body of evidence that $CD4^+$ T-cells are involved in the pathogenesis of dry eye. In several animal models, increased infiltration of $CD4^+$ T-cells in the goblet cell rich area was accompanied by increased expression of IFN-γ, IL-17, goblet cells loss, and conjunctival metaplasia.[31] This inflammation of the lacrimal glands, cornea, and conjunctiva resulted in decreased tear production and conjunctival goblet cell loss. As a confirmation of the role of $CD4^+$ T-cells in pathogenesis, adoptive transfer of pathogenic T-cells from wild type mice subjected to experimental dry eye to T-cell-deficient nude mice that had not been exposed to desiccating stress resulted in increased dry eye disease parameters such as goblet cell loss, increase in inflammatory cytokines, and increased corneal permeability.[21] Using a similar approach, $CD4^+$ T-cells adoptively transferred from animals deficient in the *autoimmune regulator* (*AIRE*) gene to immunodeficient recipient mice caused advanced ocular surface keratinization.[90]

Oxidative stress

Oxidative stress, whether the result of chronic inflammation or external sources, is thought to play a role in the pathogenesis of autoimmune diseases, resulting in apoptotic cell death and loss of immunological tolerance. Patients with rheumatoid arthritis, systemic lupus erythematosus, and SS have increased oxidative stress levels.[91–93] Several inducers, including ultraviolet-B radiation and chemical oxidants can induce the expression of antigens such as SSA/Ro-52, which can be instigating factors for antigen presentation of autoimmune antigens to T-cells at early stages of SS pathogenesis.[94,95]

Treatments for the management of dry eye

Artificial tears

A common therapy for dry eye has been the use of artificial tears. These provide temporary relief of symptoms in most cases. There are several artificial tear products on the market with different compound formulations, but all contain similar ingredients such as water, lubricants, and electrolytes. Artificial tears can control symptoms in patients with mild disease but offer only temporary relief. Different lubricants used in the formulation of artificial tears vary in their viscosity and level of hydration. More viscous solutions offer longer relief but cause blurred vision and discomfort. Many products contain preservatives such as benzalkonium chloride, sodium perborate, and sodium chlorate that can cause damage to the ocular surface. In severe cases where administration is needed four times a day or more, preservative-free artificial tears are needed to limit preservative toxicity.[65]

Punctal plugs

Punctal plugs are devices inserted into tear ducts to block drainage and increase the tear film. Insertion of punctal plugs has provided relief for patients suffering from mild severity of dry eye. However, with increased understanding of the pathogenesis of dry eye, punctual plugs can worsen long-term symptoms since without drainage, the tear film becomes saturated with inflammatory cytokines and matrix metalloproteinases.

Anti-inflammatory therapies for dry eye

Clinical studies have shown that anti-inflammatory therapies that inhibit the inflammatory mediators reduce the symptoms of dry eye syndrome. The remainder of this review will focus on anti-inflammatory therapies in general, since anti-inflammatory management of dry eye benefits both SS and non-SS forms.

Essential fatty acids

Omega-6 linolenic acid and omega-3 α-linolenic acid are important essential polyunsaturated fatty acids. Omega-6 fatty acids are eicosanoid precursors for arachidonic acid and certain pro-inflammatory lipid mediators such as prostaglandin E2 (PGE_2) and leukotriene B4 (LTB4). By contrast, some omega-3 fatty acids such as eicosapentaenoic acid (EPA) found in fish oil inhibit synthesis of these lipid mediators and block production of IL-1 and TNF-α.[96,97] The effect of fish oil omega-3 fatty acids on rheumatoid arthritis has been shown to be beneficial in several double-masked, placebo-controlled clinical trials.[98,99] A prospective placebo-controlled clinical trial of essential linoleic and gamma-linoleic fatty acids administered orally twice daily showed significant improvement in ocular irritation symptoms[100] and ocular surface lissamine green staining,[101] as well as an increase in tear secretion.[102] Recent randomized controlled trials using omega-3 fatty acids have shown benefits with conditions marked by blepharitis and meibomian gland disease.[103,104] Resolvin E1, a metabolite of the omega-3 polyunsaturated fatty acid EPA has been shown effective in murine chronic inflammation models and has completed Phase II clinical trials.[105,106]

