

## Review Article



## Some New Pharmacologic Options in Dry Eye Syndrome Treatment

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## ABSTRACT

The dry eye syndrome (DES) is a socially significant disease, caused by deficiency of the tear film and tear secretion. It alters the basic characteristics of the tear film and inflammatory changes are observed. There has been an increased incidence of DES associated with exogenous environmental factors. Patients complain about impaired visual acuity, discomfort, irritation, redness, tearing, fatigue, dryness, burning, itching, blepharospasm, etc. Typical is increased osmolarity and impaired stability of the tear film. The therapy of xerophthalmia is predominantly conservative and replacement based. Lubricants are commonly used. Some of the new medications include cyclosporine or autologous serum as well as some oral products. The main treatment involves the use of drug substances, including "artificial tears", anti-inflammatory, biological therapy, tetracyclines, secretolytics, etc. The aim of the modern treatment is to treat directly the underlying pathology with anti-inflammatory and immunomodulatory medications. One of the most potent drug for DES treatment is tetracycline, which has antibacterial, anti-inflammatory and anti-angiogenic effects. Also Cyclosporine A, can be used in DES. It is an immunomodulator blocking T-cell proliferation and signal transduction. Due to its immunomodulating properties, cyclosporin affects both subjective complaints and clinical signs in dry eye conditions. It is the only approved product that actively treats the condition. Exploring the pathogenesis of DES promotes the development of new drug substances and forms for its treatment. The trend goes from substitutional therapy with "artificial tears" to active stimulation of the regenerative processes, maintaining epithelial integrity and barrier function, and suppressing inflammatory factors.

**Keywords:** Dry eye disease, dry eye syndrome, xerophthalmia, cyclosporine.

## INTRODUCTION

The dry eye syndrome (DES) is a socially significant disease that affects more and more people in different ages.<sup>1,2</sup> It is a quantitative and / or qualitative deficiency of the tear film and tear secretion. It is a multifactorial disease that alters the basic characteristics of the tear film, and various inflammatory changes in the ocular surface may be observed.<sup>3-6</sup> In recent years there has been an increased incidence of DES associated with various exogenous environmental factors - work with displays, exposition to smoke, dust, some medications for systemic application, work in air-conditioned rooms, and last but not least, local glaucoma therapy for more than 5 years; etc.<sup>3,7</sup> Patient subjective complaints vary in severity and appearance, increasing by the end of the day, with sudden climatic changes, long-lasting visual work. Patients complain about impaired visual acuity, discomfort, irritation, redness, tearing, fatigue and dryness, burning and itching, blepharospasm, etc. Typical is increased osmolarity and impaired stability of the tear film as a result of damage to the epithelium of the conjunctiva and the cornea.<sup>3,8</sup>

The incidence of DES described in the literature varies between 3% and 30%.<sup>1,4,7,9,10</sup> According to the latest data, it has an average incidence of about 14%. The reason for these differences is the different definitions of the disease and the lack of an unified algorithm for diagnosis.<sup>3,10</sup> In the United States, about 15% of patients

over the age of 65 have a clinically manifested DES, and this is the leading reason for visiting an ophthalmologist. The highest incidence of the disease is established in Canada, Japan and USA - about 30%. According to most clinical studies, women are more affected by DES.<sup>9</sup> Other data indicate that there is no statistically significant difference in gender distribution, and some authors even find higher incidence among men.<sup>4,5</sup> Which of the two values - age or gender has a greater impact on the incidence of DES is still controversial. It is known that body water content in patients under 40 years of age is about 72% of body mass. At birth, the water is about 80% of the weight of the newborn and in the age group over 60 years the water content decreases to 60%.<sup>6,12,13</sup> This general dehydration of the body also affects the eye surface naturally and disrupts the moisturizing, barrier and nutritional function of the tear film.<sup>3,7,14</sup>

The patients subjected to chronic topical treatment, i.e. the glaucoma patients, are especially susceptible to developing this disease. This is due to the presence of excipients in the eye dosage forms and mainly to the preservatives such as Benzalkonium chloride. The therapy of xerophthalmia is predominantly conservative and replacement based. Lubricants containing different polymers are commonly used as they hydrate the ocular surface and stabilize the tear film. Some of the new medications include cyclosporine or autologous serum as well as some oral products. The most significant trend in the research and development of new ophthalmic dosage



forms is to make them preservative-free or to apply new preservatives that are less toxic than the ones already known.<sup>1</sup>

