

# Cyclosporine in Dry Eye: A Review

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## Abstract

Dry eye syndrome (DES) is a multifactorial disease with varying prevalence affecting great chunk of population worldwide. Various environmental, nutritional, hormonal and external factors altering the functional integrity of the ocular surface components have been implicated. The imbalance results in changes in epithelium causing desiccation and setting up an inflammatory cascade which causes dysregulation of the ocular surface regeneration system. With increasing knowledge of the etiology and mechanisms involved in the development of dry eye, role of cyclosporine A has been well established with numerous clinical studies. This has led to the US Food and Drug Administration (FDA) approval of the drug for the treatment of dry eye. This article reviews the pathology of development of dry eye, pharmacology of cyclosporine, use of cyclosporine A in dry eye established via various animal and clinical studies.

**Key words:** Cyclosporine, Dry Eye, Keratoconjunctivitis Sicca, Sjogren's Syndrome

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## Introduction

Dry eye has been designated as dry eye syndrome (DES). It is a multifactorial disease of the ocular surface. It is associated with either increased evaporation of tear film or decrease in the production of the tears by the meibomian glands. It can result in various ocular symptoms like discomfort in the form of burning sensation, itching, redness, stinging, pain and foreign body sensation etc. visual disturbances and tear film instability. All these things can cause potential damage to the ocular surface [1]. Various diagnostic tests are available for confirming the dry eye, however it's mostly a clinical diagnosis [2]. Tests like schirmer's test are used to measure the amount of tears produced. There has been varied reports on prevalence of dry eyes among populations. In a study on American population, prevalence was found to be 3.9% in men aging 50-54 years, up to 7.7% in men aging 80 years or more [3]. In female population, it was reported to be 5.7% in females less than 50 years and 9.8% in females aged 75 years or older [4]. DEWS study has provided with an estimated range of 14% among individuals aging from 65-85 years [5]. In a study conducted on Indian population, dry eye prevalence was 36.1% in population above 70 years of age and more in females (22.8%) [6].

Various risk factors associated with dry eye are increasing age [7, 8], female sex, post menopausal estrogen therapy, connective tissue diseases, corneal surface procedures like LASIK [9]. Various environmental factors like contact lens use, low-humidity environments, air conditioners, high altitudes, more of computer or television use, medications like antidepressants, anti hypertensive etc. have also been implicated in aggravating dry eye disease [10-12].

Dry eye can cause a great economic burden by affecting the quality of life of the individuals suffering from it [13]. This can even cause negative effects on patients mental state resulting in anxiety or depression [14]. In a study, it was found that dry eye disease affects the patient's ability to perform daily activities [15].

Treatment options for dry eye disease depend upon the severity of the disease. They can be in the form of environmental modifications or various medications. Environmental modifications like avoiding air conditioners etc. to prevent evaporation of tears or stopping medications that prevent production of tears are useful [16]. Most common medication used to treat dry eye syndrome is artificial tears or ocular lubricants. Nowadays nutritional supplementation with omega-3

fatty acids have been implicated [17]. Recent knowledge of the role of inflammatory molecules like TNF- alpha in the pathogenesis of dry eye has implicated the use of anti-inflammatory molecules like corticosteroids and cyclosporine [18]. Surgical treatment in the form of lid surgery, tarsorrhaphy or mucus membrane, salivary gland, or amniotic membrane transplantation might be needed in severe and chronic dry eye cases [16].

**Cyclosporine:** It belongs to immunosuppressant group of drugs. It was first isolated from a fungus *Tolypocladium inflatum*. This group of drugs acts by lowering the activity of inflammatory cells i.e. T-cells, thereby suppressing the immune response generated by these cells. This property made cyclosporine as the drug available to prevent graft rejection in transplant patients. Disturbance in various factors like age, hormonal status, innervation status, immune status, nutrition, pathogens and environmental stress can disturb the homeostasis in the eye [19]. These disturbances produce an imbalance between degradation and production of the various components of the tear film. This causes release of inflammatory mediators producing a vicious cycle. This warrants the use of anti inflammatory compounds in dry eye. This anti-inflammatory role of the cyclosporine founds application in conditions like psoriasis, rheumatoid arthritis, ulcerative colitis as well as ocular inflammations [20, 21].

**Mechanism of action of cyclosporine:** Cyclosporine has chemical formula of  $C_{62}H_{111}N_{11}O_{12}$  with molecular weight of 120.26 g/mol. It is a non-ribosomal peptide that contains one D-amino acid. Its structure is very rigid because of the hydrogen bonding associated with the cyclic structure. Cyclosporine has low water solubility with variable absorption at the cellular level [22].

