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Ocular Surface Inflammation and its Treatment in Different Types of Dry Eye Disease

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Abstract

Dry eye is a common disease that affects tens of millions of people worldwide and can negatively influence the quality-of-life inducing anxiety and depression and decrease visual function in most severe cases. The management of dry eye disease involves addressing the underlying causes because it is not caused solely by an inadequate quantity or quality of the tear film, but it is an alteration of the ocular surface system that involves the activation of para-inflammatory and inflammatory factors. Various treatment options are available, and the choice of therapy depends on the severity of the condition and individual patient need. In this review we analyze the key inflammatory pathogenic factors playing a role in causing dry eye disease, the role of topical anti-inflammatory agents in improving symptoms and clinical signs, and a rational approach based on a new classification of patients with dry eye.

Keywords: Dry Eye; Anti Inflammatory; Steroids

Abbreviations: DED: Dry Eye Disease; APC: Antigen Presenting Cells; PGE3: prostaglandin E3; Leukotriene B5 (LTB5).

Introduction

Dry eye disease (DED) is a prevalent and often uncomfortable condition that can significantly impact an individual's quality of life. The management of DED involves addressing the underlying causes because it is not caused solely by an alteration of the tear film composition, but by a disruption of the homeostasis of the ocular surface system [1]. Various treatment options are available, and the choice of therapy depends on the severity of the condition regarding the level of ocular surface inflammation [2]. Treatment with tear substitutes has been demonstrated to improve symptoms and signs of dry eye and improving the stability of the tear film, but in cases of moderate to severe DED it can be considered palliative in that it does not address the immuno-inflammatory process which affects the ocular surface system [3]. In fact, under physiological conditions, multiple components of the ocular surface such as cornea, conjunctiva, lacrimal glands, tear film, endocrine, immune, and nervous system cooperate to preserve local health and to react to an external stimulus bringing back a condition of homeostasis. However, after continuous stimulation, a loss of adaptation of the ocular surface can reduce the threshold for sensory terminations and can induce lacrimal gland stress and pro-inflammatory/anti-inflammatory cytokines unbalance. This inability to adapt to external or internal insults can lead to tear film instability and evaporation, increased osmolarity, nerve malfunction, decreased tear secretion and inflammation [4]. The inflammation is responsible for feeding a vicious cycle that comprises quantitative and/or qualitative tear alterations and ocular surface epithelial cells damage that are responsible for symptoms and signs of chronic dry eye. In the recent year's topical corticosteroids, cyclosporine A, lifitegrast, systemic tetracyclines, and fatty acids have been reported to be effective in treating patients with DED. In this review we focus on ocular surface inflammation mechanisms and treatment effects in patients with severe chronic DED or type III as defined recently [2].

Ocular Surface Inflammation in Dry Eye Disease

Ocular surface inflammation plays a pivotal role in dry eye pathogenesis. The first step of its genesis is probably the alteration of the para-inflammatory mechanisms that protect the ocular surface when there is a change at the level of one of its structures [5]. If this change is persistent there is an increased expression of proinflammatory mediators (cytokines, chemokines, adhesion factors). For example, an increased concentration of a number of pro-inflammatory cytokines (IL-1α and β, IL-6, IL8, TGF-β1, and TNF-α) has been observed in the conjunctival epithelium and in the tear fluid of patients with Sjögren's syndrome [6].

Other pro-inflammatory markers are adhesion molecules such as ICAM-1, which have been demonstrated to increase in mouse models as well in patients with dry eye [7]. The integrin LFA-1 in conjunctival epithelial cells binds to ICAM-18 and may mediate leukocyte binding to vascular endothelium during acute inflammation, thus promoting lymphocyte activation and migration to the ocular surface and therefore representing a possible therapeutic target [8].

