OCULAR SURFACE DISEASE IN PATIENTS UNDER TOPICAL TREATMENT FOR GLAUCOMA

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VISSUM

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INTRODUCTION

- Glaucoma is the leading cause of irreversible blindness worldwide.
- An estimated 60 million people suffer from the disease globally.
- ***Topical antiglaucoma medications remains critical in management of chronic glaucoma.***
- ***Topical IOP lowering medications are still considered the first line of treatment in glaucoma control.***

Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006 Mar;90 (3):262–267.

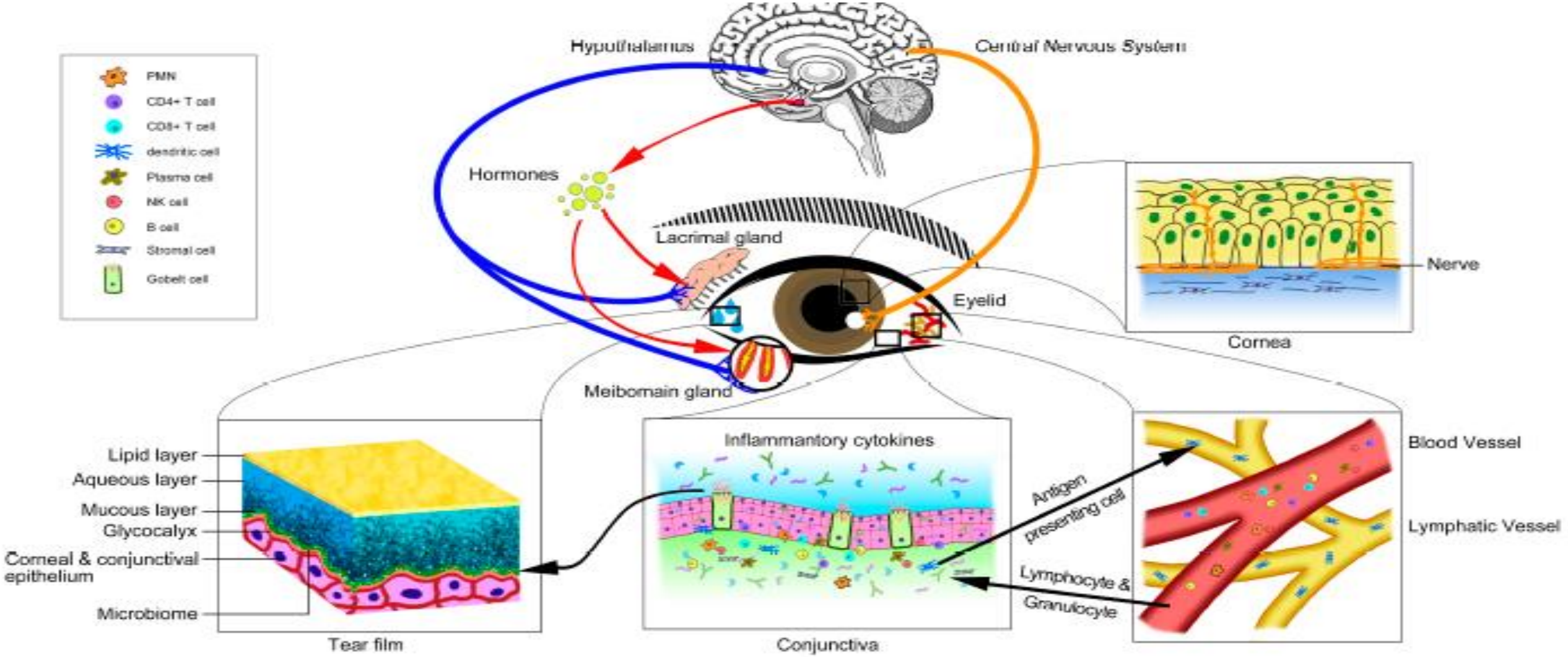
Varma R, Lee PP, Goldberg I, et al. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol. 2011 Oct;152 (4):515–522.

INTRODUCTION

- Treatment is cumbersome as it involves lifelong commitment to daily application of eye drops from once to many times per day... For lifelong!!
- 40% of glaucoma patients require more than one IOP lowering agent daily.
- The resultant effect is chronic exposure to the active ingredients and associated preservatives.

Anwar Z, Wellik SR, Galor A. Glaucoma therapy and ocular surface disease: current literature and recommendations. Curr Opin Ophthalmol. 2013 Mar;24(2):136–143

OCULAR SURFACE MICROENVIRONMENT FOR A HEALTHY OCULAR SURFACE



INTRODUCTION

- The beneficial effects of treatment are frequently counterbalanced by the adverse effects of corneal and conjunctival toxicity.

