Review Article

# Dry Eye: an Inflammatory Ocular Disease

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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

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## OVERVIEW

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.[1] 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."[2] 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.[3] 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 $mm^2$ in labial salivary gland biopsy samples.[4]

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.[5] 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.[6] 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%.[7] 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.[8]

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.[9,10] Peri- and postmenopausal females seem to be particularly at a higher risk. This perhaps suggests that dry eye is an involutional 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.[11,12] 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.[13–15] 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.[16] Dry eye may be caused by systemic medications with anticholinergic effects (e.g. antihistamines, antidepressants, antipsychotics) as well as diuretics.[17] 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.[17]

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

There is growing evidence from the past decade indicating that dry eye-related ocular surface inflammation is mediated by lymphocytes.[18] 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.[19] 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-1α and mature IL-1β) and a decrease in the biologically inactive precursor IL-1β have been found in the tear film of dry eye patients.[20] The source of increased levels of IL-1 was thought to be the conjunctival epithelium based on immunohistochemical studies.[20] More recently, reactive nitrogen species expressed by conjunctival epithelium have been recognized in the pathogenesis or self-propagation of SS-related dry eye.[21] In the same study, IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF) α 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.[22] 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.[23] In another study, MAP kinases were found to stimulate the production of inflammatory cytokines including IL-β, TNF-α, and MMP-9 and thereby cause ocular surface damage.[24]

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-1β, TNF-α, and the C-X-C chemokine IL-8.[25] 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

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

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 cyclosporine-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.[26] 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.[27] The reduction in inflammation, via inhibition of T-cell activation and down-regulation of inflammatory cytokines in the conjunctiva and lacrimal gland,[28,29] is thus thought to enhance tear production.[30–32] Topical cyclosporine also increases goblet cell density and decreases epithelial cell apoptosis.[33] 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.[34] 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.[8,35]

**Tacrolimus**

This topical anti-inflammatory agent (previously known as FK506) is a macrolide antibiotic isolated from *Streptomyces tsukubaensis* fermentation.[36] 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.[37] 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.[38–44] 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).[45–48] 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.[49] 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.[50–52]

**Corticosteroids**

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 $A_2$ and inhibit histamine synthesis in mast cells.[53] Inhibition of phospholipase $A_2$, 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.[54,55] 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.[54,56]

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.[57] In addition, there was a decrease in corneal fluorescein staining score (2.6±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.[58]

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.[59]

**Tetracycline Derivatives**

Tetracycline derivatives uniquely possess antibacterial as well as anti-inflammatory properties. Doxycyline 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-1β and TNF.[60] Doxycyline inhibits MMP-9 activity and supports ocular surface integrity.[61,62] Additionally studies demonstrated that minocycline inhibits the expression of cell-associated pro-inflammatory molecules, including major histocompatibility complex class II.[63] 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.[64–66] In addition, doxycycline has been useful in the treatment of corneal erosions.[67,68]

**Autologous Serum**

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).[69–71] 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.[72–74] 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.[75]

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±10.3 vs. 39.3±16.9). Also clinical findings such as impression cytology score (3.8±1.2 vs. 6.6±2.1), tear osmolarity (312.5±7 vs. 322±9.1 mOsm/L), and corneal sensation (measured with Cochet-Bonnet esthesiometer) (48.2±2.1 vs. 49.7±2.1 nylon/mm/length) improved significantly.[76] 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 symptom score (on a scale of 0-4, from 3.83±0.38 to 0.83±0.57), corneal sensitivity (from 52.08±6.06 mm to 57.50±3.00 mm), tear breakup time (BUT) (from 2.50±0.91 to 5.71±1.04 seconds), and corneal fluorescein staining (from 7.42±2.02 to 1.29±0.46).[77] Also shown to be effective are allogenic serum drops, prepared using blood from a family member rather than the patient's own blood. Allogeneic serum tears were used for the treatment of dry eye in patients with GVHD. After 4 weeks of continuous use, significant improvement was noted in symptom scores (as measured by OSDI Score from 32.5 to 8.9), tear osmolarity (from 311.1 to 285.1 m osmol), corneal staining (from 2.5 to 1.8) as well as increased goblet cell density (from 90.6 to 122.6 cell/mm$^2$) and tear BUT (from 2.9 to 4.4 seconds).[78]

**IL-Ra**

Interleukin-1 receptor antagonist (IL-1Ra) is an endogenous IL-1 receptor blocker primarily

produced by activated monocytes and tissue macrophages which inhibits the activities of the pro-inflammatory forms of IL-1 (IL-1α and IL-1β) by competitively binding to the IL-1 receptor-I.[79] In a murine model with environmentally induced dry eye, a significant decrease in corneal fluorescein staining was observed with slit lamp biomicroscopy after topical treatment with 3 microliters of IL-Ra applied 3 times daily for 9 days. Comparison treatments, 1% methylprednisolone and 0.05% cyclosporine A, were equally effective in this model.[80] Additionally, confocal microscopy revealed a significant decrease in the number of central corneal CD11b+ cells, lymphatic growth and interleukin-1β expression after treatment with 5% IL-1Ra and 1% methylprednisolone, but not with cyclosporine A. This suggests that IL-1Ra is comparable to topical methylprednisolone in reducing inflammation and improving clinical signs of dry eye.