Autologous serum drops

Autologous serum drops are another anti-inflammatory therapy used in the treatment of dry eye and other ocular surface diseases. Drops are prepared from the patient's own serum and then further diluted in saline. The serum contains high concentrations of essential tear components that have been shown to stabilize tear film and improve ocular surface disease.[107–110] Autologous sera contain several key components of the tear film such as epidermal growth factor, fibronectin, neurotrophic growth factor, vitamin A, and lysozyme.[111] There are no serious side effects with this treatment; however, challenges in using autologous serum drops such as frequent drawing of blood, preservation of sterility, and appropriated facilities willing to prepare them prevent the broad use of this anti-inflammatory therapy. At least two clinical trials have shown that autologous serum drops are more effective than artificial tears.[110,112]

Secretagogues

Secretagogues are a class of drugs that increase mucin secretion, improve tear film stability, and decrease ocular surface inflammation. Diquafosol tetrasodium, a mucin secretagogue, is a $P2Y_2$ receptor agonist that induces non-glandular secretion of mucin and water by activation of chloride channels.[113] A topical formulation has recently been approved for treatment of dry eye in Japan. Another drug, cevimeline, which has been used to treat dry mouth in SS, activates muscarinic M3 receptors. Patients in a randomized prospective double-blind trial to evaluate the efficacy of cevimeline showed improvements in disease as assessed by Schirmer testing, increased rose bengal fluorescein staining, and tear break-up time.[114,115] Systemic cevimeline treatment has been associated with abdominal pain, headache, nausea, dizziness, cardiac arrhythmia, and sweating. Another cholinergic agonist, pilocarpine, was approved for oral treatment of dry mouth in 1994, and a few clinical trials showed its efficacy in treating dry eye symptoms. However, it is not widely used in clinical settings. Its most common side effect is excessive sweating and cramps.[116,117]

Corticosteroids

Corticosteroids are potent anti-inflammatory drugs that can be used to control inflammation. Corticosteroids act directly via glucocorticoid receptor mediated pathways to regulate gene expression. These drugs also act in receptor-independent pathways to interfere with transcriptional regulators of pro-inflammatory genes such as NF-kB. The effect of these pathways leads to limitation of inflammatory cytokine and chemokine production, decreases in the synthesis of matrix metalloproteinases and prostaglandins, and decreased expression of cell adhesion molecules such as ICAM-1.[118–123] Treatment of corneal epithelium with corticosteroids leads to a decrease in the production of a number of inflammatory cytokines such as IL-1, IL-6, IL-8, TNF-α, GM-CSF (granulocyte-macrophage colony-stimulating factor), and MMP-9.[124]

Corticosteroid treatment for corneal epithelial disease in dry eye has been shown successful in several clinical studies.[125–127] Corticosteroid therapy proved effective even in patients suffering with severe dry eye who did not see improvements from maximum aqueous enhancement therapies. In a prospective randomized clinical trial, topical treatment of dry eye patients with non-preserved methylprednisolone and punctal plugs significantly decreased the severity of ocular irritation symptoms and corneal fluorescein staining compared to the group that received punctual occlusion alone.[128] In another double-masked, placebo-controlled, randomized study of loteprednol etabonate ophthalmic suspension, patients with the most severe inflammatory signs were treated topically with loteprednol. These patients had a significant decrease in central corneal fluorescein staining scores compared to vehicle controls. There is a current Phase IV, randomized, parallel group, investigator-masked evaluation (ClinicalTrial.gov identifier NCT02028312) of the effect of loteprednol etabonate ophthalmic gel 0.5% in combination with cyclosporine A (CsA). In addition, an open-label randomized study showed that patients with KCS who had received fluorometholone in addition to artificial tear substitutes experienced lower symptom severity scores according to fluorescein and rose bengal staining compared to patients receiving artificial tear substitute alone or artificial tear substitute with flurbiprofen.[129] Short-term use of concomitant topical corticosteroid and cyclosporine has been shown to reduce symptoms of stinging, and has improved compliance in the use of cyclosporine drops.[130,131]

These studies showed that topical corticosteroids are a valuable tool in the management of dry eye. No steroid related complications were observed in short-term clinical trials; however, there is a potential for toxicity with long-term use that could result in increased intraocular pressure and development of cataracts. This limits the use of more potent steroids for the treatment of chronic dry eye. Soft steroids such as fluorometholone and loteprednol etabonate have fewer risks since there is a lower likelihood of increasing intraocular pressure. Corticosteroids can be of significant benefit to patients with secondary SS.