- Many studies have shown preservatives, especially benzalkonium chloride to be ***toxic to the ocular surface …*** and ALSO constitute a negative variable in the success rate of glaucoma surgical filtering prodedures

Nakagawa S, Usui T, Yokoo S, et al. Toxicity evaluation of antiglaucoma drugs using stratified human cultivated corneal epithelial sheets. Investig Opthalmol Vis Sci. 2012 Aug;53(9):5154–5160.

Ayaki M, Iwasawa A, Niwano Y. Comparative study of in vitro ocular surface cytotoxicity of a fixed combination of 0.5% timolol/1% dorzolamide eyedrop and its components with 0.005% benzalkonium chloride. Biocontrol Sci. 2012;17(3):115–120.

Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. Acta Ophthalmol. 2008 Nov;86(7):716–726.

INTRODUCTION

- Topical antiglaucoma medications have different levels of impact on the health of the ocular surface.

- Preservative-free medications have fewer adverse effects compared with preserved medications.

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UNIVERSITAS Miguel Hernández

OPINION ON DRUG METABOLISM & TOXICOLOGY, 2016
12, NO. 11, 1279–1289
p://dx.doi.org/10.1080/17425255.2016.1209481

REVIEW

Ocular surface toxicity from glaucoma topical medications and associated preservatives such as benzalkonium chloride (BAK)

Alberto Aguayo Bonniard[a,*], Jacky Y. Yeung[a,b,*], Clara C. Chan[a] and Catherine M. Birt[a]
partment of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Canada; [b]Department of Opht
Ontario

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glaucoma patients. The role of topical anti
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OPINION

Glaucoma therapy and ocular surface disease: current literature and recommendations

Zane Anwar[a,b], Sarah R. Wellik[a,b],

Purpose of review
To provide an update on clinical and experimental lit
therapy and to provide practical guidelines for opht
surface disease (OSD).

Recent findings
Preservatives, notably benzalkonium chloride (BA
a variety of toxic ocular effects both in-vitro, an
compares BAK with Polyquad, SofZia, and pre
demonstrated with newer BAK-free alternative
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Ocular Surface Disease in the Glaucoma Patient

Michael Banitt
Hoon Jung

Introduction

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Review

The impact of topical intraocular pressure lowering medications on the ocular surface of glaucoma patients: A review

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Abstract

REVIEW

Ocular Surface Disease and Glaucoma Medications: A Clinical Approach

Xuemin Zhang, M.D., Saujanya Vadoothker, M.D., Wuqaas M. Munir, M.D., and Osamah Saeedi, M.D.

conditions, and here we aim to focus on the coexistence of ocular surface disease with glaucoma.
Glaucoma is the second leading cause of blindness in the world and is expected to affect 79.6 million people by 2020. At present, million Americans older than 50 years who have laucoma.[3–6] Topical medical therapy is laucoma, and 49% to 59% medications

- **LOCAL ANTIGLAUCOMA THERAPY TOXICITY: 3 factors are involved:**

1-The condition of the ocular surface before glaucoma surgery (if needed)

2- The impact of the active pharmacological agents in antiglaucoma drugs

3- The impact of preservatives in glaucoma medications.

Interaction among the 3 factors… influences the breakdown of the ocular surface and the response and prognosis of such cases.

EFFECT OF GLAUCOMA MEDICATIONS ON CONJUNCTIVA MAY INDUCE FAILURE OF GLAUCOMA FILTRATION SURGERY

- Preoperative *subclinical inflammation induced by topical medications* was identified as a risk factor for failure of trabeculectomy.

- Decrease in goblet cells.

- Increased number of lymphocytes, fibroblasts, macrophages, and mast cells of the conjunctiva.

- *Subclinical inflammation was found to be correlated with the number of drugs and the duration of therapy.*

Sherwood MB, Grierson I, Millar L, et al. Long-term morphologic effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients. Ophthalmology. 1989 Mar;96 (3):327–335.

Broadway DC, Grierson I, O'Brien C, et al. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. Arch Ophthalmol. 1994 Nov;112(11):1437–1445.

Lavin MJ, Wormald RP, Migdal CS, et al. The influence of prior therapy on the success of trabeculectomy. Arch Ophthalmol. 1990 Nov;108(11):1543–1548.

Broadway DC, Grierson I, O'Brien C, et al. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Arch Ophthalmol. 1994 Nov;112(11):1446–1454.

EFFECTS OF PHARMACEUTICAL AGENTS IN ANTIGLAUCOMA DRUGS ON OCULAR SURFACE

- The active pharmaceutical agents may induce ocular surface changes and worsen dry eye symptoms:

- Preservative free timolol affects the integrity of tear film.
- Non-preserved beta blockers induce more damage on the ocular surface compared to PGA and brimonidine-purite.

PRESERVATIVES IN GLAUCOMA MEDICATIONS

- Preservatives are needed in multidosed eye drops to maintain sterility.
- Current preservatives belong to a variety of chemical families including:

- Alcohols.
- Parabens.
- Ethylenediaminetetraacetic acid.
- Corhexidine.