The next step in the generation of adaptive immunity is antigen presentation by the antigen presenting cells (APC) to the naïve T cells in association with MHC class II molecules, leading to T cell priming and subsequent proliferation of antigen- specific T cells. In patients with Sjögren's syndrome a significant infiltration of T-cells was observed in conjunctival stroma and epithelium [9]. Interestingly, conjunctival epithelial cells may acquire antigen-presenting capability, and the immunologically activated epithelial cells may play a role in recruiting and activating inflammatory cells in the ocular surface, thus perpetuating the pathogenic vicious cycle of DED. Much remains to be elucidated regarding the immunopathogenesis of DED, such as for example the progression from functional to dysfunctional parainflammation,5 but it is important to note that the changes described above are not seen in all patients with DED [2]. From a clinical point of view in the everyday practice the only way to diagnose ocular surface inflammation is the use of vital dyes. In particular, a direct correlation between the degree of inflammation and the extent of lissamine green staining has been proposed by Yang et al [10]. who demonstrated that staining scores significantly correlate with the expression of IFN-γ, IL-6, IL-17, and MMP9 in Sjogren's syndrome (SS) and non-SS DED groups. It is worth noting that correlation coefficients of all cytokines were much higher in SS DED compared to non-SS DED. In addition, a pilot study reported a significant correlation between Lissamine green staining and CD45+CD14+ cells infiltration of the conjunctiva only. These data are very important because they could be used to differentiate patients with different severity of DED and to target patients with chronic dry eye with the appropriate anti-inflammatory treatment. Anti-inflammatory therapy for dry eye disease as described above, inflammation is a concomitant part of dry eye through various mediators. Anti-inflammatory treatment may be considered in those patients with DED whose symptoms fail to resolve on tear substitutes alone, or, according to the new classification of patients, in type II and III dry eye [2].

Topical Corticosteroids

Immunomodulation with topical non-preserved corticosteroid therapy reduces inflammation in DED [11,12] The effect is due to potent inhibition of many inflammatory pathways mediated by the NF-κB signal transduction pathway. Some of these include inhibition of inflammatory cytokine and chemokine production, decreased expression of cell adhesion molecules (like ICAM-1), stimulation of lymphocyte apoptosis, and decreased synthesis of matrix metalloproteinases and lipid mediators of inflammation (e.g., prostaglandins) [13,14]. Topical methylprednisolone therapy, for two weeks, three to four times a day, has been shown to provide moderate to complete relieve of moderate to severe irritation symptoms in Sjögren's syndrome-associated signs of corneal epithelial damage in patients with non-significant changes with tear substitutes.11 A concomitant decrease in corneal fluorescein staining and complete resolution of filamentary keratitis was also demonstrated [11]. Topical steroids can be used as pulse therapy or by tapering down the number of instillations. Pulse therapy, meaning instillation of topical steroids in intermitted manner, could be used in patients with type II dry eye to modulate inflammatory flares. In patients with severe chronic dry eye the number of instillations could be reduced, but not interrupted, to control inflammation over time. A recent study showed a significant improvement of symptoms and decrease of HLA-DR expression in CD45+ conjunctival cells in patients with severe DED treated with this regimen with the use of topical loteprednol at least twice a day [12]. The long-term use of topical steroids, however, could be associated with severe side effects such as ocular hypertension and cataract, and therefore this treatment in patients with chronic DED should carefully consider the different steroids properties [15].

Topical Cyclosporine A

Cyclosporin A (CsA) is a naturally occurring fungal metabolite that inhibits T cell activation by blocking the transcription of cytokine genes, including those of IL-2 and IL-4 [16]. In ophthalmology, topical CsA was initially investigated to prevent graft versus host disease after transplantation of donor corneal tissues. In DED topical CsA reduces lacrimal gland and conjunctival lymphocytic infiltration with reduced apoptosis of lacrimal gland and conjunctival epithelial cells [17], possibly due to blockage of the opening of mitochondrial permeability pores [18]. In clinical trials topical CsA 0.05% twice daily has been shown to relieve the signs and symptoms of DED in randomized multicenter, double-blinded, 6-months studies in patients with moderate to severe DED [19]. In particular, topical CsA improves symptoms of dry eye like burning and foreign body sensation, and reduces the use of tear substitutes, a critical aspect that reflects its usefulness in patients

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with chronic DED. It also improves tear secretion measured with the Schirmer test and corneal epithelial cells damage measured with fluorescein staining after three months of treatment. The benefits of restoring the ocular surface includes improvement of the quality of vision and normalized lacrimal gland response to blinking and other stimuli.