### Dry eye treatment

The dry eye treatment strategy depends largely on the severity of the condition and the causative agent and can be both pharmacologic and operative. The main dry eye treatment is conservative and involves the use of a relatively large range of drug substances, including so-called "artificial tears", anti-inflammatory, biological therapy, tetracyclines, secretolytics, etc.<sup>1,15,16</sup>. Medicaments can be applied topically and systematically. In the initial stages, treatment requires the inclusion of tear substitutes, and anti-inflammatory agents are included in later stages. The term "artificial tears" is mistakenly used for most products as they do not imitate the composition of human tears.<sup>1,17</sup> This group includes liquid and semi-solid products containing various high molecular weight compounds, the main role of which is lubricating and relieving subjective sensations. Most of these (cellulose derivatives, carbomer, polyvinyl alcohol, dextrans, polyethylene glycol, etc.) are characterized by an increased viscosity, which results in long-lasting retention on the ocular surface.<sup>1,18</sup> Excessive viscosity (above 8.3 mPa) require higher eyelid force when blinking, which can cause pain. In addition, it is possible blurred vision to appear in the first few minutes after administration of this products. Other substances used, such as sodium hyaluronate and carboxol, are characterized by a linear multi-charged structure and high viscosity between blinking and low viscosity during blinking movements (viscoelastic properties), which determines effective coating and protection of the ocular surface without causing soreness.<sup>1,19,20</sup> Furthermore, hyaluronic acid has mucoadhesive properties that significantly prolong the ocular surface coating time compared to other substances.<sup>17</sup> In semi-solid dosage forms, a higher viscosity is observed. They are more difficult to administer to patients and are more often associated with blurred vision.<sup>21</sup> In the products of this group used to treat dry eye, it is noted that it is mainly gels. They are characterized by thixotropic behavior and, therefore, their viscosity is reduced by application of tension (release from packaging or blinking). Furthermore, some of them such as carbomer (carbopol) at a pH of about 4 forms a weak viscose suspension which, when the pH increases to slightly alkaline (7.4-8.5), dissolves and produces a gel in situ on the conjunctiva.<sup>1,19</sup> Another characteristic of dry eye patients is the higher osmolarity of the tear film (crystalline osmolarity). This is associated with the induction of morphological and biochemical changes of the corneal and conjunctival epithelium and with proinflammatory action. Therefore, some of the drops that are offered are hypotonic with respect to normal tear osmolarity (320mOsmol / L).<sup>1</sup>

### New pharmacologic options in dry eye treatment

The aim of the modern treatment for xerophthalmia is to treat directly the underlying pathology with anti-inflammatory and immunomodulatory medications. One of the most potent drug for dry eye treatment is tetracycline, which, in addition to antibacterial, has anti-inflammatory and anti-angiogenic effects. It is used in patients with rosacea or chronic blepharitis with meibomian dysfunction.<sup>1,17</sup>

A new drug for the treatment of xerophthalmia is cyclosporine A, approved by the US Food and Drug Administration (FDA) in 2003. In 2015, EMA allowed cyclosporin to be used in dry eye syndrome, making it available on the European market. It is an immunomodulator blocking T-cell proliferation and signal transduction. The cell-mediated inflammatory response is modulated by down-regulation in the expression of the interleukin 2 receptor, thereby limiting the transcriptional activity.<sup>22</sup> Due to its immunomodulating properties, cyclosporin affects both subjective complaints and clinical signs in dry eye conditions. It is the only approved product that actively treats the condition. The modern development of personal medicine allows the preparation of autologous serum free of preservatives. It has an anti-inflammatory effect due to the inhibition of matrix metalloproteinases and inflammatory cytokines.<sup>23</sup> This drug also provides significant opportunities to improve the patients' objective condition. However, its efficacy data are quite controversial due to the significant differences in patient populations, the way of preparation, storage and route of administration.<sup>17</sup>

In very severe forms of xerophthalmia, oral drugs such as tear secretion stimulants (cholinergic agonists such as pilocarpine and sevilimine) may be used.<sup>17</sup> However, there is a risk of systemic side effects.<sup>1</sup>

### CONCLUSION

Exploring in detail the pathogenesis of the dry eye and the factors related to it promotes the development of new drug substances and forms for its treatment. The trend goes from substitutional therapy with "artificial tears" to active stimulation of the regenerative processes, maintaining epithelial integrity and barrier function, and suppressing inflammatory factors.

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