- **BUT** quaternary ammonium compounds are the most widely used because of their low allergenic properties and good safety profiles.

Baudouin C, Labbé A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010 Jul;29(4):312–334.

PRESERVATIVES IN GLAUCOMA MEDICATIONS

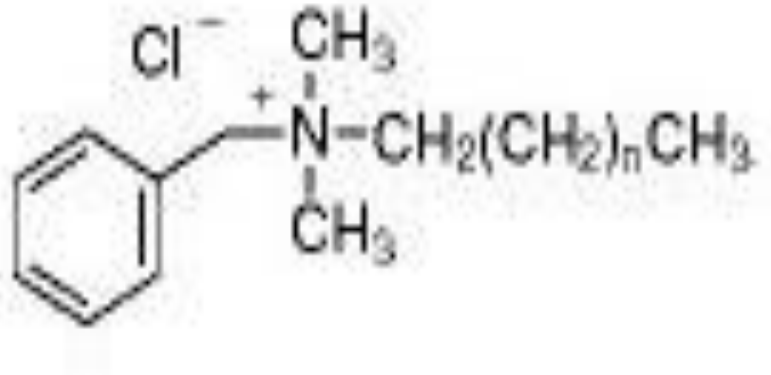
Preservative	Antihypertensive brand name	Preservative concentration*	Frequency	Manufacturer
Benzalkonium chloride (BAK)*	Simbrinza	0.0030%	BID[1]	Alcon
	Betagan	0.0040%	BID	Allergan
	Combigan	0.0050%	BID	Allergan
	Cosopt	0.0075%	BID	Merck
	Iopidine	0.0075%	TID[2]	Alcon
	Trusopt	0.0075%	BID	Merck
	Azopt	0.0100%	BID	Alcon
	Betoptic	0.0100%	BID	Alcon
	Pilocarpine	0.0100%	QID[3]	Alcon
	Timolol	0.0075%	BID	Various
		0.0120%		
	Lumigan	0.0200%	QHS[4]	Allergan
	Xalatan	0.0200%	QHS	Pfizer
	Xalacom	0.0200%	QHS	Pfizer
Benzododecinium Bromide	Timoptic XE	0.0120%	QAM[5]	Merck
Polyquaterium-1	Duotrav	0.0010%	QAM	Alcon
Purite®	Alphagan-P	0.0050%	TID	Allergan
SofZia®	Travatan-Z	0.0040%	QHS	Alcon
Preservative-free formulation	Cosopt, Pilocarpine, Timoptic, Zioptan	N/A		Various

Aguayo Bonniard A, Yeung JY, Chan CC, Birt CM. Ocular surface toxicity from glaucoma topical medications and associated preservatives such as benzalkonium chloride (BAK). Expert Opin Drug Metab Toxicol. 2016 Nov;12(11):1279-1289.

BENZALKONIUM CHLORIDE (BAK)

- The most commonly used preservative in eye drops is benzalkonium chloride (BAK).

- Present in 70% of ophthalmic glaucoma drops at concentrations ranging from 0.003% to 0.02%.



Freeman PD, Kahook MY. Preservatives in topical ophthalmic medications: historical and clinical perspectives. Expert Rev Ophthalmol. 2009;4(1):5.

BENZALKONIUM CHLORIDE (BAK)

- The bacteriostatic and bactericidal property of BAK prevents contamination and colonization of the bottle by Gram +ve and Gram –ve bacteria, fungus, and amoeba.

- The effect that BAK has on cell membranes is not selective to microorganisms; it can also injure epithelial cells lining the ocular surface by the same mechanism of action.

- *Charnock C. Are multidose over-the-counter artificial tears adequately preserved? Cornea. 2006 May;25(4):432–437.*

EFFECT OF BAK ON THE CORNEA, TEAR FILM AND CONJUNCTIVA

- Interfere with lipid layer of tear film with subsequent decreased tear film BUT and increased aqueous tear evaporation.
- Reduction in the density of goblet cells which impairs mucin production and affects tear film stability.
- Alterations in the corneal stroma, when the integrity of the epithelium is compromised.
- Can induce inflammation within the conjunctival tissue which may ultimately result in dry eye symptoms.
- Direct effects on corneal epithelial cells.

Alternatives to topical medications with BAK

Active ingredient	BAK alternative or preservative free
Brimonidine tartrate 0.1%	0.1% Purite
Travaprost Z	SofZia
Tafluprost 0.0015%	Disodium EDTA, polysorbate, or preservative free
Echothiophate iodide	0.125% chlorobutanol
Timolol maleate 0.5%/dorzolamide 2%	Individual ampules of buffered solution
Timolol maleate 0.25%, 0.5%	Individual ampules of buffered solution versus bottle with benzododecinium bromide§ preservative

- ***Toxicity from medications can lead to***:

- Patient discomfort.
- Lack of compliance.
- Induction of scarring
- Tachyphylaxis.
- Failure of glaucoma filtration surgery (as mentioned before).

