

# The impact of inflammatory flares in dry eye disease



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## HIGHLIGHTS

The role of inflammatory response and its exacerbations ('flares') in dry eye disease syndromes is underlined. The topical therapy with 0.335% hydrocortisone eye drops, as an addition to artificial tears, is reported to be efficient and safe in mild and moderate dry eye disease.

## ABSTRACT

Dry eye disease is a condition treated commonly by most of the ophthalmologists. The current understanding of the disease puts impact on its newly discovered components – 'flares'. Flares are defined as exacerbations of dry eye disease. They take place in response to the triggers, which may be environmental or internal factors. During the 'flare' the immunological response is being activated and the patients experience the worsening of the symptoms. The introduction of the anti-inflammatory treatment (e.g. topical hydrocortisone solution) is the effective treatment in the cases of inflammatory state exacerbations.

**Key words:** flare, immunological response, inflammatory state, exacerbations, dry eye disease

## INTRODUCTION

According to the TFOS DEWS 2017 definition, dry eye syndrome (DES) is a multifactorial disorder of the ocular surface characterized by a lack of tear film homeostasis with associated symptoms caused by tear film instability and hyperosmolarity, damage and inflammation within the ocular surface, and neurosensory abnormalities. Basic research studies is shedding new light on the components of the etopathogenesis of DES and its exacerbations.

## DRY EYE SYNDROME – PATHOPHYSIOLOGY, INFLAMMATION EXACERBATIONS, TREATMENT

Tear film instability and tear hyperosmolarity, as well as inflammation and damage to the ocular surface, play a key etiological role in the pathogenesis of DES [1]. There are two main subtypes of DES: dry eye from excessive evaporation and dry eye from aqueous component deficiency; the two subtypes often coexist [2]. Studies on the pathophysiology of the disorders associated with DES have identified a vicious circle model for DES, in which tear film instability and tear hyperosmolarity involve a chain of related inflammatory events, ultimately leading to damage to the ocular surface and self-perpetuating disease [3]. Any external trigger for DES (e.g., low ambient humidity, high wind speed, excessive time in front of a computer screen, contact lens use, cataract and refractive surgery) or internal factor (e.g., aging, female gender, autoimmune disease) can be considered an entry point into the vicious cycle [3].

The immune responses of the ocular surface are similar to those observed on the surface of other mucous membranes in response to triggers (e.g., environmental conditions, allergens, microorganisms) [4]. Both innate (epithelial and myeloid cells; fast and non-specific response) and acquired (T lymphocytes, B lymphocytes; slower and more specific response) branches of the immune system are involved [4]. Inflammation in dry eye syndrome has been well documented and includes infiltration of the conjunctiva and lacrimal glands by immune cells and elevated levels of cytokines in the tear film.

Elevated levels of cytokines are found in the composition of the tear film in patients with DES:

- interleukins: IL-1, IL-6, IL-8
- monocyte chemoattractant protein-1 (MCP-1, monocyte chemoattractant protein-1), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ , tumor necrosis factor  $\alpha$ )
- interferon  $\gamma$  (IFN- $\gamma$ ).

DES is a chronic condition with cyclic exacerbations of symptoms, influenced by systemic and environmental factors, as well as past eye surgeries.

Recently, the importance of these periodic exacerbations has been increasingly emphasized. The consensus defi-

nition of DES presented by Tsubota [2] distinguishes the following factors contributing to inflammation of the ocular surface: microinjuries, hyperosmotic stress, age-related changes, and irritation by bacterial antigens, ultraviolet radiation, infections, and exacerbations of autoimmune systemic diseases.

Perez et al. described the mechanisms (pathways) of inflammation that are activated during episodes of exacerbations of DES. In the immune model of DES, exacerbation begins with a non-specific innate immune response mediated by epithelial cells and other elements of the immune system. In addition, the slower and more specific component of acquired immunity plays a major role in some cases [5]. Innate immunity is crucial to the immune response of the ocular surface. It is made up of epithelial cells that detect increased tear film osmolarity through pattern receptors on their surface and, together with neutrophils, monocytes, macrophages and dendritic cells, trigger episodes of exacerbation, stimulating the so-called cytokine storm. Ultimately, further signaling pathways activate the innate, as well as acquired, immune response, resulting in the development of inflammation and an increase in the clinical manifestations of the disease. In chronic DES, pathogenic T lymphocytes previously sensitized to antigen have already penetrated deep into the tissues of the ocular surface. In such a case, the well-established acquired immune response may activate with relatively low intensity triggers, leading to a continuous exacerbation of inflammation.

Understanding the cascades of inflammatory responses activated during relapse can inform therapeutic guidance and improve patient outcomes in chronic therapy.

Thus, artificial tears remain the mainstay of treatment for DES, while anti-inflammatory treatment is necessary to break the vicious cycle of inflammation and damage to the ocular surface [5, 6]. Modern anti-inflammatory therapy includes topical cyclosporine, corticosteroids, plasma drops, tacrolimus/pimecrolimus, lifitegrast (which blocks adhesion molecules), and macrolides and tetracyclines (antibiotics with anti-inflammatory, collagenase-inhibiting activity).

Glucocorticosteroids inhibit the synthesis and release of cytokines, including blocking the production of NF- $\kappa$ B – so they remain a mainstay of treatment in inflammatory conditions of DES [7–9]. Hydrocortisone is a low-potency glucocorticosteroid with low penetration potential into the tissues of the eye [10, 11], especially increasing intraocular pressure [12].

A study by Kallab et al. [13] showed that a low dose of preservative-free hydrocortisone reduces conjunctival redness, increases tear film thickness and relieves the symptoms of DES. The use of a glucocorticosteroid has been studied in patients with mild to moderate DES in two regimens:

- intensive regimen: 4 times a day for 12 days, then twice a day for 2 days
- standard regimen: 3 times a day for 8 days, then twice a day for 4 days.

In addition to topical hydrocortisone therapy without preservatives at a concentration of 0.335%, all patients received concomitant therapy – artificial tears used according to previous recommendations. The authors demonstrated the effectiveness of both treatment regimens. Moreover, the therapeutic effect was also seen 2 weeks after the end of therapy, indicating the prolonged effect of hydrocortisone treatment. Finally – no change in intraocular pressure (IOP) was observed, highlighting the good safety profile of hydrocortisone. In conclusion, the study showed that treatment with low doses of preservative-free hydrocortisone was a safe and well-tolerated new therapeutic approach in patients with chronic DES.

In another study [14], the authors evaluated the clinical efficacy of the glucocorticosteroid 0.335% hydrocortisone in patients with mild to moderate DES. The drug was adminis-

tered twice a day for 14–15 days together with the previously used hydration drops. Improvement was observed in the examined tear film parameters: tear film thickness, Schirmer test and OSDI (ocular surface disease index) scores. This study showed a beneficial effect of anti-glaucoma therapy on OSDI in both glaucoma and non-glaucoma patients. No variation in IOP was noted in either group [15].

## CONCLUSIONS

1. DES is a chronic condition with periodic exacerbations.
2. Exacerbations can be triggered by environmental, systemic, and iatrogenic factors.
3. The immune system of the ocular surface plays an important role in the pathomechanism of exacerbations of the symptoms of DES.
4. Treatment with preservative-free artificial tear drops is the mainstay of DES treatment.
5. During exacerbations without signs of infection, the combination of therapy with a low-level glucocorticosteroid shows high efficacy.

## CORRESPONDENCE

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Justyna Izdebska: idea, data collection, manuscript preparation; Katarzyna Samelska: data collection, editing of the manuscript.

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The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.