


WHAT'S UP, OPTOMETRY?
A LOOK AT NEW OCULAR THERAPEUTICS

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Disclosures

- Peabody
 - ▣ None
- Perotti
 - ▣ None


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Goals/Objectives

- I. Introduction
- II. Anti-bacterials
- III. Anti-bacterial/corticosteroid combinations
- IV. Anti-virals
- V. Anti-inflammatories
- VI. Anti-allergy
- VII. Ocricplasmin

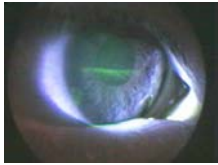

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Anti-Bacterials



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Case 1

- Chief complaint
 - ▣ Corneal paper cut
- Clinical pearl
 - ▣ Anesthetic to enable the patient to keep eyes open during VA and prelims
- Objective
 - ▣ Large superficial abrasion
 - ▣ Trace cells; no flare
- Assessment
 - ▣ Corneal abrasion
 - ▣ Anterior uveitis



www.eyedoctor.com


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Anti-Bacterials

- Ocular TRUST
 - ▣ Over 50 centers and one reference laboratory
 - ▣ In 2006, 16.8% of all staph. aureus isolates were MRSA
 - ▣ In 2008, 48.1% of all staph. aureus isolates were MRSA



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Table 2. Resistance to Commonly Used Antibiotics for Conjunctivitis

Antibiotic	Organism Resistant?			
	<i>H influenzae</i>	<i>S pneumoniae</i>	<i>S aureus</i>	MRSA
Aminoglycosides Gentamicin Tobramycin	No	Yes		Yes
Polymyxin B/trimethoprim	No	Yes		No*
Erythromycin	Yes		Yes	
Azithromycin		Yes	Yes	Yes
Newer fluoroquinolones Levofloxacin Moxifloxacin Gatifloxacin Besifloxacin	No	No		Yes

*Trimethoprim maintained 92% activity against MRSA in the Ocular TRUST (Tracking Resistance in the United States Today) study.

*Besifloxacin was not evaluated in 2008 Ocular TRUST.

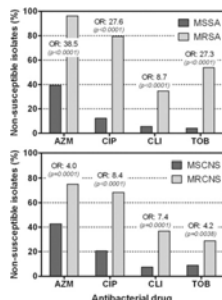
Key: MRSA—methicillin-resistant *Staphylococcus aureus*.Source: Ashbell RA, et al. *Am J Ophthalmol*. 2008;145:951-958.

ARMOR (2009-Present)

- 592 ocular isolates studied by same lab
 - 200 staph. aureus
 - 144 coag-neg staph. aureus
 - 75 strep pneumonia
 - 73 haemophilus influenzae
 - 100 pseudomonas aeruginosa
- Tested against
 - Azithromycin (macrolides)
 - Ciprofloxacin (fluoroquinolones)
 - Clindamycin (lincosamides)
 - Tobramycin (aminoglycosides)

ARMOR

- 39% of staph. aureus isolates were MRSA
- 80% of MRSA showed resistance to fluoroquinolones
 - Besivance showed least resistance of fluoroquinolones
- Pseudomonas
 - 13% resistant to ciprofloxacin
 - 7% resistant to tobramycin



Most Effective, Least Resistant Ophthalmic Anti-Bacterial

- Staph. aureus and staph. epidermis
 - Gentamicin
 - Polytrim (polymyxin B with trimethoprim)
 - Besivance (besifloxacin)
 - Vancomycin (only available via compounding)
- Pseudomonas
 - Fluoroquinolones
 - Aminoglycosides
 - Polymyxin B

Gentamicin vs. Fluoroquinolones

- Use Gentamicin for staph. epidermis or MRSA
 - 97% staph. epidermis isolates are sensitive
 - 32-40% of staph. epidermis isolates are resistant to fluoroquinolones
 - High levels of resistance among various fluoroquinolones

Besivance

- Besifloxacin 0.6% ophthalmic suspension
- Bi-halogenated quinolone
- Very thick consistency
 - Durasite
- Expensive
 - \$90/5 mL bottle