Tetracyclines and derivatives

Tetracyclines have both anti-inflammatory and antibacterial properties. This makes them useful in the management of chronic inflammatory diseases. Tetracyclines are potent inhibitors of collagenase, phospholipase A2, and several matrix metalloproteinases. Treatment also results in a decrease in the production of IL-1α and TNF-α in a wide range of tissues, including the corneal epithelium.[70,132,133]

Tetracyclines are commonly used to treat rosacea.[134–137] Rosacea, which has ocular manifestations, is an inflammatory disorder occurring mainly in middle-aged adults and is characterized by vasomotor instability (flushing) of the face, neck, and upper chest. Chronic facial inflammation can lead to persistent facial erythema and telangiectasia formation, as well as permanent deformity of the face. The tetracycline derivatives minocycline and doxycycline are common treatment options for chronic blepharitis. These are useful because of their high concentration in tissues, low renal clearance, long half-life, high level of binding to serum proteins, and decreased risk of photosensitization.[138]

Doxycycline was discovered about 50 years ago as a semi-synthetic long-acting tetracycline derivative useful as a bacterial ribosome inhibitor in a wide variety of microbes. It is also an effective primary treatment for rosacea, sterile corneal ulceration, and effective adjunctive treatment for adult periodontitis in sub-antimicrobial doses.[139–141] Doxycycline effectively inhibits MMP-9 in a wide variety of mouse and human cells, including prostate epithelium, epidermal keratinocytes, and the aortic endothelium.[142–145]

Based on positive results of several small clinical trials of patients with meibomianitis,[137,146] the American Academy of Ophthalmology recommends the chronic use of either doxycycline or tetracycline for the management of meibomianitis.[147] Beneficial effects have been observed with the use of minocycline and other tetracycline derivatives such as doxycycline in the treatment of chronic blepharitis.[139,148–150] Significant changes in the aqueous tear parameters such as tear volume and flow have been observed following treatment with tetracycline derivatives such as minocycline.[151]

Cyclosporine

Cyclosporin A (CsA) is a lipophilic cyclic undecapeptide isolated from the fungus *Hypocladium inflatum gams.*[152] CsA is a potent immunosuppressant drug that was first used in the early 1980s to prevent organ rejection after transplant. Since then, CsA has been used in the treatment of inflammatory diseases such as psoriasis, rheumatoid arthritis, ulcerative colitis, and others. The main action of CsA is its ability to lower the inflammatory response and activation of T-cells. CsA binds calcineurin, thereby inhibiting its action and preventing the transcription of IL-2, which leads to inhibition of T-cell activation.[153,154] CsA was first used in the late 1980s to treat dry eye disease in dogs that developed spontaneous KCS.[155] Since then, the therapeutic efficacy of CsA in the treatment of human KCS has been widely investigated in several small single-center randomized double-masked clinical trials and several large multicenter, randomized, double-masked clinical trials.[156–158] To date, more than 50 clinical trials have investigated the efficacy of CsA.

The first two independent Phase III clinical trials compared twice daily treatment with 0.05% and 0.1% CsA or vehicle in 877 patients with moderate to severe dry eye disease.[158,159] Results of the trials were combined for statistical analysis. Results showed that patients treated with CsA 0.05% and 0.1% showed a statistically significant ($P \leq 0.05$) improvement in two objective signs of dry eye disease, corneal fluorescein staining and anesthetized Schirmer test values, than those treated with vehicle. Increased Schirmer test score results were observed in 59% of patients treated with CsA and 15% had an increase of ≥10 mm. By contrast, only 4% of vehicle-treated patients had this magnitude of change in their Schirmer test scores ($P < 0.0001$). Treatment with CsA 0.05% also produced significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease: blurred vision symptoms, need for concomitant artificial tears, and global response to treatment. No dose-response effect was noted. CSA treatment showed no significant systemic or ocular adverse events except for transient burning symptoms after instillation in 17% of patients; burning was reported in 7% of patients receiving the vehicle. Patients treated with CsA also showed improvements in other disease parameters. For example, an approximate 200% increase in conjunctival goblet cell density was observed.[160] Furthermore, there was decreased expression of immune activation marker HLA–DR, apoptosis markers, and inflammatory cytokine IL-6 by the conjunctival epithelial cells.[161,162] The overall numbers of T-lymphocytes in the conjunctiva decreased in the cyclosporine-treated eyes while vehicle-treated eyes showed an increased number of T-cells.[160] Based on these results, the FDA approved CsA 0.05% ophthalmic emulsion for treatment of dry eye disease in 2002.

