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*DIPARTIMENTO SPECIALITA' CHIRURGICHE*  
*SEZIONE DI OFTALMOLOGIA*  
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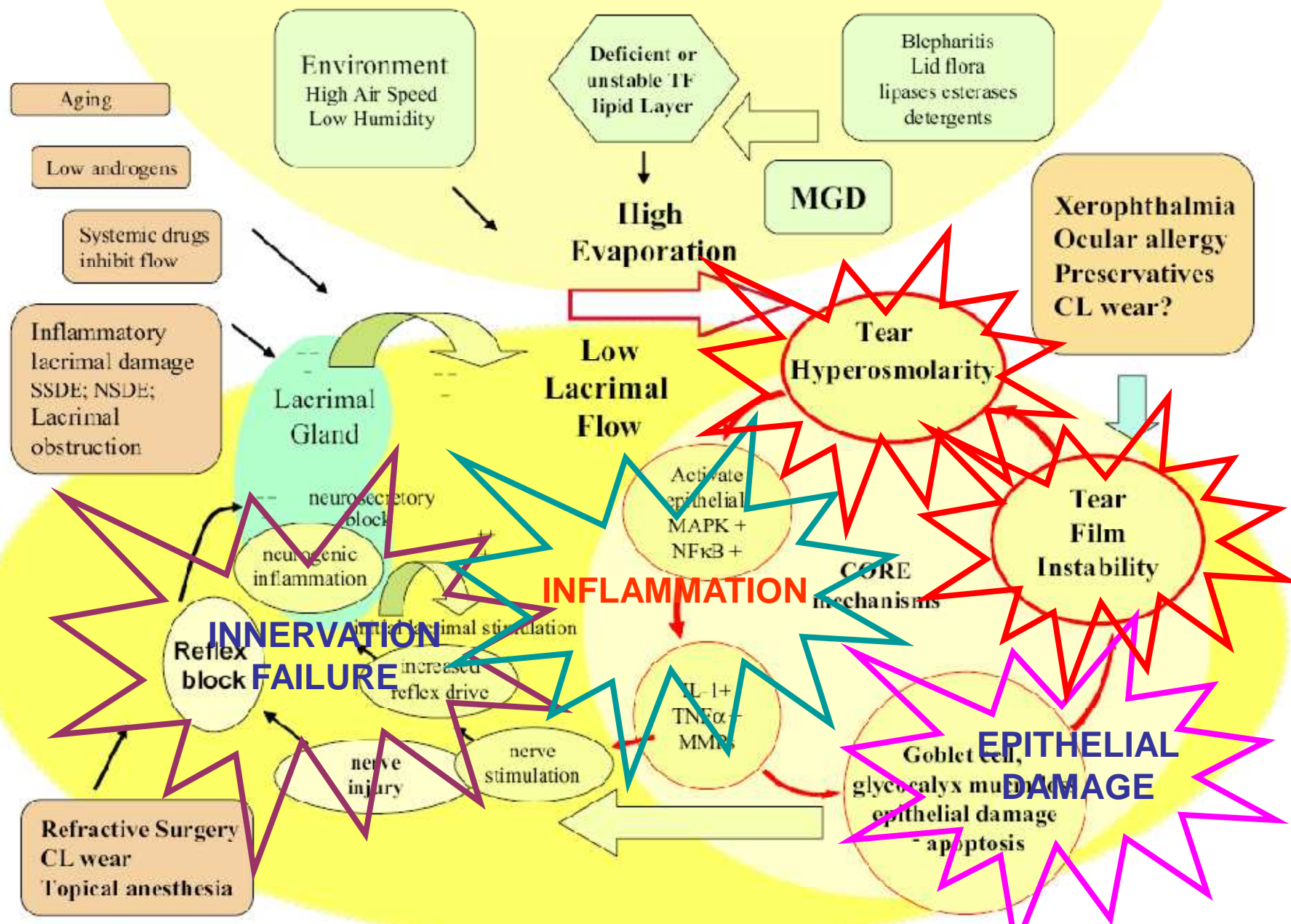
# ***DANNO IATROGENO ALLA SUPERFICIE OCULARE***