OCULAR SURFACE DISEASE (OSD)

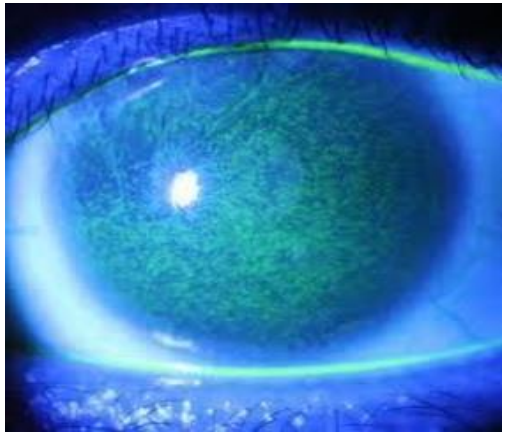
- OSD is a broad term describing dysfunction of the cornea and conjunctiva with symptoms of:

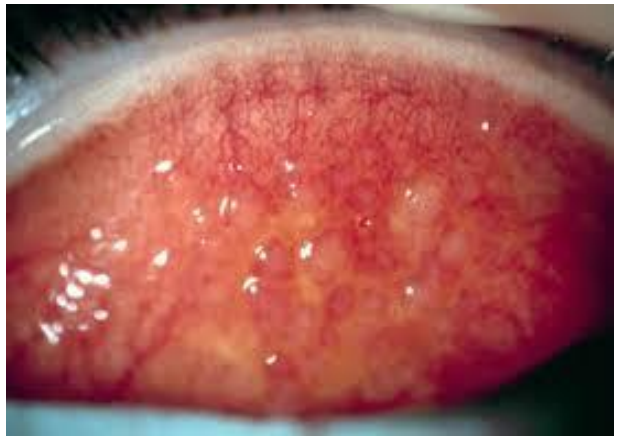
- Dryness.
- Redness.
- Tearing.
- Irritation.
- Burning.
- Itching.
- Foreign body sensation.
- Light sensitivity.
- Intermittent decreased vision.

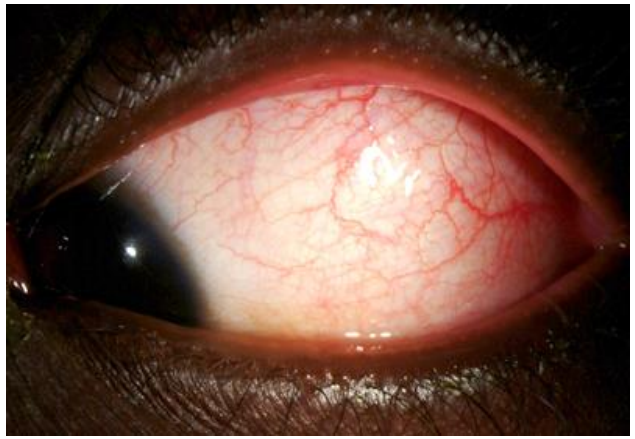
OCULAR SURFACE DISEASE (OSD)

- **Clinical signs of OSD include**:

- Superficial punctate keratitis.
- Tear film instability (decreased tear film BUT).
- Conjunctival erythema.
- Papillary conjunctivitis.

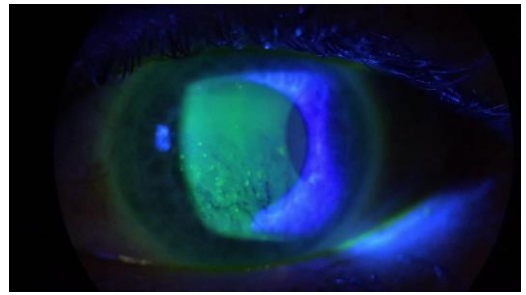


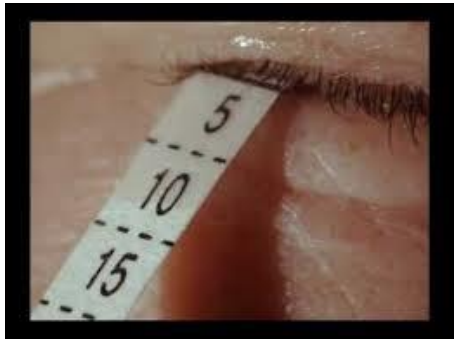




MONITORING OCULAR SURFACE …

- Clinical examination.
- Functional questionnaires to quantify the effects of ocular surface disease on patient quality of life.
- Tear breakup time (TBUT).
- Schirmer's testing.
- Conjunctival reaction.
- Meibomian gland dysfunction.
- Evaluation of the corneal epithelium.





OCULAR SURFACE DISEASE (OSD) & GLAUCOMA

- Both dry eye and glaucoma diseases are more common in older patients.

- OSD are present in 15% of the elderly population and have been reported in several studies to be more common in patients with glaucoma.