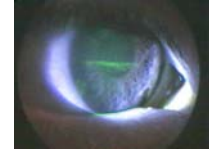
Future Durasite Formulations

- PHASE III
 - ▣ Azasite Plus – azithromycin and dexamethasone
 - ▣ Dexasite – dexamethasone
 - ▣ Bromsite– bromfenac
- RESEARCH
 - ▣ ISV-102 – tetracycline
 - ▣ ISV-620 – prostaglandin analog for eyelashes
 - ▣ ISV-215 – prostaglandin analog for GLC

http://www.insitevision.com/product_pipeline

Case 1: Treatment Plan

- Besivance or Polytrim or Gentamicin 1 drop 4X/day for seven days (affected eye)
- Homatropine 5% 1 drop 1-4 X/day for 2-7 days (depending on severity)
- RTC seven days (sooner for more severe cases)



Anti-bacterial/Corticosteroid Combinations

Case 2

- Chief complaint
 - ▣ Contact lens wearer/abuser with red eye
- Objective
 - ▣ Moderate injection
 - ▣ Old Bowman layer scars
 - ▣ Microcystic edema
 - ▣ SEIs (subepithelial infiltrates)
 - ▣ Trace cells in anterior chamber



www.oculist.net/download/502/prof/ebook/duanes/pages/v4/v4c016a.html

Case 2

- Assessment
 - ▣ CL related cornea edema
 - ▣ Anterior uveitis (364.0 - Acute and subacute iridocyclitis)



Combination Drugs

- Useful in cases of epithelial compromise
 - ▣ Thygeson's superficial keratitis
 - ▣ Epidemic keratoconjunctivitis (EKC)
 - ▣ Contact lens-associated keratitis
 - ▣ Corneal abrasions
 - Especially if no history of vegetative traumatic agent
 - ▣ Phlyctenular keratoconjunctivitis (PKC)
 - ▣ Staph. marginal ulcers

TobraDex ST

- Tobramycin 0.3%/Dexamethasone 0.05% ophthalmic suspension
- Xanthan gum prevents settling of active ingredients – more uniform suspension
- 1/2 the dexamethasone of original TobraDex



TobraDex ST

- More effective bactericidal activity and higher relative tissue concentration for anterior segment compared to TobraDex



Zylet

- Tobramycin 0.3%/Loteprednol etabonate 0.5% ophthalmic suspension
- Decreased incidence of IOP increase



Case 3: Treatment Plan Options

- Option 1
 - Tobradex 1gtt 4X/day OS for 7 days
 - Shake bottle
 - RTC 1 week
- Option 2
 - Zylet 1gtt 4X/day OS for 7 days
 - Shake bottle
 - RTC 1 week

Anti-Virals

Case 3

- Chief complaint
 - Discomfort and redness OS
 - Previous Hx of same red eye
- Objective
 - Moderate conjunctival injection
 - Corneal involvement



Zirgan

- Ganciclovir 0.15% ophthalmic gel
- Approved in 15 SEP 2009
- Safe for individuals > 2 years of age
- Mechanism of Action
 - ▢ Competitive inhibition of DNA polymerase AND direct incorporation into viral DNA primer strand
- Dosing
 - ▢ 1 drop 5X/day until epithelial defect resolves
 - ▢ Then 1 drop 3X/day for 7 days
- Adverse effects
 - ▢ Blur, irritation, punctate keratitis, conjunctival hyperemia

Zirgan

- Off label use for EKC
 - ▢ Speeds resolution
 - ▢ Less keratitis
 - ▢ Use early for maximum effect



Topical Antivirals for HSK

- | | |
|---|---|
| <ul style="list-style-type: none"> □ Viroptic <ul style="list-style-type: none"> ▢ Indiscriminate expression ▢ Potential for more toxicity ▢ 9X/day dosing ▢ Must refrigerate until open ▢ Preserved with thimerosal ▢ ~ \$40 for 7.5 ml bottle ▢ Available as generic | <ul style="list-style-type: none"> □ Zirgan <ul style="list-style-type: none"> ▢ Works only on infected cells ▢ Minimally toxic ▢ Maximum 5X/day dosing ▢ No refrigeration ▢ BAK preserved ▢ ~ \$125 for 5 g tube ▢ No generic |
|---|---|

Antivirals: Herpes Simplex Keratitis

- Topical
 - ▢ Zirgan
 - ▢ Ganciclovir 0.15% ophthalmic gel
 - ▢ Viroptic
 - ▢ Trifluridine 1% solution
- Oral
 - ▢ Valtrex
 - ▢ Valacyclovir 500 mg and 1000 mg
 - ▢ Available as a generic
 - ▢ Zorivax
 - ▢ Acyclovir 200 mg, 400 mg, and 800 mg
 - ▢ Available as a generic