## ***Trattamento Riabilitativo***

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# Epithelial Cells and Inflammation

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- (1) Adhesion molecules expression responsible for leukocytes tissue infiltration (ICAM-1)
- (2) Expression of MHC class II responsible for antigen presentation and T lymphocytes activation
- (3) Production and release of PG, leukotrienes e cytokines (GM-CSF) that activates leukocytes
- (4) Production of pro-inflammatory cytokines (IL-1, 3, 6, 8, TNFalpha, MMP)

# Drugs and Ocular Surface

## TOPICAL

- Preservatives
- Anti Glaucoma
  - Beta-blockers
  - Carbonic Anhydrase Inhibitors
  - Prostaglandins/  
Prostamides
- NSAIDs

## SYSTEMIC

- Diuretics
- Beta-blockers
- Anti-histamines
- Anti-cholinergics
- Antidepressants
- Systemic Retinoids  
(Isotretinoin)
- Estroprogestinics

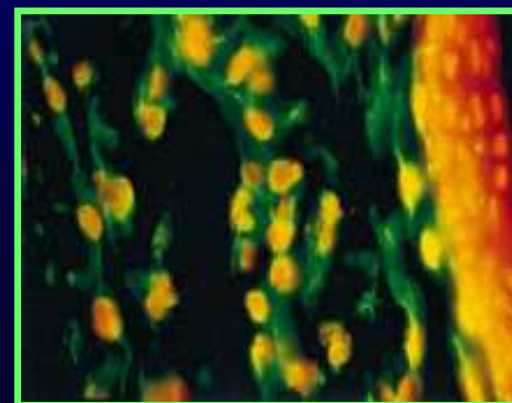


## Chronic Treatment in Glaucoma

**Irritation**



**Structural Modifications**



# GLAUCOMA TREATMENT AND OCULAR SURFACE

- ACTIVE SUBSTANCE EFFECT
- PRESERVATIVE EFFECT

# Preservatives and Glaucoma

- Prolonged administration
- Several eye drops with adding effect of the preservatives
- Increased number of lymphocytes, mastcells, macrophages and fibroblasts in the Tenon capsule and in the conjunctiva in long term treatments

# Preservatives and Glaucoma

- The association of BAK +  $\beta$ -blockers induces a non reversible activation of fibroblasts in vitro
- After long term topical treatment the results of trabeculectomy are often not satisfactory



## Suggested Pathogenesis for Altered Tear Secretion due to Preservatives



# ANTI-GLAUCOMA DRUGS

## ACTIVE SUBSTANCES

- $\beta$ -Blockers
- Carbonic Anhydrase Inhibitors
- $\alpha$ -Agonists
- Prostaglandins/ Prostanoids

# $\beta$ -blockers

- Decreased Tear Secretion
- Corneal Hypoaesthesia
- Irritation (blepharitis, conjunctivitis, keratitis)
- Conjunctival Inflammation and Fibrosis (in association with BAK)
- Ptosis

Mietz H et al. IOVS 2001

Weissman SS, Asbell PA *Br J Ophthalmol* 1990

Ferreri G et al. 1994

Manni G et al, *Am J Ophthalmol* 2005

# Carbonic Anhydrase Inhibitors

- Epithelial Damage :
  - Corneal Epithelium: loss of microvilli, increased cellular shedding, cellular membrane damage
  - Inflammatory cells infiltration in conjunctival stroma
- Stromal and Endothelial Damage:
  - Endothelial Cells Reduction (3.6%/year)
  - Increased Corneal Thickness (0.47%/year)
- Corneal Sensitivity Reduction in both adult (60-86 aa.) and young (23-40 aa.) subjects

Noecker RJ et al. *Cornea* 2004

Lass JH, et al. *Arch Ophthalmol* 1998

Kohlaas M, et al. *Ophthalmologe* 1997

Wirtitsch MG, et al. *Arch Ophthalmol* 2003

# $\alpha$ -Agonists

Brimonidine: alfa-2 Receptors Agonist

- Ocular hyperemia and burning (22-25%)
- Allergy (12,7%)
- Blepharitis
- Punctate Superficial Keratitis
- Dry Eye
- Conjunctival whitening