OCULAR SURFACE DISEASE (OSD) AND GLAUCOMA MEDICATIONS

- Approximately *60% of glaucoma patients on topical medications have been found to have OSD with major impact on quality of life and drug compliance*.

- Ocular surface disease in glaucoma patients can be a pre-existing condition that is exacerbated by topical therapy or a novel disease that manifests after initiation of topical glaucoma therapy.

OCULAR SURFACE DISEASE (OSD) AND GLAUCOMA MEDICATIONS

- ***Hollo et al.*** defined glaucoma therapy–related ocular surface disease well as:

"imbalance of the ocular surface homeostasis caused by the toxic effect of chronic topical medication, which leads to tear-film instability, epithelial damage, and inflammation".

Hollo G, Katsanos A, Boboridis KG, et al. Preservative-free prostaglandin analogs and prostaglandin/timolol fixed combinations in the treatment of glaucoma: efficacy, safety and potential advantages. Drugs. 2018;78:39–64.

OCULAR SURFACE DISEASE (OSD) & GLAUCOMA

- This interaction is further complicated by treatments for each condition.
- Both ocular surface disease and glaucoma can affect the quality of life.
- Increasing number of glaucoma drops is significantly associated with an increased percentage of severe dry eye symptoms.

OCULAR SURFACE DISEASE (OSD) AND GLAUCOMA MEDICATIONS

- A large multinational European cross-sectional survey of 9658 glaucoma patients showed patients on preservative free drops (12% of the study population) reported less OSD symptoms versus patients on drops with preservatives (74% of the study population).

Jaenen N, Baudouin C, Pouliquen P, et al. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol. 2007 May–Jun;17(3):341–349.

OCULAR SURFACE DISEASE (OSD) AND GLAUCOMA MEDICATIONS

- In a prospective epidemiological survey of over 4000 patients, the incidence of OSD symptoms was approximately *two times higher in patients using preserved than PF drops.*

Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative-free glaucoma medication. Br J Ophthalmol. 2002 Apr;86(4):418–423.

THINK BEFORE SELECTING GLAUCOMA MEDICATIONS IN DRY EYE PATIENTS

- *Topical beta-blockers*, whether preserved or unpreserved, have been shown to have *the greatest adverse effects* on the ocular surface compared to other medications.

- Among the prostaglandin analogs, trovoprost, even with preservatives, *has less impact on the ocular surface* compared to latanoprost, bimatoprost, and even non-preserved tafluprost.

THINK BEFORE SELECTING GLAUCOMA MEDICATIONS IN DRY EYE PATIENTS

- In the choice of an adjunctive therapy for a glaucoma patient, on either beta blockers or prostaglandins analogs, alpha agonist appears to have less risk for dry eye symptoms, when compared to carbonic anhydrase inhibitors and miotics like pilocarpine.

TREATMENT CONSIDERATIONS

- Stepwise decreasing the number of treatments with the same offending agent may provide a controlled decrease in exposure while balancing the desire therapeutic effects.

- Combined medications can be used to decrease the overall BAK amount.

