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Cyclosporine: effective treatment for patients with inflammation of the ocular surface

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HIGHLIGHTS

Cyclosprin A in dry eye syndrome, by treating inflammation, restores homeostasis to the ocular surface.

ABSTRACT

Dry eye syndrome is a multifactorial and multisymptomatic disease affecting millions of people worldwide. Statistics show that depending on geographic location, 15% to 30% of a country's population suffers from dry eye syndrome. Chronic inflammation leads to structural changes on the surface of the eye, causing pain and a range of other distressing symptoms. If left untreated, these symptoms can eventually result in reduced visual acuity and difficulties performing typical daily activities. The decline in quality of life strongly correlates with a deterioration in mental health. Recent studies indicate that one in three dry eye syndrome patients may struggle with depression. Chronic dry eye syndrome triggers the development of neurogenic inflammation. The aim of this study is to present the indications for and mechanism of action of cyclosporine A in the treatment of this condition.

Key words: cyclosporine A, dry eye syndrome, inflammation, tear film, ocular surface

INTRODUCTION

As defined by the TFOS DEWS II™ Report (The Tear Film & Ocular Surface Society International Dry Eye Workshop II), dry eye syndrome (DES) is a multifactorial disease of the ocular surface, characterized by tear film instability and hyperosmolarity, ocular surface inflammation and damage, neurosensory abnormalities, and structural changes to the ocular surface [1]. Meibomian gland dysfunction, environmental pollution, history of laser eye surgery, autoimmune diseases (such as Sjögren's syndrome, rheumatoid arthritis, and lupus), contact lens wear, hematopoietic stem cell transplantation, and the use of certain medications—including psychotropic drugs, diuretics, β-blockers, and oral contraceptives [2, 3]—are considered major etiological factors. Hormonal changes associated with menopause also affect tear production, which is why DES is more prevalent in women and older adults. Epidemiological data indicate that between 15% and 30% of the population is affected by DES, depending on geographic latitude. Due to a deficiency or poor quality of the tear film, the predominant symptoms of DES include a sensation of ocular dryness and the feeling of a foreign body, often described as "sand under the eyelids". Patients with DES commonly report symptoms such as a burning sensation, itching, and redness — often misinterpreted as allergic reactions. Paradoxically, excessive tearing may occur as a reflex response to ocular surface dryness. Patients with DES also tend to experience faster eye fatigue, along with increasingly frequent complaints of blurred vision and heightened sensitivity to light. Symptoms are exacerbated during tasks that require prolonged visual concentration, such as working at a computer, and in dry, air-conditioned, or brightly lit environments. All of the above symptoms significantly affect patients' quality of life, and an increasing number of studies confirm a strong association between DES and depressive disorders. A recent meta-analysis from 2021 found that up to 40% of patients with DES experience symptoms of depression — almost twice the risk observed in healthy individuals [1].

The diagnosis of DES begins with taking a detailed patient history. Once symptoms have been established, it is important to ask about current medications, past ocular surgeries, the presence of ophthalmic and autoimmune chronic conditions that frequently co-occur with DES, as well as the environmental conditions in which the patient lives on a daily basis. This should be followed by diagnostic tests that provide a more comprehensive assessment of the disease. These tests help guide the selection of optimal therapy for each patient. Commonly used diagnostic methods include the Schirmer test, tear film break-up time (BUT), fluorescein staining of the cornea and conjunctiva, tear osmolarity measurement, mucin production tests, meibography, evaluation of tear film stability and thickness, as well as neurosensory testing. Given the multifactorial etiology of DES and its increasing prevalence, diagnostic tools have been developed for use not only in ophthalmology clinics but also by primary care physicians. These include standardized questionnaires such as the OSDI (Ocular Surface Disease Index), DEQ-5 (Dry Eye Questionnaire), SANDE (Symptom Assessment in Dry Eye), McMonnies Dry Eye Questionnaire, IDEEL (Impact of Dry Eye on Everyday Life), and NEI VFQ-25 (25-item National Eye Institute Visual Function Questionnaire). The most widely used is the OSDI, which consists of 12 questions designed to assess dry eye symptoms, their impact on daily activities, and environmental triggers. These questionnaires facilitate diagnosis, improve efficiency, and are also useful in monitoring treatment outcomes [5].

Depending on the source, different classifications of DES severity can be found, most of which focus on tear film abnormalities. To help organize the understanding of the condition, the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes categorized dry eye into 2 main types: aqueous-deficient and evaporative dry eye [6] (fig. 1).