# Prostaglandins/ Prostamides

- Eyelashes: Increased number, thickness, length
- Blepharitis
- Conjunctival Hyperemia
- Peri-ocular pigmentation
- Discomfort symptoms (Burning, Itching, Tearing, Dry eye)

# Prostaglandins/ Prostamides

- Corneal thickness reduction

(Viestenz A et al. Klin Monatsbl Augenheilkd. 2004)

- Corneal sensitivity reduction

(Kozobolis VP et al. Am J Ophthalmol 2005)

- Corneo-conjunctival epithelial damage (BAK?)

Noecker RJ et al. Cornea 2004

# Prostaglandins/ Prostamides

- Increased HLA-DR expression in conjunctival epithelium of patients treated with Latanoprost  
Guglielminetti E et al. *J Ocul Pharmacol Ther* 2002

- MMP3 expression and fibroblast infiltration in conjunctival stroma  
Mietz H et al. *IOVS* 2001

- Latanoprost, Travoprost and Bimatoprost toxicity show a direct correlation with BAK content  
Guenoun JM et al. *Invest Ophthalmol Vis Sci* 2005



# Prostaglandins/ Prostamides

- High BAK concentrations (0,02%). (Bimatoprost BAK 0,005%)
- Concentrations of BAK  $> 0,01\%$  induce cellular death within 24 hours by apoptosis
- At a concentration of  $\leq 0,005\%$  the cell damage is dose dependant

(De Saint Jean M, et al. IOVS 1999)

# Glaucoma Treatment and Tear Osmolarity

- Increased tear osmolarity in patients with multiple treatment for glaucoma
  - 15 pts (8 M; age  $54.3 \pm 8.9$ ), treated for at least 6 months with 2 or more eye drops  
tear osmolarity:  $329.4 \pm 10.5$
  - 15 ctr (7M; age  $59.7 \pm 11.3$ ), non treated,  
tear osmolarity:  $307.8 \pm 8$

# TEAR SUBSTITUTES

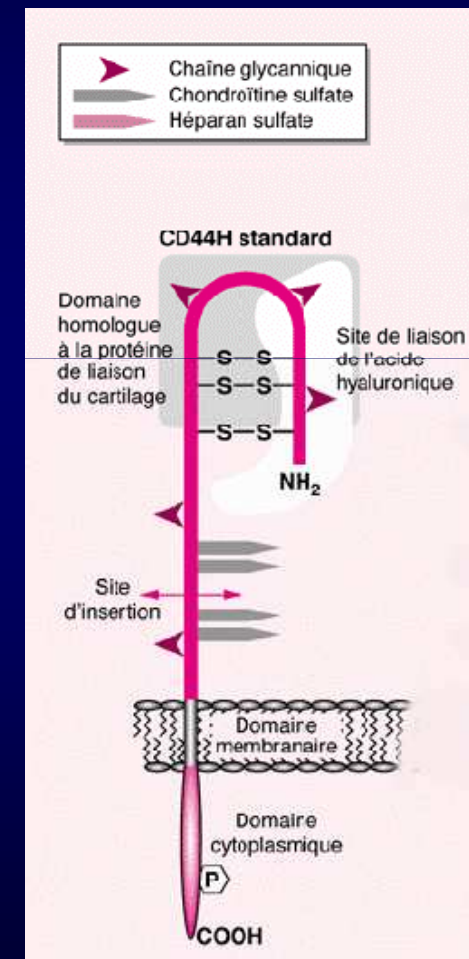
- TEAR OSMOLARITY REDUCTION
  - Hypoosmolar tear substitutes
- AMELIORATE THE EPITHELIUM
  - Hyaluronate
  - Potassium
  - Bicarbonate

# Hyaluronate

Binds high volumes of water due to its negative charges

A SPECIFIC RECEPTOR IS PRESENT ON THE OCULAR SURFACE

Help cicatrization and riepithelialization



## CLINICAL SCIENCE

# Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye

Pasquale Aragona, Vincenzo Papa, Antonio Micali, Marcello Santocono, Giovanni Milazzo