TREATMENT CONSIDERATIONS

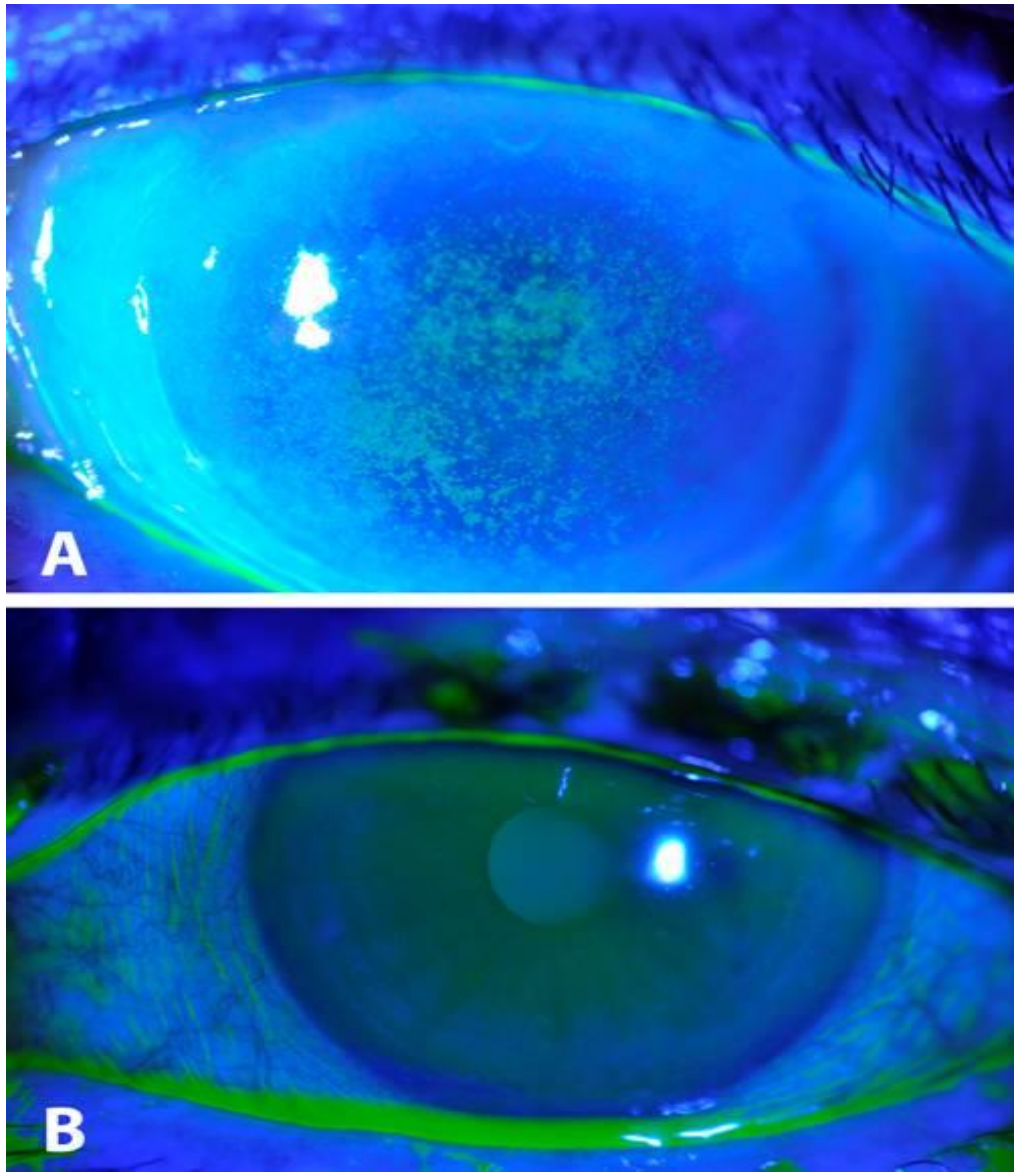
- Switch to medications without BAK or preservative free.
- LASER trabeculoplasty earlier may be a helpful consideration.
- Minimally invasive glaucoma surgery alone or in combination with cataract surgery may yield benefits not only to the pressure but also to the OSD.

TREATMENT OF OSD AFTER ADJUSTEMENT OF GLAUCOMA THERAPY

According to severity of symptoms

- Preservative free artificial tears.
- Platelet rich plasma (PRP) eye drops.
- Use of topical 0.05% cyclosporine should also be considered.
- Punctal occlusion.

- **Platelet rich plasma (PRP)** eye drops was proved to be an effective monotheraby for OSD.
- The figure show a case with superficial punctate keratitis from severe dry eye (A) before and 1 month after ttt by PRP eye drops (B).



Alio JL, Rodriguez AE, Ferreira-Oliveira R, Wróbel-Dudzińska D, Abdelghany AA.

Treatment of Dry Eye Disease with Autologous Platelet-Rich Plasma: A Prospective, Interventional, Non-Randomized Study. Ophthalmol Ther. 2017 Dec;6(2):285-293

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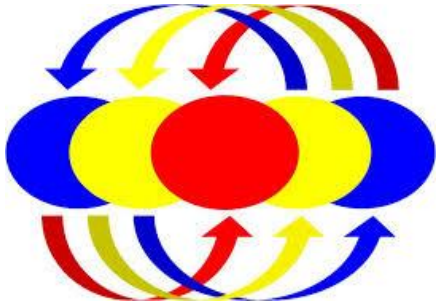
ALTERNATE DRUG DELIVERY SYSTEM

- Alternative routes for the delivery of glaucoma medications are being developed but none have yet been approved for clinical use and clinical trial data are preliminary only.



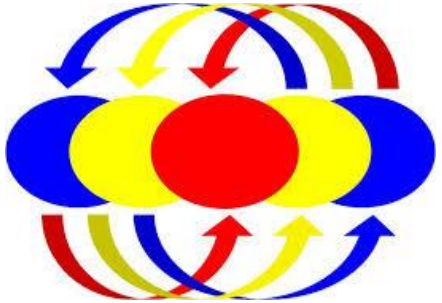
- One format currently in Phase 3 trials is a sustained release pellet containing bimatoprost that is injected into the anterior chamber.

Brandt JD, DuBiner HB, Benza R, et al. Reduction in IOP from a sustained-release bimatoprost ocular insert: mid-term results of an open-label extension study (OLE study). American Glaucoma Society Annual meeting; 2016 Mar 3–6; FL, USA.

Franca JR, Foureaux G, Fuscaldi LL, et al. Bimatoprost-loaded ocular inserts as sustained release drug delivery systems for glaucoma treatment: n vitro and in vivo evaluation. PLoS One. 2014;9(4):e95461.

