# Topical Cyclosporine in the Treatment of Ocular Surface Disorders

***Essay***

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Master Degree in Ophthalmology

***By***

**Mostafa Ahmed Taha Abd Al-Salam**
M.B.B.Ch.

***Supervised By***

**Prof. Dr. Zafer F. Ismail**
Faculty of Medicine
Ain Shams University

**Ass. Prof. Dr. Maged Maher Salib**

Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
Cairo-Egypt
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Abstract:
Mounting evidence and studies suggests that inflammatory process is the key factor in the pathogenesis of different ocular surface diseases, with a complex interplay of genetic, environmental, and psychosocial factors.
The topical CsA preparation proved its efficacy in controlling and treatment of many ocular surface disorders, which considered one of the leading cases of blindness worldwide, particularly the DED and chronic allergic keratoconjunctivitis.

# Acknowledgement

# Table of Contents


- LIST OF ABBREVIATIONS ---------- I
- LIST OF FIGURES ---------- II
- INTRODUCTION ---------- 1
- AIM OF THE WORK ---------- 5
- ANATOMY AND HISTOLOGY ---------- 7
- PHARMACOLOGY ---------- 19
- CLINICAL UESES OF CYCLOSPORINE A--------- 33
  - Dry eye disease ---------- 33
  - Posterior blrphritis ---------- 53
  - Ocular rosacea ---------- 57
  - Vernal keratoconjunctivitis ---------- 59
  - Atopic keratoconjunctivitis ---------- 62
  - Acute corneal graft rejection ---------- 65
  - Conjunctival graft versus host disease ---------- 67
  - Less common uses of topical Cyclosporin A ----- 69
- RECOMMENDED REGIMEN ---------- 71
- SAMMARY ---------- 73
- REFERENCES ---------- 75
- ARABIC SAMMARY ---------- 1

# List of Abbreviations

| | |
|---|---|
| **AKC** | Atopic keratoconjunctivitis |
| **APC** | Antigen presenting cell |
| **ATD** | Aqueous tear deficiency |
| **BAK** | Benzalkonium chloride |
| **CAM** | Cell adhesion molecule |
| **CSA** | Cyclosporine A |
| **DED** | Dry eye disease |
| **GvHD** | Graft-versus-Host disease |
| **HLA** | Human Leukocyte Antigen |
| **HSCT** | Hematopoietic stem cell transplantation |
| **IFN-γ** | Interferon-γ |
| **IL** | Interleukin |
| **KCS** | Kerato-Conjunctivitis Sicca |
| **LASIK** | laser-assisted in situ keratomileusis |
| **MMP** | Matrix Metalloproteinase |
| **MPT** | Mitochondrial permeability transition |
| **mRNA** | messenger Ribonucleic acid |
| **NF-AT** | Nuclear Factor for T-Cell Activation |
| **NGF** | Nerve growth factor |
| **NSTD** | Non-Sjogren tear deficiency |
| **OCT** | Optical coherence tomography |
| **OSD** | Ocular Surface Disorder |
| **PAS** | Periodic Acid Schiff |
| **PCR** | Polymerase chain reaction |
| **SSTD** | Sjogren syndrome tear deficiency |
| **TGF** | Transforming growth factor |
| **TNF** | Tumor necrosis factor |
| **VEGF** | Vascular Endothelial Growth Factor |
| **VKC** | Vernal keratoconjunctivitis |

# List of Figures


| FIGURE | | Page |
|---|---|---|
| 1 | Sagittal section of the eyelids showing the conjunctival Sac and the different parts of the conjunctiva. | 7 |
| 2 | Normal conjunctival fornix. | 9 |
| 3 | Normal bulbar conjunctival. | 10 |
| 4 | Normal palpebral conjunctiva showing surface microvilli. | 10 |
| 5 | Transmission electron micrograph showing the subsurface vesicles of conjunctival epithelial cell fusing with the surface and releasing their contents onto the cell surface. | 11 |
| 6 | Scanning electron micrograph of goblet cell discharging its mucus content onto the conjunctival surface as mucus secretory vesicles. | 12 |
| 7 | structure of cyclosporine A. | 19 |
| 8 | Role of calcineurin in T-cell activation. | 20 |
| 9 | The three layers of precorneal tear film. | 34 |
| 10 | Function of the mucin layer. | 34 |
| 11 | Schematic of National Eye Institute's dry eye classification. | 36 |
| 12 | Immuno-inflammatory pathways. | 39 |
| 13 | Analysis of corneal lymphangiogenesis in a normal eye. | 42 |
| 14 | Permanent punctual occlusion. | 45 |
| 15 | Lid telangiectasia in a patient with blepharitis and ocular rosacea. | 54 |
| 16 | Corneal pannus, neovascularization and scarring secondary to uncontrolled ocular rosacea. | 57 |
| 17 | Giant papillae of the upper tarsal palpebral conjunctiva. The classic cobblestone appearance of VKC. | 59 |