Other immune regulatory agents

Clinical trials of other immune mediators have shown promise. In several studies, inhibition of interleukin-1 significantly reduced symptoms in dry eye patients.[163,164] Another

study showed that using the integrin antagonist SAR 1118 improved symptoms of dry eye compared to placebo.[165] Other studies that limited T-cell function have also shown promise such as how tofacitinib interferes with Janus kinase signaling of STAT1.[166]

Anti-inflammatory therapy in mice: lessons from animal models

The use of animal models has greatly increased understanding of the pathogenesis of SS and dry eye disease. The similarities in the anatomic structure of human and mouse eyes greatly outweigh the differences. Similarly, the immune systems of both human and mice share more similarities than disparities, which make mice invaluable in the study of immune responses of SS and dry eye. Extensive use of an experimental dry eye model induced by environmental stress and lacrimal gland blockade has provided a considerable volume of evidence supporting the presence of inflammation and autoimmunity in the pathogenesis of dry eye. Mice experienced goblet cell loss and corneal barrier disruption that mimics human disease.[31,167,168] Results show the following: increased expression of inflammatory cytokines IL-1α, IL-6, and TNF-α transcripts in the corneal epithelium and conjunctiva; increased concentrations of MIP-1α (CCL3), MIP-1β (CCL4), in IFN–γ, IL-17A, CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (ITAC), and CCL20 in the corneal epithelium and conjunctiva.[56,77,78,169,170]

Studies using the experimental dry eye model have laid the groundwork for exploring and understanding the mechanisms of many anti-inflammatory therapies. It was first demonstrated that doxycycline was efficacious in decreasing gelatinolytic activity in the ocular surface epithelia, decreasing levels of MMP-9 mRNA transcripts, and preventing experimental dry eye-induced increase in inflammatory cytokines IL-1 and TNF-α.[74] Doxycycline also improved corneal surface regularity and improved corneal barrier function[168] as well as preserving apical epithelial cell area and the tight-junction protein occludin, resulting in a decreased number of desquamating epithelial cells from the surface of the cornea.[168,171] These findings were also confirmed in cultured human corneal epithelial cells treated with doxycycline subjected to osmotic stress that increased their production of MMP-9.[73]

Corticosteroids such as methylprednisolone were observed to preserve corneal epithelial smoothness and barrier function in an experimental murine model of dry eye.[168] This was attributed to corticosteroid ability to maintain the integrity of corneal epithelial tight junctions and decrease desquamation of apical corneal epithelial cells.[168] It was also demonstrated that methylprednisolone prevented an increase in MMP-9 protein in the corneal epithelium as well as gelatinase activity in the corneal epithelium in response to experimental dry eye.[74]

In animal model compounds that inhibit leukocyte migration into the ocular surface tissues such as integrin α4β1 integrin-chemokine receptor 2 (CCR2), or that used other topical therapies such as topical epigallocatechin-3 gallate or alpha-linolenic acid, significantly decreased corneal fluorescein staining compared to both vehicle and untreated control groups. In addition, results showed decreases in CD11b (+) cell numbers, as well as decreased expression of corneal IL-1α, TNF-α, and conjunctival TNF-α.[172–176] Other studies have shown that blocking T-cell migration to the ocular surface can be a viable therapeutic option.[77,78] Natural killer (NK) cells also a play a role in pathogenesis of dry eye. Compounds that neutralize NK cells may also offer therapeutic possibilities.[41,177]

Animal models have been instrumental in the development of cyclosporine A as a therapeutic agent. In mouse models, cyclosporine A has been shown to increase the density of goblet cells while decreasing apoptosis of the corneal epithelium, and preventing desiccating stress-induced increase of IL-17A and IFN-γ while reducing the number of $CD4^+$ T-cells infiltrating the conjunctiva. It also retained the intra-epithelial lymphocyte population in the same area.[178–181]

Animal studies have shown that therapies that directly or indirectly block T helper cytokines IL-17A and IFN-γ may be useful. Blocking the actions of the cytokines has been shown efficacious in murine dry eye models and shown great promise for future human studies.[56,57,182,183] Potent inhibitors of these molecules could be valuable therapeutic tools.

Conclusion

SS and non–SS dry eye are chronic diseases that can significantly affect quality of life. There are many options for treatment on the market; however, after a decade, cyclosporine A is the only approved drug specifically designed to treat inflammation in dry eye syndromes. As our understanding of the pathogenesis of dry eye increases, we hope that this newfound knowledge will translate into the design of drugs that specifically target immune pathways.

Disclosure

The authors report no conflicts of interest in this work.

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