ALTERNATE DRUG DELIVERY SYSTEM

- Ocular surface ring inserts that contain bimatoprost and fit into the conjunctival fornices have been created.
- latanoprost and travoprost punctal plugs.
- The creation of a contact-lens-based platform for the delivery of glaucoma medications.
- Subconjunctival depot injections are also being tried



Voss K, Falke K, Bernsdorf A, et al. Development of a novel injectable drug delivery system for subconjunctival glaucoma treatment. J Control Release. 2015 Sep 28;214:1–11.

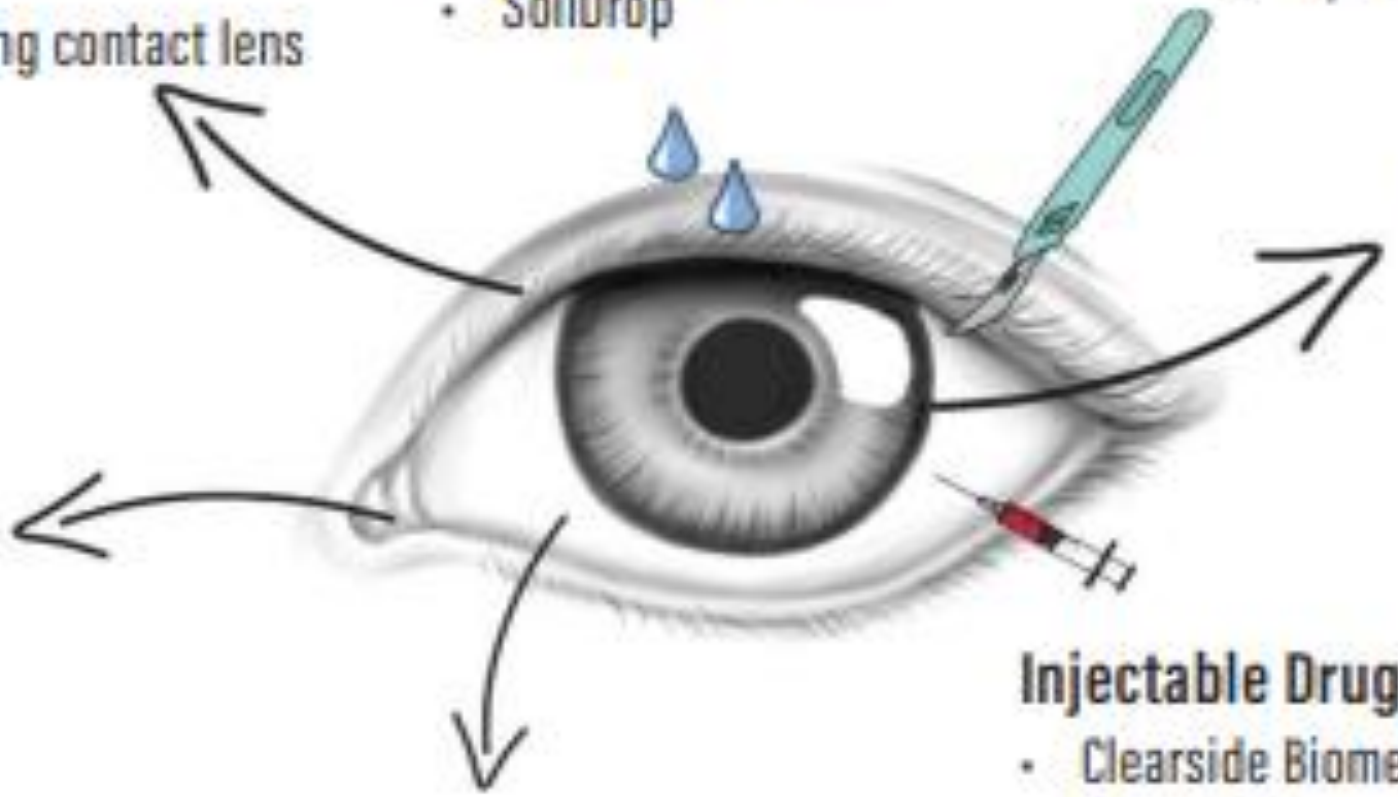
Williams DF, Phase A. 2 study evaluating safety and efficacy of the latanoprost punctal plug delivery system (L-PPDS) in subjects with 1288 A. AGUAYO BONNIARD ET AL. ocular hypertension (OH) or open-angle glaucoma (OAG). Invest Ophthalmol Vis Sci. 2012;53(14):5095.

ALTERNATE DRUG DELIVERY SYSTEM

Surface Implants
- Bimatoprost Ring
- Latanoprost-eluting contact lens
- TODDD

Gel-Forming Drops
- SoliDrop

Intrascleral Implants
- Ophthalmic MicroPump



Intracameral Implants
- Bimatoprost SR
- iDose
- Travoprost XR

Punctal Plugs
- Evolute
- OTX-TP

Injectable Drugs
- Clearside Biomedical/Santen
- IBI-60089
- Graybug

Subconjunctival Implants
- Durasert

TAKE A HOME MESSAGE

- Glaucoma treatement, which is required for life of the patient, remains a challenge.
- OSD can be a limiting factor in the treatment of glaucoma patients.
- The possibility of preservative intolerance should be considered in the ‘multiple drop allergic’ glaucoma patient.
- Preservative free medications are very helpful and should be considered as first line of treatment.