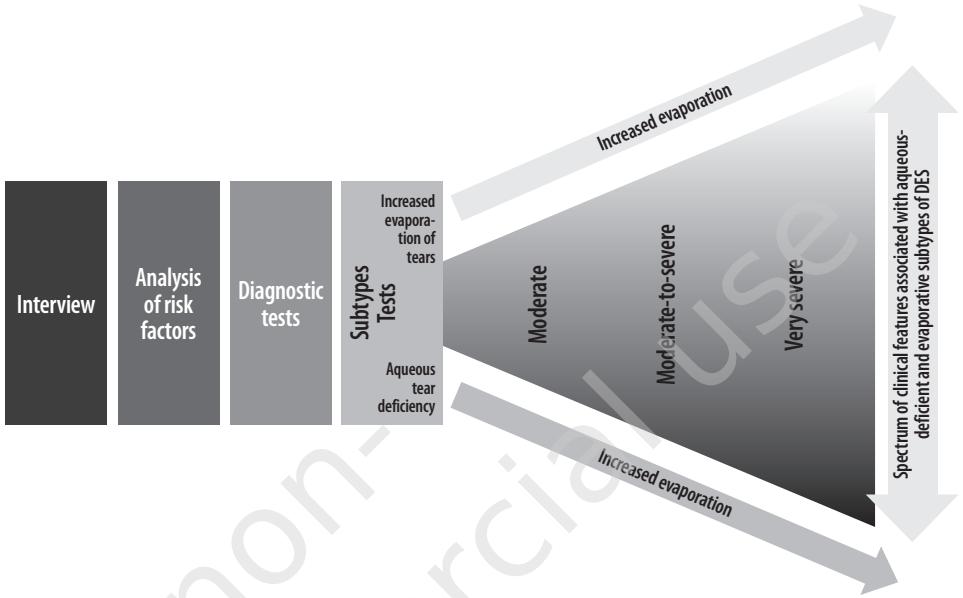
Treatment is tailored to the severity and type of clinical symptoms. The primary goal is to reduce inflammation, thereby improving the quality and stability of the tear film. Key therapeutic approaches include the use of artificial tears, eye drops, creams, and ointments that hydrate and soothe the ocular surface. Lifestyle and environmental modifications are also recommended, such as avoiding air-conditioned environments, practicing regular and frequent blinking during computer use, and wearing sunglasses to protect the eyes from wind and sunlight. Supplementation with omega-3 fatty acids and regular eyelid hygiene are recommended. Punctal occlusion may be used to prevent tear drainage [7]. Additionally, warm compresses are applied to improve circulation and relieve congestion in the Meibomian glands, which are responsible for lipid secretion. If these measures are insufficient, more advanced therapies may be considered, such as LipiFlow or IPL (intense pulsed light) treatment, both of which target Meibomian gland dysfunction [8].

Successful DES treatment often requires an individualized approach and a combination of multiple methods tailored to the severity and type of symptoms. Identifying the underlying etiological factor frequently proves to be a key element of effective therapy.

The purpose of this paper is to present the treatment of the inflammatory component of dry eye syndrome using the immunosuppressive drug cyclosporine A. Its efficacy in treating Meibomian gland dysfunction (MGD) has been confirmed in numerous studies and meta-analyses [9]. Early introduction of the drug — starting at moderate disease severity — helps prevent serious complications such as

FIGURE 1

Management of DES according to the TFOS DEWS II Management and Therapy Report (2017).



conjunctival scarring, corneal filaments, epithelial defects of the cornea and conjunctiva, and even corneal ulceration [1] (fig. 2).

CYCLOSPORINE A - THE "MOTHER OF TRANSPLANTATION"

Cyclosporine A, produced by the fungus *Tolypocladium inflatum*, is a potent immunosuppressant belonging to the calcineurin inhibitor class [10]. Its introduction in the 1980s revolutionized the field of transplantation. By effectively suppressing the recipient's immune response to foreign tissue, it significantly reduced the risk of graft rejection and markedly improved long-term patient survival. However, oral administration of the drug has been associated with a range of systemic side effects, including nephrotoxicity, hepatotoxicity, hypertension, an increased risk of opportunistic infections, and malignancy development [11]. As a result, there were initial concerns regarding its use for other indications.