**Resolvin E1 (Rx-10001)**

Resolvin E1 (RvE1) is a new class of endogenous immune response mediators derived from the lipoxygenation of the essential dietary omega-3 polyunsaturated fatty acids, eicosapentaenoic acid, and docosahexaenoic acid.[81] In animal models, treatment applied 4 times per day for one week, using topical 100μg/mL (0.01%) omega-3 derivatives has been shown to reverse corneal epithelial damage associated with dry eye. A specialized corneal tomography module (Rostock Cornea Module of the Heidelberg Retina Tomograph) was used to study the corneas in vivo. Increased tear flow promoting a healthy epithelium, decreased cyclooxygenase-2 expression by Western Blot Analysis, and decreased macrophage infiltration were also noted.[82] In a murine model of dry eye it was shown that RvE1, delivered topically at 300μg/ml concentration 4 times a day, improved corneal staining and goblet cell density.[83] The synthetic analog of RvE1 (RX-10045) is being tested in a Phase II clinical trial for treatment of chronic dry eye. Preliminary data of a 28-day, randomized, placebo-controlled, 232-patient trial showed dose-dependent and statistically significant improvement using RX-10045;[84] however, final data have not been published.

**Chemokine Receptor Antagonist**

Monocyte chemotactic protein 1 is secreted by monocytes, memory T cells, macrophages, fibroblasts, endothelial cells and mast cells. It stimulates the movement of leukocytes along a chemotactic gradient after binding to its cell surface receptor chemokine receptor antagonist.[85] The critical role of the coupled monocyte chemotactic protein 1/chemokine receptor antagonist in inflammation has been demonstrated using monocyte chemotactic protein 1 and chemokine receptor antagonist knockout mice, suggesting that inhibition of migration of chemokine receptor antagonist-bearing mononuclear cells may be an effective mechanism to modulate disease progression in chronic inflammation.[86] A study of dry eye disease in a murine model, which received topical chemokine receptor antagonist (5.0 mg/ml) twice daily for 7 days, showed a significant decrease in corneal fluorescein staining. Real-time polymerase chain reaction revealed decreased infiltration of corneal CD11b(+) cells and conjunctival T cells compared with vehicle treated and untreated dry eye groups.[87] The chemokine receptor antagonist also significantly decreased messenger RNA expression levels of IL1-alpha and 1-beta in the cornea, and TNF-alpha and IL1-beta in the conjunctiva.

**Tofacitinib (CP-690,550)**

Tofacitinib (CP-690,550) is a selective inhibitor of the janus kinase (JAK). Janus kinase signaling is essential for immune cell activation, pro-inflammatory cytokine production and cytokine signaling.[88] Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular selectivity for JAK1 and JAK3 over JAK2.[89] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common γ chain containing receptors for several cytokines, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as

IL-6 and interferon-γ. Tofacitinib subsequently modulates adaptive and innate immunity with limited effect on hematopoiesis.[90]

In Phase I/II trials, topical tofacitinib (CP-690,550) at a concentration of 0.0003%-0.005% was used in 327 patients with clinically significant aqueous deficient dry eye for a period of 8 weeks. A trend for improving both signs (Schirmer's test without anesthesia and corneal fluorescein staining) and symptoms of dry eye, with a reasonable safety profile was noted.[91] In addition, a sub-study of Phase I/II trials showed a reduction in inflammation assessed by change from baseline in conjunctival cell surface expression of human leukocyte antigen DR-1 studied by flow cytometry and tear levels of several cytokines and inflammation markers by microsphere-based immunoassays.[92]

### SAR 1118 (LFA-1 antagonist)

SAR 1118, a novel investigational small-molecule lymphocyte function-associated antigen-1 antagonist, was engineered for topical ophthalmic delivery.[93,94] The binding of lymphocyte function-associated antigen-1 on the surface of T cells to intercellular adhesion molecule-1 on endothelial, epithelial, and antigen presenting cells is a critical step in T-cell activation (normal immune response and inflammation). Thus, it has been proposed that blockade of lymphocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction may give a therapeutic benefit in patients with dry eye, breaking the chronic cycle of T-cell mediated inflammation and thus aiding in the recovery of the ocular surface. SAR 1118 is an effective inhibitor of T-cell activation, adhesion, migration, proliferation and cytokine release.[93] A multicenter, prospective, double-masked, placebo-controlled trial included 230 dry-eye subjects randomized to receive SAR 1118 (0.1, 1.0, 5.0%) or placebo eye drops twice daily for 84 days. SAR 1118 showed dose-dependent and statistically significant improvement in corneal staining scores, symptoms measured with OSDI (both total ocular surface disease index and visual related function questions) as compared to placebo. Improvements in tear production and symptoms were noted as early as day 14. It was well tolerated and no serious ocular adverse events were reported.[94] Several Phase III trials are underway and results are yet to be published.

### Mapracorat

Mapracorat (formerly ZK-245186 and subsequently BOL-303242-X) is a novel selective glucocorticoid receptor agonist currently under investigation for its anti-inflammatory effects as it pertains to dry eye. The anti-inflammatory effects of mapracorat were assessed in an in vitro osmotic stress model which simulates some of the pathophysiological changes seen in dry eye.[95] Incubation of cells with mapracorat 0.1-1.0% applied 3 times a day for 7-8 days inhibited hyperosmolar-induced cytokine release with comparable activity and potency as a commonly used steroid, dexamethasone. In addition, another study observed mapracorat to be effective in maintaining tear volume and tear break-up time with no increase in intraocular pressure in a rabbit model.[96]

## SUMMARY

Regardless of whether or not an underlying systemic inflammatory condition can be identified, dry eye seems to be associated with chronic and sometimes subclinical inflammation that might eventually cause ocular surface damage. Novel treatments targeting specific mediators in inflammatory reactions known to be associated with dry eye are currently evolving.

### Conflicts of Interest

This study was supported in part by Jerome L. Greene Discovery Fund. Dr. Akpek has received institutional research grants from Alcon and Allergan Inc. as well as National Institutes of Health (ID#: 107364) in the past 2 years. Dr. Akpek has received ad hoc consultant income from Bausch & Lomb.

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