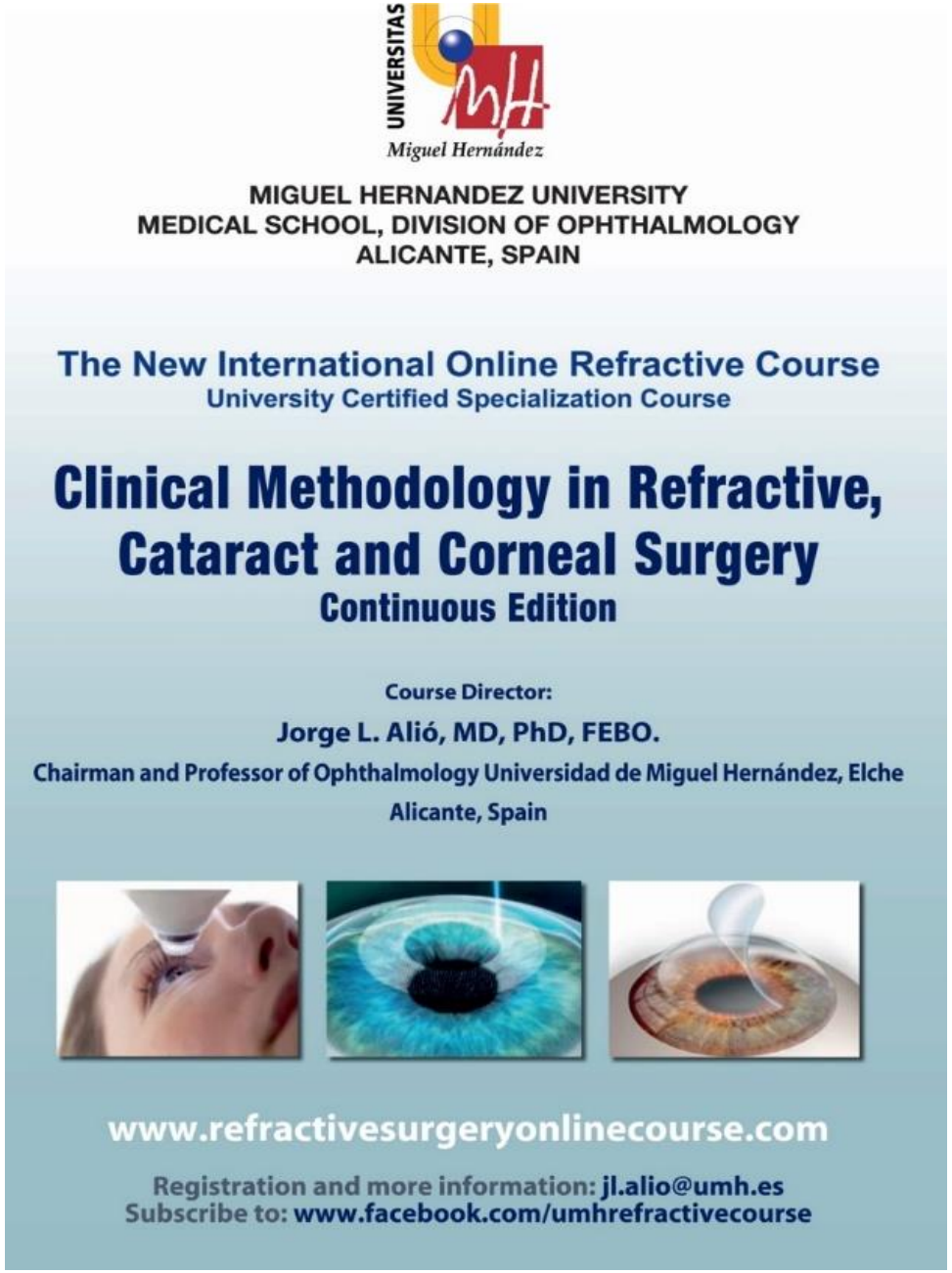
TAKE A HOME MESSAGE

- Increasing options in glaucoma medical topical therapy are becoming available.
- Topical beta-blockers, whether preserved or unpreserved, should be used cautiously in patients with moderate to severe dry eye.
- Alternate delivery systems semms to be promising in the future.

Surgery videos:

https://goo.gl/PNdZCT

YouTube



Thank you!!

Jorge L. Alió MD. PhD

Chairman & Medical Director

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THANK YOU

Sackler Faculty of Medicine
Tel Aviv University
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אוניברסיטת תל אביב