# INTRODUCTION

The ocular surface is one of the most complex and unique tissues in the body. It is also one of the few areas in the body not protected by skin, which is the body's most valuable defense against both desiccation and infection. The ocular surface must remain stable not only to provide protection to the eye, but also to maintain eye comfort, maintain optical clarity of the cornea, serves as a refractive surface for accurate projection of light through the ocular media, and provides protection of the eye structures against microorganisms, trauma and toxins. Creation of an unstable ocular surface from trauma or disease can compromise the integrity of any one of these protective functions and can lead to various forms of corneal and conjunctival dysfunction, broadly ranging from a mild corneal abrasion to severe stem cell loss, decreased vision, and ultimate blindness in the most severe disease ***(Holland et al,. 2013 ).***

The current definition of the ocular surface includes mainly the cornea and conjunctiva with the lacrimal support from the main and accessory lacrimal glands and meibomian glands. Also included is the connective tissue of the conjunctiva, as Plugfelder has suggested. Thus, when any one portion of the ocular surface is

compromised, normal lacrimal support of the ocular surface can be impaired ***(Garget al., 2006).***

Ocular surface diseases are a large group of disorders with a variety of etiologies, symptoms, and clinical findings. These disorders range from simple meibomian gland dysfunction, with excellent prognosis, to Stevens-Johnson syndrome, which can cause permanent scarring of the conjunctiva, loss of corneal transparency and hence loss of vision, with considerable impairment in quality of life. Ironically, most patients with ocular surface disease have a healthy posterior segment with otherwise favorable visual prognosis. Whatever the initial etiological factor of ocular surface disease, once the disease has developed, inflammation becomes the key mechanism of injury to the ocular surface. There is a diversity of initiating insults, such as tear film insufficiency, chemical injury or hypersensitivity mechanisms. When present, inflammation is augmented by mediators released from damaged cells and invading leucocytes. Hence, eyes with ocular surface disease may be trapped in a vicious cycle of inflammation and resultant injury ***(Tatlipinar et al., 2005).***

Two of the most common OSD challenges remain dry eye disease and blepharitis. Our knowledge of both of these conditions has expanded over the last few decades with both clinical and basic science research to support the key role of inflammation as a major

factor in the development of symptoms and clinical findings of these diseases. The combination of factors leading to dry eye states, often referred to as 'dysfunctional tear syndrome' refers to the compilation of lid margin disease, altered tear film composition, decreased tear volume, diminished corneal sensation, and the presence of anti-inflammatory factors in the tear film (***Pflugfelder 2007 ).***

Current medical treatment advances for OSD include new topical and oral therapies for allergic eye disease, limbal stem cell deficiency and dysfunctional tear syndrome. Topical non-steroidal anti-inflammatory agents, Cyclosporine A (CsA), mast cell stabilizer antihistamine agents, and various new formulations of corticosteroids can aid in difficult inflammatory eye conditions, such as severe atopic keratoconjunctivitis and dysfunctional tear syndrome. Medical management of limbal stem cell deficiency includes therapeutic agents from topical vitamin A formulations to autologous serum, various topical growth factors, oral omega 3 fatty acid supplementation, and topical vascular endothelial growth factor (VEGF) inhibitors to counteract corneal neovascularization. In addition, new therapeutic devices, such as meibomian gland probing, intense pulse light therapy, and LipiFlow® can be additive to topical and oral medication regimens for relief of signs and symptoms of various types of OSD ***(Geerling et al., 2011).***

Systemic CsA is a powerful anti T-cell immuno-suppressive agent, which does not lead to bone marrow suppression. Its main complications are hypertension and nephrotoxicity but when used in low doses nephrotoxicity is usually not a problem ***(Strong et al., 2005)***.

CsA is a neutral, hydrophobic, cyclic Polypeptide metabolite of the fungus Tolypocladium inflatum ***(Nussenblatt et al,. 1986)***

Topical treatment with immuno modulatory agent CsA has been shown to reduce cell mediated inflammatory responses associated with inflammatory ocular surface disease ***( El-Asrar et al., 1996).***

Topical CsA ophthalmic emulsion 0.05% (Restasis®; Allergan Inc., Irvine, CA, USA) was approved in 2003 to increase tear production in patients with reduced tear production presumed due to ocular inflammation ***(Karl et al., 2013).***

# AIM OF THE WORK

This review of literature aims to summarize the potential uses of topical Cyclosporine in ocular surface diseases.