*Br J Ophthalmol* 2002;86:181-184

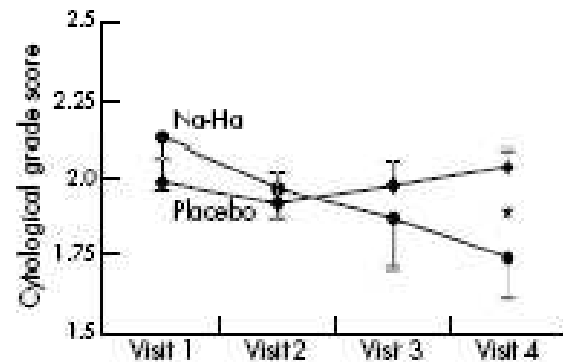
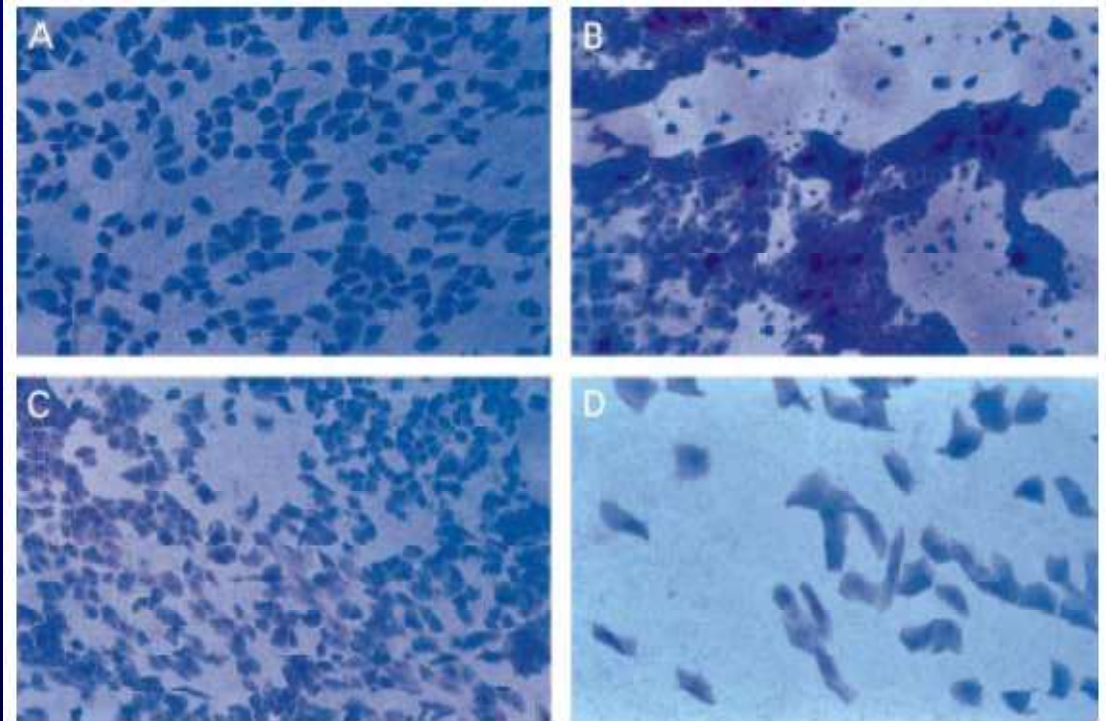


Figure 1 Impression cytology scores after treatment with sodium hyaluronate (Na-Ha) or saline (placebo). Data are expressed as mean values (SEM) of left and right eye scores obtained at each day visit (V1 = baseline; V2 = 1 month; V3 = 2 months; V4 = 3 months). Between groups comparison (Na-Ha v saline): V1:  $p = 0.115$ ; V2:  $p = 0.720$ ; V3:  $p = 0.479$ ; V4:  $*p = 0.036$ . Within groups comparison: saline: V2 v V1:  $p = 0.776$ ; V3 v V1:  $p = 0.752$ ; V4 v V1:  $p = 0.259$ . Na-Ha: V2 v V1:  $p = 0.083$ ; V3 v V1:  $p = 0.156$ ; V4 v V1:  $*p = 0.024$ .