In ophthalmology, cyclosporine A was first used orally in the 1980s to prevent corneal transplant rejection. In the 1990s, research began on its use in the form of eye drops for the treatment of DES. Studies demonstrated that topical administration of cyclosporine A effectively reduces ocular surface inflammation, leading to its introduction as an ophthalmic drug – particularly for chronic forms of DES. After years of research, it has been concluded that topical administration of cyclosporine A at concentrations ranging from 0.05% to 2% carries minimal risk of the systemic side effects associated with oral use. Therefore, the initiation of this therapy should not be a cause for concern. Today, topical cyclosporine A is also used in the treatment of various other autoimmune and inflammatory ocular conditions.

The mechanism of action of cyclosporine A involves the inhibition of T-lymphocyte activity and the associated inflammatory cascade. This is achieved through the binding of cyclosporine A to the intracellular protein cyclophilin, forming a complex that inhibits the enzyme calcineurin. Calcineurin plays a crucial role in T-cell activation. Its inhibition prevents the transcription of pro-inflammatory cytokines and, consequently, the proliferation of T lymphocytes. The reduction in T-lymphocyte activity and proliferation leads to decreased secretion of inflammatory mediators such as interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor alpha (TNF-α) on the ocular surface [12]. However, cyclosporine A does not affect the function of phagocytic cells, including polymorphonuclear cells, neutrophils, or macrophages, and therefore does not impair the body's ability to fight infectious agents. By reducing inflammation, it minimizes damage to the ocular surface epithelium and promotes regeneration of lacrimal gland cells by enhancing tear production and improving tear quality. This results in stabilization of the tear film and a reduction in DES symptoms.

However, when introducing cyclosporine A into the treatment of dry eye syndrome (DES), it is important to note that the drug has a relatively slow onset of action. The effectiveness of therapy depends on the regular use of eye drops over several weeks or months. Given that T lymphocytes have a lifespan of approximately 100 days, treatment should last for at least 3 months. In clinical practice, how-

FIGURE 2

Treatment strategies in DES according to the TFOS DEWS II Management and Therapy Report (2017).

Stage 1	Stage 2	Stage 3	Stage 4
Patient education regarding the disease, its management, treatment options, and prognosis Modification of environmental factors Guidance on possible dietary changes, including oral supplementation with essential fatty acids Identification and, if necessary, modification or discontinuation of systemic and topical medications that may contribute to symptoms Use of various types of moisturizing eye drops (artificial tears) Eyelid hygiene and the application of different types of warm compresses	If first-line methods prove insufficient, consider the following interventions: **Use of preservative-free moisturizing drops to minimize toxic effects of preservatives** • Tea tree oil–based preparations in cases of Demodex infestation • Implementation of tear conservation strategies • Punctal occlusion (temporary or permanent) • Use of moisture chamber glasses (e.g., Blephasteam) • Overnight treatments, such as ocular ointments or moisture chambers • In-office heating and decongestion of Meibomian glands • Including the use of devices such as LipiFlow • Intense pulsed light (IPL) therapy, performed in-office **Pharmacological therapy (prescription-based):** • Topical antibiotics, or combination antibiotic-steroid preparations, applied to the eyelid margins in anterior blepharitis (if present) • Topical corticosteroids (for short-term use only) • Secretagogues (agents that stimulate tear secretion) • **Topical immunomodulatory agents that do not contain glucocorticosteroids (e.g., cyclosporine A)** • LFA-1 antagonists (e.g., lifitegrast) • Oral macrolide or tetracycline antibiotics, particularly in cases of associated meibomian gland dysfunction	If previous methods remain insufficient, consider the following advanced interventions: • Use of orally administered secretagogues (tear secretory stimulants) • Application of autologous or allogeneic serum eye drops • Therapeutic contact lenses, including: • Bandage soft contact lenses • Scleral (rigid gas -permeable) lenses	If all previous interventions prove insufficient, consider the following advanced or surgical treatments: • Topical glucocorticosteroids for long-term use (with careful monitoring) • Amniotic membrane transplantation • Surgical punctal closure • Other surgical methods, such as: • Eyelid suturing (tarsorrhaphy) • Salivary gland transplantation

ever, cyclosporine A is typically administered for a minimum of 6 months in cases of DES [13]. During the initial phase of treatment, cyclosporine A may temporarily worsen symptoms such as burning and ocular irritation. The lack of immediate improvement, combined with the need for regular and long-term administration, can negatively impact patient compliance and may even discourage continuation of therapy. Moreover, given that DES is a condition with a complex etiology, the use of cyclosporine A is effective primarily in cases where chronic inflammation is the predominant component. Considering these factors, patient education should be emphasized as an essential element of the treatment process.