Similar results have been demonstrated with a formulation of CsA 0.1% cationic emulsion once a day approved by the European Medicines Agency in 2015 for the management of severe keratitis in DED [20]. The clinical changes observed with the treatment with topical CsA therapy correlate with improvement at the cellular level as well. In fact, topical CsA determines a significant decrease expression of immune activation markers (CD11a, HLA DR) in conjunctival epithelial cells, the number of activated CD3+ T cells, and inflammatory cytokines such as IL-6 [21]. Systemic hypertension and nephrotoxicity are possible side effects of oral and intravenous CsA administration. However, due to very low systemic absorption, these have not been reported with topical CsA treatment in DED [19]. The most common adverse reaction is mild burning sensation on instillation that does not necessitate therapy discontinuation in most cases. Effective DED management requires education of patients on the chronic nature of the disease and its prognosis, and therefore the need for prolonged therapy. Being an immunosuppressant topical CsA should be considered in patients with chronic severe dry eye and clinically evident ocular surface inflammation, also defined Type III dry eye [2].

Lifitegrast

Lifitegrast is a small-molecule integrin antagonist that selectively binds to LFA-1 and inhibits it from interacting with its ligand, ICAM-1, which is expressed by endothelial cells and in corneal and conjunctival epithelial cells in patients with DED. By inhibiting the interaction between LFA-1 and ICAM-1, lifitegrast prevents the adhesion, activation, migration, and proliferation of lymphocytes, thus reducing the inflammatory response in the ocular surface. The efficacy of lifitegrast was first demonstrated in studies in mice where showed a significant decrease of pro-inflammatory mediators and the recovery of goblet cells, and in dogs with keratoconjuctivitis where a significant increase in tear secretion was demonstrated [22].

In patients with DED the most notable studies are the OPUS-1, -2, and -3 trials which demonstrated that lifitegrast 5% solution administered twice daily significantly improves symptoms of dry eye compared to placebo. Patients treated with lifitegrast reported a reduction in dryness score and improved eye comfort after 12 weeks of use [22]. In addition to symptomatic relief, lifitegrast has been shown to improve objective signs of dry eye, such as tear break-up time and ocular surface staining scores [23]. Lifitegrast is well-tolerated, with the most common side effects being eye irritation, a transient burning sensation upon instillation, and dysgeusia. Further studies evaluating the effect in the long period and the comparison of the efficacy of lifitegrast and topical cyclosporine and steroids would be useful to better understand its use in patients with DED. Considering the mechanisms of action its use could be recommended in patients with type II DED to control ocular surface inflammation flares and in patients with severe chronic dry eye (Type III). Lifitegrast is currently not available in Europe.

Tetracyclines

Tetracyclines are a class of broad-spectrum antibiotics that have been widely used since their discovery in the 1940s. They are effective against a variety of bacterial infections and are commonly prescribed for conditions such as acne, respiratory infections, and certain types of pneumonia. The primary mechanism of action for tetracyclines involves inhibiting protein synthesis in bacteria, which ultimately leads to the cessation of bacterial growth. Beyond their antimicrobial properties, tetracyclines have been recognized for their anti-inflammatory and immune-modulating effects. These characteristics have made them valuable in the treatment of various non-infectious conditions, including rosacea, periodontitis, and more recently, ocular surface diseases like dry eye. Tetracyclines include drugs such as doxycycline, minocycline, and tetracycline itself, a cost-effective agent, but because of its short half-life (8.5 hours), it requires a regimen of four times daily. Instead, doxycycline has a longer half-life (15-17 hours) which permits a daily dosage of one tablet. Recent studies have explored the potential benefits of tetracyclines, particularly doxycycline, in the management of DED. A randomized controlled trial by Kheirkhah et al. [24] found that oral doxycycline significantly improved symptoms and signs of dry eye, particularly in patients with MGD. The study noted improvements in tear break-up time (TBUT) and the Schirmer test scores. Similarly, a review article of Vernhardsdottir et al. [25] concluded that patients with blepharitis- or MGD-related DED experience short-term benefits of antibiotics. The mechanisms through which tetracyclines may alleviate dry eye symptoms and signs include the inhibition of matrix metalloproteinase (MMP) activity and synthesis, nitric oxide synthesis, IL1 synthesis, collagenases activity, B cell activation [26]. The expression of stimulated MMP-1, -13, and -10 at the mRNA and protein levels, MMP-9 production, and IL1 expression and activity by human corneal epithelial cells are decreased by tetracyclines [27]. In our opinion, further masked and placebo-controlled prospective studies are necessary to clarify the long-term benefits, common side effects, and increasing antibiotic resistance seen globally. Also, further studies of the effect of topical application of either eye drops or ointment on the different forms of DED should be performed.