**CLINICAL SCIENCE**

Sodium hyaluronate eye drops of different osmolarity for the treatment of dry eye in Sjögren's syndrome patients

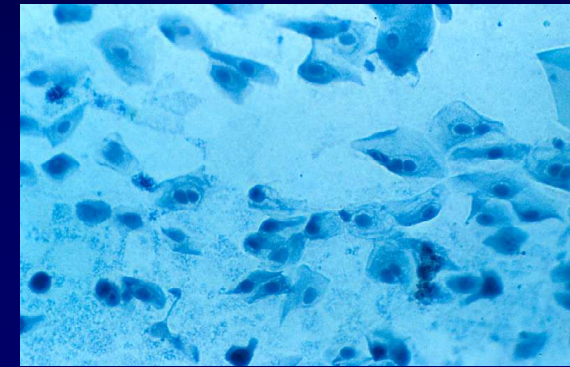
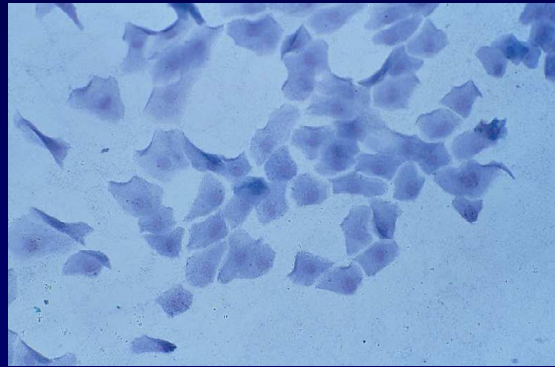
P Aragona, G Di Stefano, F Ferreri, R Spinella, A Stilo

*Br J Ophthalmol* 2002;86:879-884

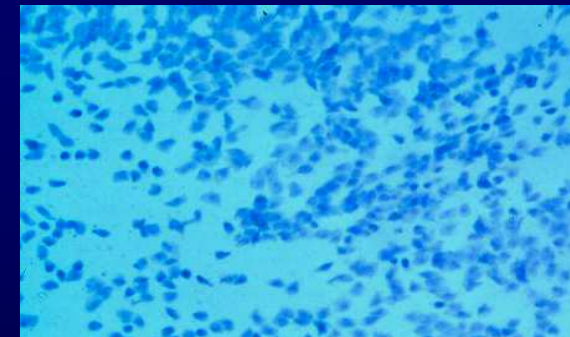
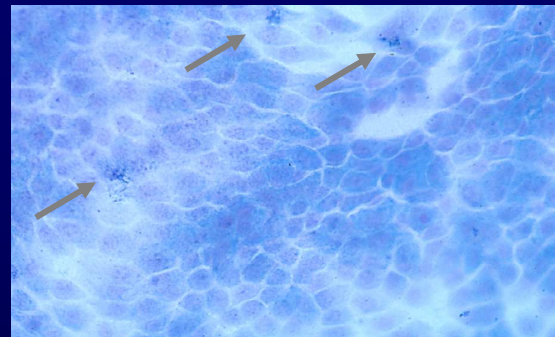
**Hypotonic HA**