Cyclosporine A has been used in the DES treatment for over 20 years, and to date, no ophthalmic complications such as cataract formation, increased intraocular pressure, delayed wound healing, or other serious ocular disorders have been reported [14]. Moreover, the use of cyclosporine A has been extended to a variety of other indications, including uveitis, systemic diseases such as sarcoidosis, idiopathic uveitis syndromes (e.g., sympathetic ophthalmia), corneal transplantation, corneal melting (deliquescent necrosis), fungal infections, pterygium, ocular cicatricial pemphigoid, posterior blepharitis, chronic allergic conditions, Thygeson's superficial punctate keratitis, and contact lens intolerance [14–17].

Adult patients with DES who have not responded to treatment with artificial tear preparations may be eligible for reimbursement from the National Health Fund. Patients diagnosed with Sjögren's syndrome (M35.0), interstitial and deep keratitis (H16.3), or keratitis/keratoconjunctivitis associated with other diseases classified elsewhere (H19.3), according to the ICD-10 classification, are entitled to a 70% reimbursement and thus pay only 30% of the drug's cost [18]. The drug Ikervis® is provided free of charge to senior citizens.

Cyclosporine A is administered once or twice daily, depending on the formulation. In the case of Ikervis, the use of nanoemulsion technology prolongs the drug's retention time on the ocular surface, allowing for once-daily dosing. This formulation improves patient adherence to treatment, which is particularly important in the management of chronic ocular diseases.

The effects of 6 months of cyclosporine A treatment in the patient are shown below (fig. 3). According to the patient, symptoms of dryness and burning decreased, and photophobia resolved. Objective improvements were documented in the Schirmer test, OSDI score, Marx line, tear film break-up time (BUT), and meibography. In addition, tear drainage remained patent, and conjunctival redness was eliminated. An increase in the width of the eyelid crease was also observed, indicating relaxation of the frontalis muscle, which contributed not only to symptom relief but also to a softer facial expression.

CONCLUSIONS

Successful treatment requires an accurate diagnosis as well as sufficient patient motivation and cooperation. According to the TFOS DEWS II report, cyclosporine A may be introduced as early as the moderate stage of the disease. Given that cyclosporine A is an immunomodulatory agent, it is important to recognize that time is required to interrupt the self-perpetuating inflammatory cascade characteristic of DES. Therefore, proper patient motivation and a clear understanding of the underlying mechanisms and disease course are essential. Cyclosporine A remains the only drug of its kind that can be used long term without the risk of serious adverse effects.

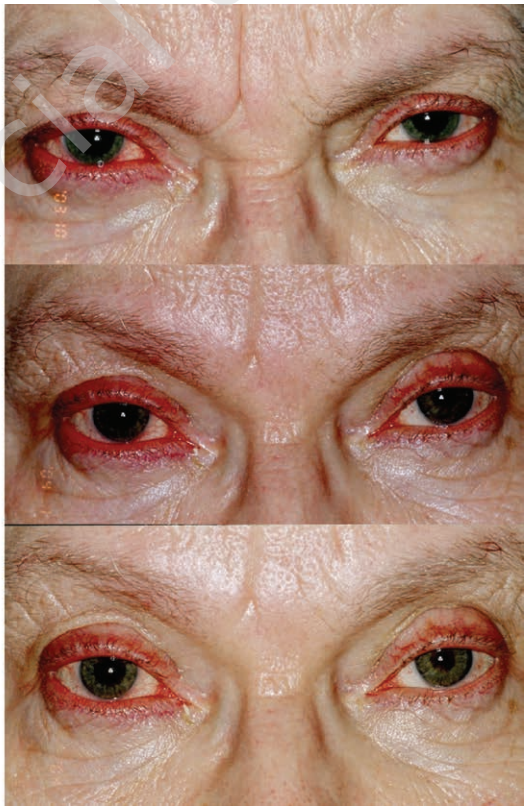
All figures are from the authors' authors' own materials.

FIGURE 3

Photos from private archives.

Patient age: 63
Treatment: Cyclosporine A for 6 months

OSDI score:	35
CSF (Conjunctival Staining Fluorescein):	Grade 2+
Schirmer test:	7 mm
Marx line:	Grade 1
BUT (tear film break-up time):	8 seconds
Meibum quality (Meibography):	Grade 2
Gland permeability:	Good



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