Oral HSV Therapy

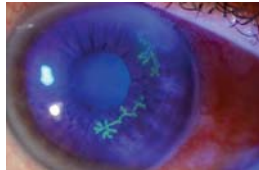
- Tx with oral therapy
 - ▢ 9X less likely than untreated to develop recurrent keratitis
- Recurrence rates
 - ▢ 27% at 1 year
 - ▢ 50% by 5 years
 - ▢ 57% by 10 years
 - ▢ 63% by 20 years
- Stromal disease more likely to recur
- Length of prophylaxis
 - ▢ 5 disease-free years

Oral Antiviral for Recurrent HSV

- Valacyclovir - Generic
 - ▢ 500 mg daily
 - ▢ \$234/month
- Acyclovir - Generic
 - ▢ 400 mg BID
 - ▢ \$31/month

Case 3: Treatment Options

- Option 1
 - ▣ Zirgan
 - 1 gtt 5X/day until ulcer heals then 3X/day for 7 days
 - ▣ Oral Acyclovir
 - 400 mg PO BID up to 5 years



Case 3: Treatment Options

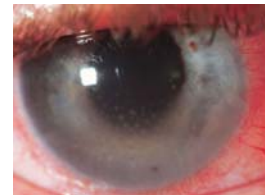
- Option 2
 - ▣ Viroptic q2h X 5 days
 - ▣ ~9x/day then 4X/day for 5 days
 - ▣ Oral Acyclovir
 - 400 mg PO BID up to 5 years



Anti-Inflammatories

Case 4

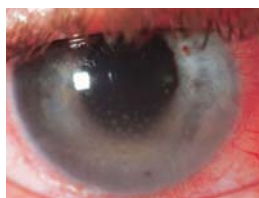
- Chief complaint
 - ▣ Pain and photophobia OS X 2 days
 - ▣ Hx of ulcerative colitis
- Objective
 - ▣ Grade 3+ cells OS
 - ▣ Limbal injection OS
 - ▣ Keratic precipitates OS



http://www.eyesurgeryinberkshire.co.uk/information_tatiz_uveitis.html

Case 4

- Assessment
 - ▣ Anterior uveitis OS



Clinical Pearls - Steroids

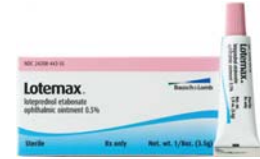
- Topical NSAIDs may be used, but typically don't work as well for these cases
- If using steroid for less than two weeks, ketone vs. ester-based is largely irrelevant
- If longer, ester-based is preferred
- Treat aggressively initially

Clinical Pearls - Steroids

- Our top three
 - ▣ Pred Forte
 - Prednisolone acetate 1% suspension
 - Generic available
 - ▣ Lotemax
 - Loteprednol etabonate 0.5% suspension
 - ▣ Durezol
 - Difluprednate 0.05% ophthalmic emulsion

Loteprednol

- Available as
 - ▣ 0.5% suspension (Lotemax)
 - ▣ 0.2% suspension (Alrex)
 - ▣ 0.5% preservative-free ophthalmic ointment (Lotemax ointment)
 - ▣ 0.5% ophthalmic gel (Lotemax gel)
- Approximately 90% as effective as Pred Forte and Durezol



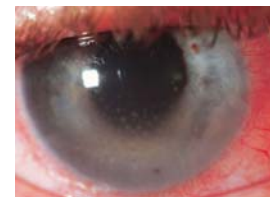
Durezol

- Difluprednate 0.05% ophthalmic emulsion
- Very potent
 - ▣ Dosed with 1/2 frequency of Pred with equal efficacy
- Emulsion - so no need to shake
- Can cause marked increase in IOP



Case 4: Plan

- Durezol
 - ▣ 1 gtt q1hour x 2 day OS
- No need to shake bottle
- Homatropine 5%
 - ▣ 1 drop BID to TID OS



Anti-Allergy

Case 5

- Chief complaint
 - ▣ Itchy, watery eyes; has been mowing recently
- Objective
 - ▣ Mild-moderate chemosis
 - ▣ Trace to mild injection
- Assessment
 - ▣ Seasonal allergic conjunctivitis