**Isotonic HA**

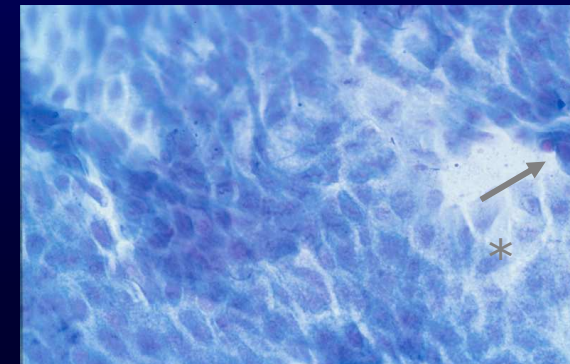
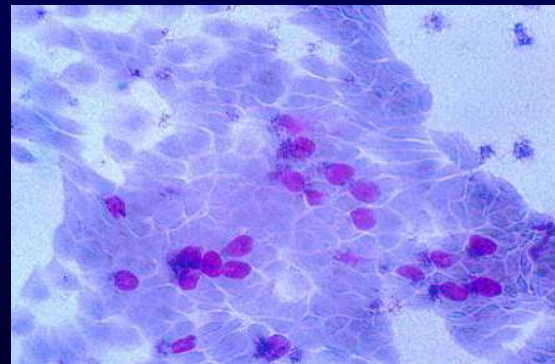
**Baseline**



**1 Month**



**3 Month**



# Potassium and Ocular Surface

- Maintains the corneal thickness in culture
- Increases the corneal glycogen content
- Increases the number of goblet cells in experimental models and in patients with post-Lasik dry eye

Green K, et al. *Ophthalmic Res* 1992

Gilbard JP, Rossi SR. *Ophthalmology* 1992

Lenton LM, Albietsz JM. *J Refract Surg* 1999

# Bicarbonate and Ocular Surface

- Barrier function restoring of damaged corneal epithelial cells obtaining a normal cellular ultrastructure
- Plays a fundamental role for the formation and maintaining of the mucin gel of the stomach and might play a similar role also for ocular surface mucins.

Ubels JL et al Arch Ophthalmol 1995

Lopez Bernal D et al Cornea 1993

Slomiany BL, Slomiany A J Physiol Pharmacol 1991



# Materials and Methods

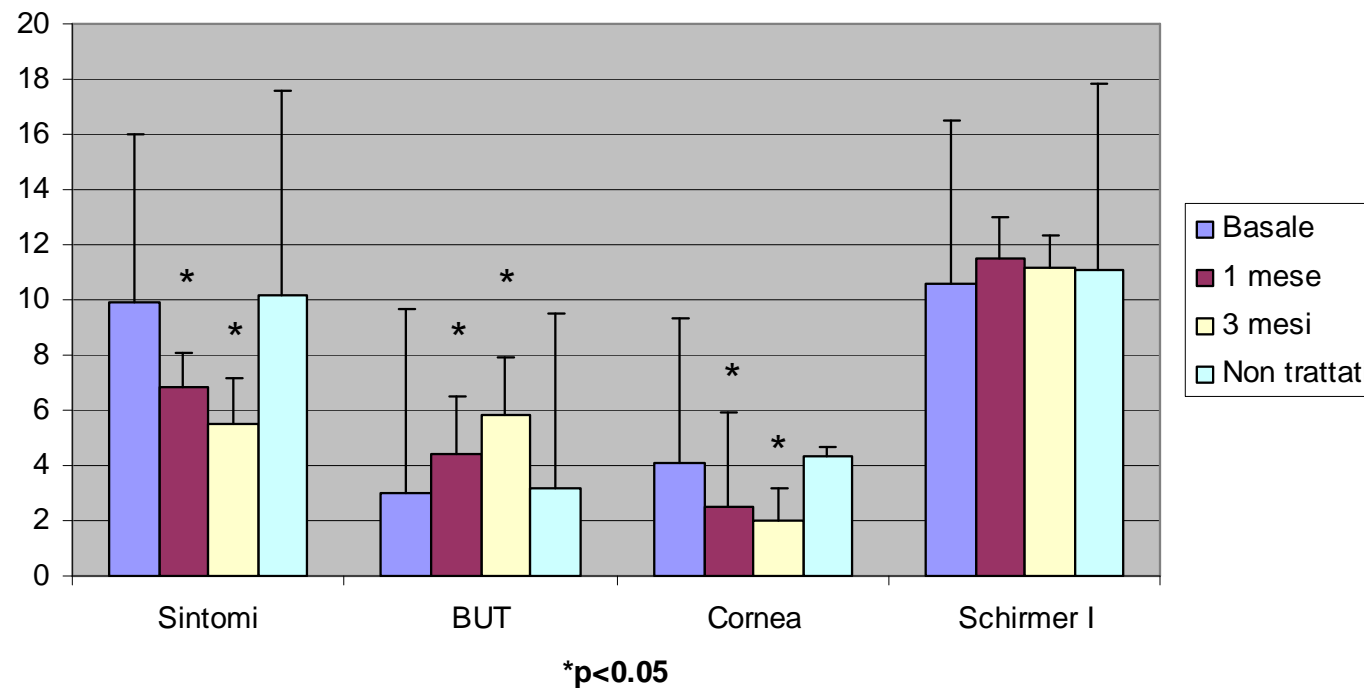
- 40 pts. treated for Glaucoma for at least 6 months with 2 or more eye drops
  - 20 treated for Glaucoma + 0,4% Hypotonic HA and solutes [Oftaial, Alfa Intes, Casoria (NA)] (12 M; age  $66,7 \pm 9.3$ )
  - 20 treated for Glaucoma (11 M; age  $63.7 \pm 11.3$ )