Systemic Fatty Acids

Omega -3 and -6 are essential fatty acids (EFAs) that cannot be produced by the body and therefore need to come from our diet. Omega-3s are primarily found in certain fish, nuts, and seeds. Once consumed they are elongated by enzymes to produce anti-

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inflammatory prostaglandin E3 (PGE3), and anti-inflammatory leukotriene B5 (LTB5). The omega -6 fatty acids, linoleic acid and γ-linolenic acid are found in eggs, fried foods, processed foods and most vegetable oils. They are precursors of pro-inflammatory molecules, but also of PGE1, a potent anti-inflammatory agent successfully used in animal models of ocular inflammation [28]. Horrobin [29] in 1986 published the first paper regarding the possible role of essential fatty acids supplements in patients with systemic sclerosis, rheumatoid arthritis, and Sjögren's. The first randomized placebo-controlled study on the effects of systemic fatty acid in DED demonstrated that systemic linoleic acid (LA, 28.5 mg) and γ-linolenic acid (GLA, 15 mg) are able to improve symptoms and reduce markers of inflammation, such as HLA-DR, on conjunctival epithelial cells when administered twice daily for 45 days [30]. A clinical trial analyzing the effect of a dose of 112 mg of LA and 15 mg of GLA supplementation showed a significant increase of PGE1 levels in tears after 1 month of intervention [31].

These results have been confirmed by many different studies in the literature.28 However, a multicenter, randomized, placebo-controlled, double-masked, prospective clinical trial (the DREAM study) that assessed systemic omega 3 efficacy in patients with moderate-to-severe DED did not show significant improvement in symptoms and clinical signs [32]. In our opinion, the results obtained with the supplementation with EFAs are encouraging, but further studies are necessary to better understand what patients could benefit of this treatment. For example, patients enrolled in the DREAM study had moderate to severe dry eye, but we have no data regarding patients with mild dry eye. Also, it is very important to consider the quantity of omega-3 and omega-6 fatty acids used, and the treatment in the control group. In the DREAM study the supplementation with olive oil was used in the placebo group. However, olive oil contains several fatty acids and should not considered a placebo. Finally, it could be of great interest to study the effects of EFAs on parainflammation and the role of topical formulations.

Conclusion

Anti-inflammatory therapy in DED is essential to break the vicious cycle of lid margin inflammation/MGD - dry eye - ocular surface inflammation, which leads to tear film alteration, corneal and conjunctival epithelial damage, and therefore to the symptoms and signs experienced by patients. The correct diagnosis and the classification of patients in different stages based on the alteration of the ocular surface homeostasis, the level of inflammation, and the chronicity of symptoms, is certainly the first step to build up an efficient treatment for each patient with DED [2]. Therefore, in the clinical practice the use of fluorescein and liquid lissamine green is recommended, because today it is the only way to evaluate the alterations of the different parts of the ocular surface system and the level of inflammation. To interrupt the pathogenesis of dry eye the main therapeutic action should be improving environmental conditions, avoiding cosmetics that could induce tear film and Meibomian gland changes, considering a diet rich in essential fatty acids, treating Meibomian gland disease by hot compresses and / or antibiotics when clinically significant, improving tear film quantity and stability with tear substitutes or ocular surface modulators. Recently, we provided a classification of tear substitutes that could be used as a guide to choose the correct molecules based on their mechanism of action [33]. However, in patients with moderate to severe DED the topical anti-inflammatory therapy is necessary. In our opinion it is necessary to increase our knowledge of DED pathogenesis to identify new targets for developing new effective treatments, with regard to the mechanisms of Para inflammation and the progression to chronic inflammation.

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