<http://www.stamfordallergy.com/Services.php>

Allergy Tx: Non-Pharmacologic

- Avoid allergen
- Use air conditioning
- Shower before bed
- Undress in room other than bedroom
- Artificial tears
- Cold compresses

Allergy Tx: Pharmacologic

- Decongestants
- Antihistamine / decongestant combo
- Antihistamines (oral, topical)
- Mast cell stabilizing antihistamines
- Mast cell stabilizers
- Topical NSAIDs
- Corticosteroids

Limitations

- Decongestants
 - ▢ Only affect redness and chemosis
 - ▢ Rebound hyperemia
- Anti-histamines
 - ▢ Only effective for early signs/symptoms
- Mast cell stabilizers
 - ▢ Lag time before benefit realized
- NSAIDs
 - ▢ Not effective against early mediators
- Corticosteroids
 - ▢ Adverse effects from long term use

Anti-Allergy: Minimal Signs

- H1 blockers
 - ▢ Bepreve (bepotastine 1.5% solution)
 - > 2 years of age
 - Twice a day dosing
 - 10 mL - \$190
 - ▢ Lastacraft (alcaftadine 0.25% solution)
 - > 2 years of age
 - Once a day dosing
 - 3 mL - \$112

Anti-Allergy: Minimal signs

- H1 blockers
 - ▢ Patanol (olopatadine 0.1% solution)
 - > 3 years of age
 - Twice a day dosing
 - 5 mL - \$127
 - ▢ Pataday (olopatadine 0.2% solution)
 - > 3 years of age
 - Once a day dosing
 - 2.5 mL - \$127
 - ▢ Alaway, Zaditor, Refresh, Zyrtec, Claritin, etc. (ketotifen 0.025% solution)
 - > 3 years of age
 - Twice a day dosing
 - 10 mL - < \$20

Anti-Allergy: ≥ Moderate Signs

- Alrex (loteprednol 0.2% suspension)
 - ▢ QID
 - ▢ 5 mL - \$120
- Lotemax (loteprednol 0.5% suspension)
 - ▢ TID to QID
 - ▢ 5 mL - \$118
- FML (fluorometholone 0.1% suspension, ointment)
 - ▢ > 2 years of age
 - ▢ BID to QID
 - ▢ 10 mL - \$65
 - ▢ Generic
- Used 1-2 weeks to get inflammatory signs under control

Case 5: Plan

- Alaway (ketotifen 0.025% solution)
 - ▣ 1 drop 2X/day PRN
 - ▣ Stings upon instillation
- Refrigerate
 - ▣ Cold helps itching



Ocriplasmin

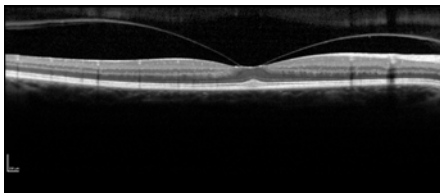
Case Presentation

- 67 YOF presents with sudden onset of flashes, floaters OS
- Onset: yesterday
- Floaters remain constant, flashes have substantially subsided
- Acuties – normal
- Preliminaries (pupils, EOMs, CT, screening VF) – normal

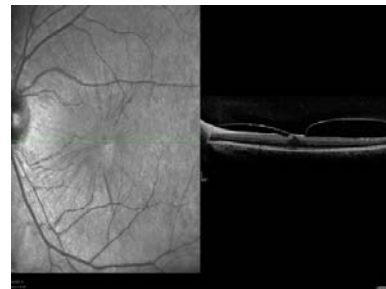
Case Presentation

- Anterior – normal
- IOPs – normal
- Posterior
 - ▣ OD – No BHT 360
 - ▣ OS - PVD, blood anterior vitreous, scattered pre-retinal hemes, no BHT 360
- Assessment
 - ▣ 379.21 – Vitreous degeneration
- Plan
 - ▣ RD education; RTC 1 month

Vitreo-Macular Adhesion

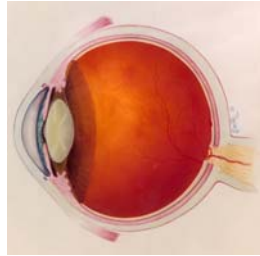


Vitreo-Macular Adhesion



Vitreo-Retinal Attachments

- Strongest
 - ▣ Vitreous base – overlying ora serrata
- Strong
 - ▣ Posterior lens
 - ▣ Optic nerve
- Less strong
 - ▣ Macula
 - ▣ Retinal blood vessels