# Materials and Methods

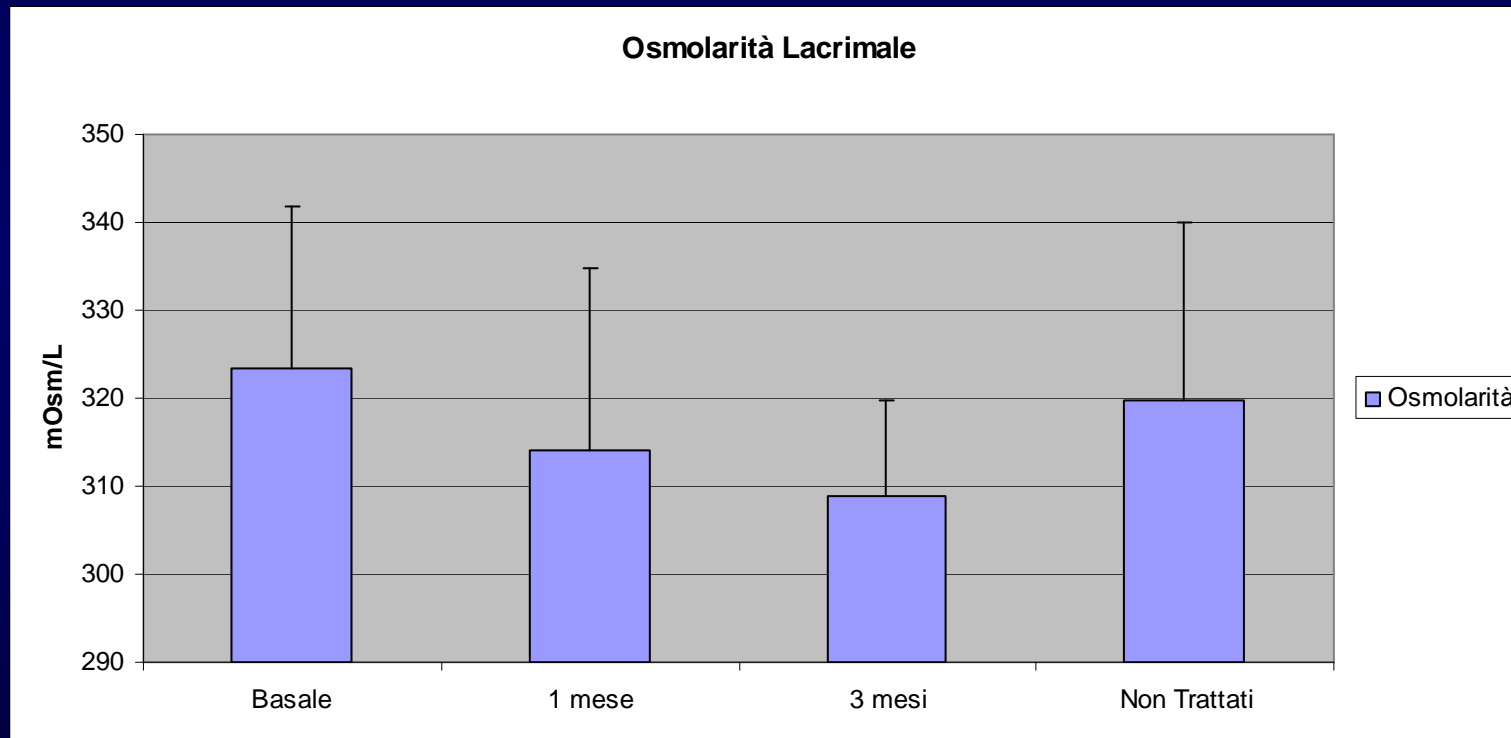
- Tests performed:
  - Symptoms Questionnaire (score)
  - Tear Osmolarity (TearLab<sup>®</sup>)
  - BUT
  - Ocular Surface Fluorescein Stain (van Beijsterveld score)
  - Schirmer's I Test
  - Conjunctival Histochemistry for HLA-DR expression