It belongs the group of Calcineurin inhibitors. It binds to cyclophilins (lymphocytes) and this complex in turn inhibits calcineurin, thus, preventing the formation of interleukin-2. Cyclosporine is a potent inhibitor of T-cell proliferation and thus, inhibits T-cell mediated immune responses. It might also prevent mitochondrial permeability transition pore opening [23].

The cyclosporine emulsion has been shown to be an effective therapeutic agent to treat moderate to severe dry eye disease in various clinical trials leading to the US Food and Drug Administration (FDA) approval of

the drug in 2003. The exact mechanism of enhanced tear production is not well delineated, but it is hypothesized that it may be related to immunomodulatory activity which reduces local inflammation [24].

**Results of animal studies:** In a study conducted on rabbits with induced autoimmune dacryoadenitis, it was proved that topical use of cyclosporine A improved tear production [25]. In another study conducted on dogs with bilateral keratoconjunctivitis sicca (KCS) the topical use of cyclosporine A resolved clinical signs of KCS, improved schirmer's tear test scores and restored normal conjunctival histology [26].

**Adverse effects:** Renal toxicity is the main adverse effect observed with the systemic use of cyclosporine. Neurotoxicity is enhanced if use along with sirolimus [27]. It is also observed to enhance neoplasm and can cause neurotoxicity, hypertension, hyperlipidemia and nephrotoxicity [28].

**Ophthalmic uses:** Most common clinical ophthalmic use of cyclosporine is to enhance tear production especially in conditions associated with ocular inflammation. Topical use is associated with less systemic adverse effects due to negligible systemic absorption [29]. Earlier formulations available in oil based vehicles had various adverse affects. Now an 0.05% aqueous based formulation is available [30]. The main ocular adverse effects observed are redness, burning sensation and itching. In a study, 64% of the patients treated with cyclosporine were free of the adverse events [31]. In another study, it was observed that even prolonged use of topical cyclosporine for 12 months in patients with dry eye did not cause substantial changes in corneal endothelium [32].

**Efficacy in dry eye:** Various clinical studies have been conducted on use of 0.05% preparation of cyclosporine in dry eye. In one of the study conducted on patients with moderate to severe dry eye, it was observed that most of the patients (72%) were relieved of the symptoms. Ocular symptoms as well as the schirmer's test scores were improved. However, adverse effects observed in this study were only ocular irritation and pain [33].

Role of cyclosporine has been studied even in secondary dry eye states. In a study conducted in patients with Stevens-Johnson syndrome significant improvement was observed in dry-eye symptoms,

conjunctival injection, corneal staining, Schirmer I test and fluorescein clearance test [34].

In another study conducted on patients suffering from dry eye secondary to ocular graft versus host disease or Sjogren's syndrome it was observed that dry eye symptoms were improved in 68.2% whereas physicians assessment of dry eye improved in 72.7% of the patients [35]. Efficacy of dry eye in Sjogren's syndrome was evaluated in a comparative trial with the observation that the symptoms as well as the diagnostic parameters were improved after treatment with cyclosporine [36].

Role of topical cyclosporine therapy has also been implicated in dry eye states secondary to contact lens wear or ocular surgeries like cataract surgery or refractive surgery. In a study conducted on dry eye induced in contact lens wearers, it was observed that topical use of cyclosporine emulsion 0.05% has positive effect on morphofunctional parameters of ocular surface and promotes basal tear secretion and precorneal tear film stability.<sup>37</sup> Efficacy of topical cyclosporine has also been studied in post cataract dry eye. In one study, it was observed that cyclosporine use in post cataract surgery patients improved the dry eye symptoms as well as tear film break up time three months after surgery [38]. Another study proved that topical cyclosporine A treatment is effective therapy for optimizing patients for refractive surgery and treatment of new onset or worsened after refractive surgery [39]. Also, topical use of cyclosporine A has been proven to be effective in treatment of dry eye, especially for dry eye states associated with conjunctival injury [40].

Even benefit of topical cyclosporine A therapy was established in dry eye patients who had discontinued the therapy earlier with repeated treatment after 3 months for a duration of three months. 80% of the patients were observed to have clinical benefit from the second course of treatment [41].

## Conclusion

Cyclosporine A 0.05% is the only FDA approved therapy for the treatment of dry eye syndrome. Most of the studies have shown consistent positive effects in treatment of DES with cyclosporine A. As topical use is associated with very few adverse effects, especially with aqueous preparation of cyclosporine as compared to the systemic use, topical therapy has gained widespread use in various dry eye states.

Seeing the positive effects of cyclosporine therapy in DES improving the quality of life of the sufferers, cyclosporine therapy can have great impact in decreasing the economic and social burden created due to this disease state.

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