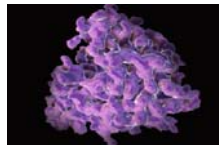
National Eye Institute, National Institutes of Health
Ref#: NEA04

FDA Approval, Product Launch

- 17 OCT 2012
 - ▣ FDA approves Jetrea (ocriplasmin, ThromboGenics) for treatment of symptomatic vitreo-macular adhesion (VMA)
- 14 JAN 2013
 - ▣ Jetrea Day!
 - ▣ Launch of Jetrea in the US
 - ▣ \$3,950 for 0.125 mg (0.1 mL) single dose injection

Ocriplasmin Molecule

- A recombinant protease (enzyme) with activity against fibronectin and laminin – two components of the vitreo-retinal interface



Study

- Enrollment criteria
 - ▣ Age – 18+
 - ▣ VMA on OCT
 - ▣ ETDRS BCVA in study eye – 20/25 or worse
 - ▣ ETDRS BCVA in non-study eye – 20/800 or better
 - ▣ Generally – no ocular co-morbidities except epi-retinal membrane

Study Enrollment

- 652 eyes enrolled with symptomatic vitreo-macular adhesion (VMA)
 - ▣ 464 treated with single 0.10 ml injection of ocriplasmin (125 µg of medication)
 - ▣ 188 treated with a single 0.10 ml placebo injection

Endpoints

- Primary endpoint
 - ▣ Complete resolution of VMA at day 28 by OCT
- Secondary endpoints
 - ▣ Complete PVD on day 28 by B-scan
 - ▣ Need for vitrectomy at 6 months
 - ▣ Closure of a macular hole at 6 months
 - ▣ BCVA gain ≥ 3 lines without vitrectomy at 6 months

Results

- Complete resolution of VMA on day 28 by OCT
 - ▢ ~27% in ocriplasmin group
 - ▢ ~10% in placebo group
- Complete posterior vitreous detachment on day 28 by B-scan
 - ▢ ~13% in ocriplasmin group
 - ▢ ~04% in placebo group
- Need for vitrectomy at 6 months
 - ▢ ~18% in ocriplasmin group
 - ▢ ~27% in placebo group

Results

- Closure of a macular hole
 - ▢ ~41% in ocriplasmin group
 - ▢ ~12% in placebo group
- BCVA gain ≥ 3 lines without vitrectomy at 6 months
 - ▢ ~12% in ocriplasmin group
 - ▢ ~06% in placebo group

Adverse Effects

- Transient and mild
 - ▢ Related to PVD, injection
 - ▢ Ocriplasmin group – 68%
 - ▢ Placebo group – 54%
- Serious
 - ▢ Retinal tear/detachment, macular hole, reduced acuity
 - ▢ Ocriplasmin group - 08%
 - ▢ Placebo group - 10%

Conclusions and Future Directions

- Ocriplasmin statistically better than placebo at completely resolving VMA on OCT
- Sex differences
 - ▢ Worked almost 2X better in women than men
- Lens status
 - ▢ Better results in phakic v. pseudophakic eyes
- Potential for study and use in other conditions where vitreo-retinal traction is an issue
 - ▢ Diabetes
 - ▢ Etc.

The End

Credits

Updated: September 24, 2014
Software: Microsoft PowerPoint

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References

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- [Haas W, Pillar CM, Torres M, Morris TW, Sahm DE.](#) Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) 2009 surveillance study. *Am J Ophthalmol.* 2011 Oct;152(4):567-574.e3. Epub 2011 Jun 8.
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Zioptan

- Tafluprost ophthalmic solution 0.0015%
- Single use, non-preserved vials
- Prostaglandin analog indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
- FDA approval: 10 FEB 2012
- Manufacturer: Merck
- One drop qhs
- 30 vials - \$110

Zioptan



Moxeza

- FDA approval: 19 NOV 2010

Prolensa

- FDA approval: 05 APR 2013

Resure

- FDA Executive summary 19 SEP 2013
- Safety established.
- Better than sutures.

AmbioDisc