

New Therapies and Treatments for Severe Dry Eye

Introduction

A. History of Dry Eye and Physiology

- a. Demtschenko (1872)⁹ and Teplichine (1894)¹⁰ determined that lacrimal secretion was produced by stimulation of different nerves. The original idea to measure lacrimal secretion in humans with an absorbent material was by Koster in 1900
- b. Otto Schirmer developed Schirmer test as a modified practical version around 1905. His father Rudolf was an ophthalmologist who published a number of papers on dacryological topics



c.

Lacrimal secretion and excretion in dacryocystectomized patients (1902)¹; physiology and pathology of lacrimal flow (1903)^{2,3}; the influence of blinking on tear drainage (1904)⁴; histology and physiology of the lacrimal apparatus (1904)⁵; function of the lacrimal mucus in the canaliculi and tear drainage (1906)⁶; Toti's dacryo-cysto-rhinostomy (1908)⁷; and innervation of the lacrimal gland

B. Dry Eye Causes

- a. Medications/Environment/Allergies/Auto-immune conditions/Hormones/Diet

C. Blepharitis

- a. Dry Eye Blepharitis Syndrome (DEBS)
 - i. Biofilm grown by bacteria, communicate by secreting homoserine lactone (HSL). Increase in bacterial load increases levels and an inflammatory response is elicited with lipases, proteases, cytolytic toxins.
 - ii. Folliculitis, MG Dysfunction, Lacrimilitis,

Topical Therapies

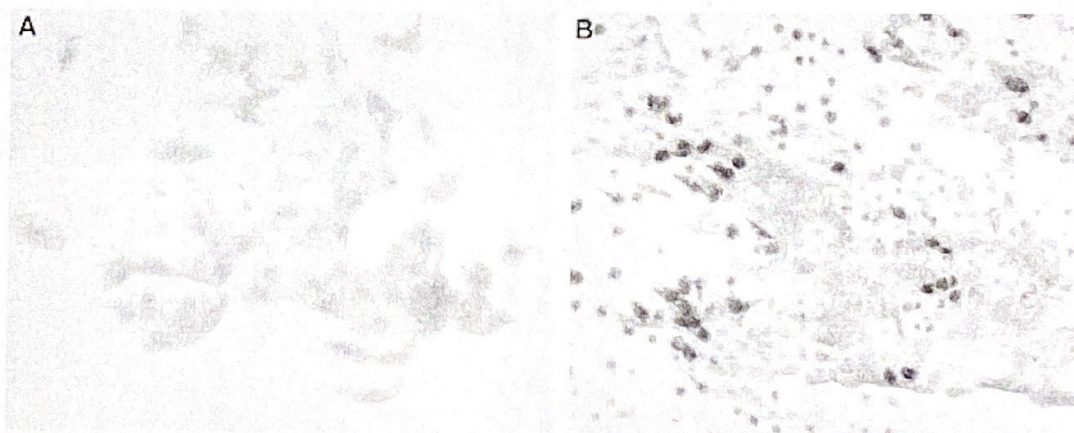
A. Hematopoietic Therapy

B. Evidence suggests substances like epidermal growth factor, fibroblast growth factor, immunoglobulins, fibronectin, Vitamin A are what enhance healing and reduce DED symptoms

1. Allogeneic or Autologous serum tears
2. Use patient's blood, biomolecules perform anti-inflammatory, antimicrobial and epitheliotropic functions, can be used hourly.
3. Allogenic from blood donors
 - i. Biochemical composition of serum in Patients with systemic Autoimmune disease may be altered
 - ii. In South Korea allogeneic serum tears are now covered by government insurance, and allogeneic blood-derived products are being successfully used in Denmark

Representative conjunctival impression cytology specimens before and after 4 weeks of allogeneic serum eye drop use. (A) Before treatment. High-grade squamous metaplasia with the presence of a few goblet cells. (B) Four weeks after allogeneic serum eye drop use. Note obvious improvement of squamous metaplasia and increase in the number of goblet cells.

iii. Allogeneic Serum Eye Drops for the Treatment of Dry Eye Patients with Chronic Graft-Versus-Host Disease