	Sintomi	BUT	Epitelio	Schirmer I
HA basale	9,9±6,1	3±1,3	4,1±1,7	10,6±7,4
HA 1 mese	6,8±6,7	4,4±2,1	2,5±2,1	11,5±6,3
HA 3 mesi	5,5±5,2	5,8±3,4	2±1,2	11,2±0,4
Non Trattati	11,1±5,9	3,2±1,5	4,3±1,1	11,1±6,7

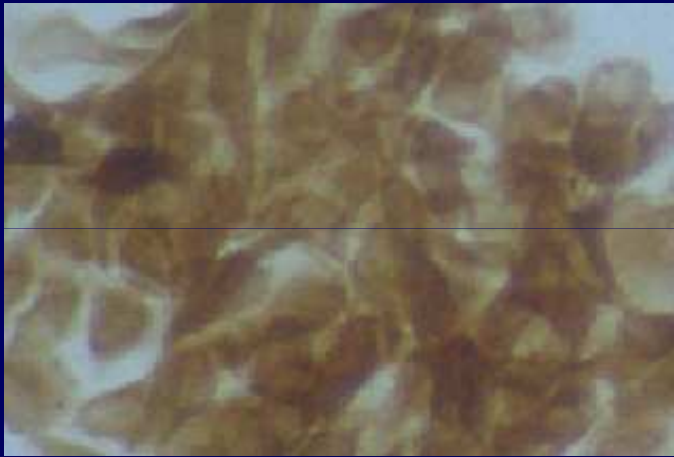
### Segni e Sintomi



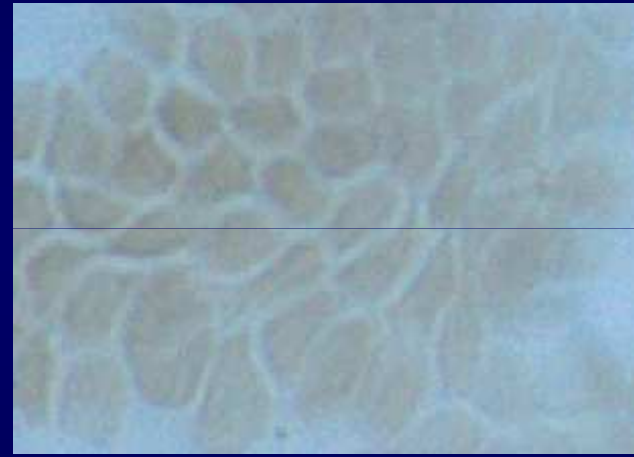
	Basale	1 mese	3 mesi	Non Trattati
Osmolarità	323,4±18,4	314,1±20,7	308,8±10,9	319,8±20,1



# Espressione di HLA-DR



Baseline



3 mesi

# CONCLUSIONS

- Glaucoma treatment should also consider the ocular surface condition to avoid annoying side effects.
- Prolonged treatments significantly modify the conjunctival structure
- A therapy aimed to improve the ocular surface should be considered
- Hypotonic Hyaluronate and solutes such as Potassium and Bicarbonate are helpful to restore a normal ocular surface