C. Platelet-derived plasma products

- a. Platelet-rich plasma (PRP), which contains numerous growth factors, has been used for over a decade to facilitate healing by multiple surgical specialties, including orthopedic, oral and maxillofacial, reconstructive, cardiovascular, and plastic surgery

- b. Compared with autologous serum, PRP has a higher content of vitamins and growth factors, anti-inflammatory and wound healing components. Also platelets can secrete growth factors and adhere to the ocular surface, facilitating healing of corneal wounds

D. Umbilical cord blood serum

- a. 20% concentration instilled 4-6x daily
- b. Studies have shown increased goblet-cell density

E. Cequa

- a. (cyclosporine ophthalmic solution 0.09%), a calcineurin inhibitor immunosuppressant

A. Stem-cell therapy

1. Mesenchymal stem-cell therapy in experimental dry-eye syndrome models was found to improve tear volume and tear-film stability, increasing epithelial recovery and the number of goblet cells and decreasing the number of meibomian gland injuries in the conjunctiva
2. Regeneration of MG

Oral Therapies

A. Omega-3 Fatty Acids

- a. Alpha-linolenic acid omega 3
- b. Linoleic acid omega 6
- c. Oleic Acid Omega 9

Procedures/ New Modalities

A. Lipiflow - Vectored Thermal Pulsation Treatment (VTPT)

1. Studies have shown a single 12 minute treatment maintained improved MG secretion, TBUT and symptoms of DED for 9 months
2. Heat at 42.5 C to "inner" eyelid while applying pulsatile pressure to "outer" eyelid to express the Meibomian glands. Lid warmer is silicone-lined

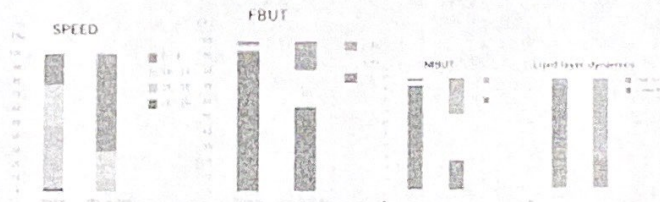
B. Bleph-ex

1. spinning medical grade micro-sponge soaked in cleaning solution that removes biofilm from a patient's lid margins and reduces inflammation

C. IPL - Intensed Pulse Light

1. Rosacea Treatment initially, facial rejuvenation. Targets oxyhemoglobin, there is a thrombolytic destruction of telangiectatic blood vessles. Bacterial counts are dramatically lowered also, due to antiseptic effect of UV light. Increase in mitochondrial output in MG cells and some collagen remodeling in the surrounding tissues.
2. Actual Treatment to Meibomium Glands, require chilling plate to prevent skin burns. Energy levels and Pluses for eyelids.
3. Studies have shown significantly improved DED scores, TBUT and interferometric fringe pattern, lid margin abnormality scores, meibum grade CFS (conjunctival and corneal fluorescein staining after series of 4 treatments

1. Change in the SPEED questionnaire score between baseline and 4 weeks after the final IPL-MGX treatment session, 2. Change in the FBUT between baseline and 4 weeks after the final IPL-MGX treatment session. 3. Changes in the NIBUT (A) and dynamics of the lipid layer of the tear film, as revealed by a tear interferometric fringe pattern (B) between baseline and 4 weeks after the final IPL-MGX treatment session.



Future Treatments

A. Phase I/II trial clinical trial of enzyme-based treatments using a biosynthetic form of DNase

- a. Dnase breaks up nucleic acid-based material. Increase in WBCs in DED (neutrophils) on surface. They release strands of DNA shown to form webs (NETs = neutrophil extracellular traps) on the surface of the cornea to clear material and bacteria. Therefore creating an inflammatory response believed to be from the production of autoantibodies, ACPAs (anti-citrullinated protein autoantibodies) Not enough enzymes present in DED to clear

B. Lubricin

- a. Protein in the tear film which facilitates lubrication between lid and cornea with blinking. Similar to proteins in joints

b. ECF843 (Novartis) is a manufactured protein being used in Orthopedics and DED

C. Proteins developed for replacement in tear film