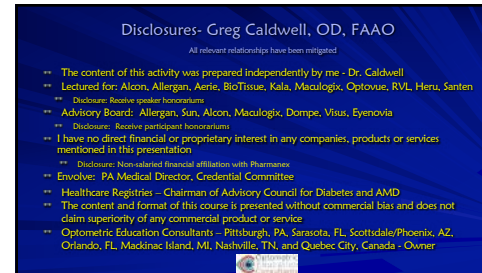
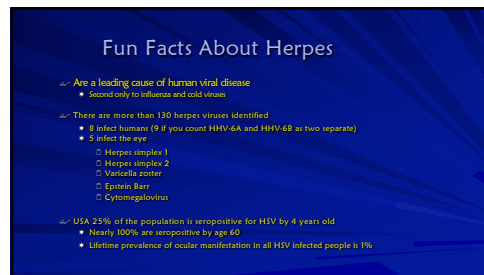


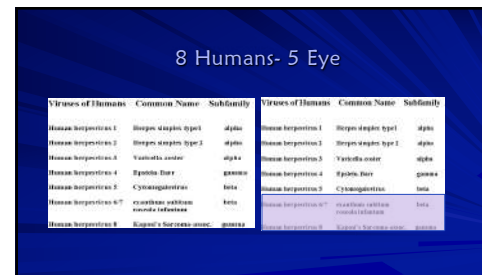
2



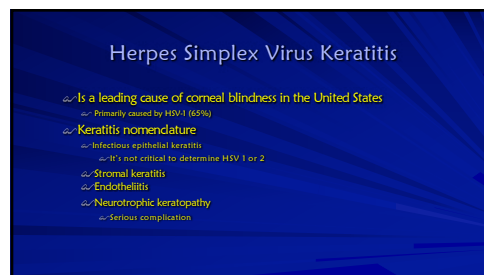
3



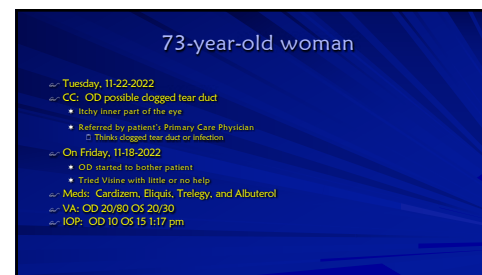
8



9



10



11



12



13

Herpes Viruses are Classified by Their Location in the Latent State

Location	Host	Latent Site	Latent Site	Latent Site	Latent Site
1	Herpes simplex virus (HSV-1)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion
2	Herpes simplex virus (HSV-2)	Sacral ganglion	Sacral ganglion	Sacral ganglion	Sacral ganglion
3	Varicella-Zoster virus (VZV)	Dorsal root ganglion	Dorsal root ganglion	Dorsal root ganglion	Dorsal root ganglion
4	Cytomegalovirus (CMV)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion
5	Epstein-Barr virus (EBV)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion
6	Herpes zoster virus (HZV)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion
7	Herpes zoster virus (HZV)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion
8	Herpes zoster virus (HZV)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion
9	Herpes zoster virus (HZV)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion
10	Herpes zoster virus (HZV)	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion	Trigeminal ganglion

14

Treatment 11-22-2022

Herpes Simplex Keratitis x 7 lesions

- Educated patient on finding
- Photo and video documents
- Valtrex 1000 mg PO TID
- Watch closely
- Prokera not covered by insurance, patient declined Prokera
- Add steroid at sign of reversal
- RTC 1 day for HSV keratitis check

16

1 Day Follow UP 11-23-2022

Feels slightly better

VA: OD 20/70 OS 20/25

Valtrex 1000 mg

- 3 times yesterday
- 2 today

17



18


### 1 Day Follow Up 11-23-2022

- Improving
- Continue Valtrex 1000 mg PO TID
- Watch closely
- Photos and video documents
- Add steroids when reversal
- RTC in 2 days

19

### 3 Day Follow Up Friday 11-25-2022

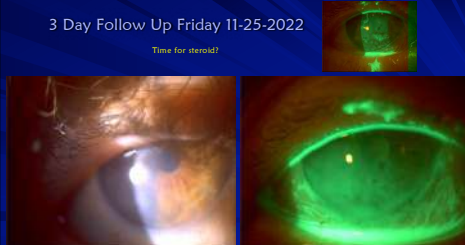
- Patient taking Valtrex as prescribed
- Reports watering over the last 2 days
- VA OD 20/70 OS 20/25
- IOP OD 11 OS 15



20

### 3 Day Follow Up Friday 11-25-2022


Time for steroid?



21

### 3 Day Follow Up Friday 11-25-2022

- Improving
- Responding to treatment
- Finish Valtrex PO
- Add Ioteprednol OD QID
- RTC 1 day, leaving town for weekend
- RTC Monday, gave patient my cell number



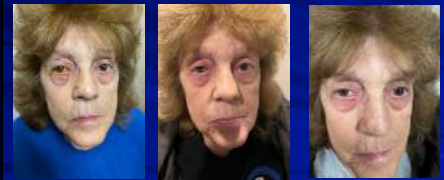
22

### 6 Day Follow Up Monday 11-28-2022

- Patient reports improvement since LOV
- Still some watering
- VA OD 20/70 OS 20/25
- IOP OD 15 OS 16

23

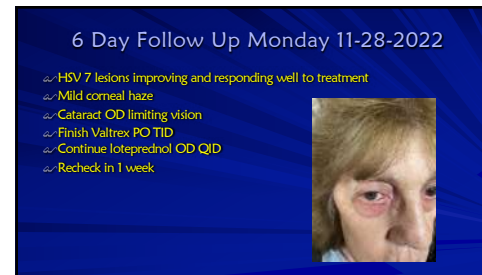
### 6 Day Follow Up Monday 11-28-2022



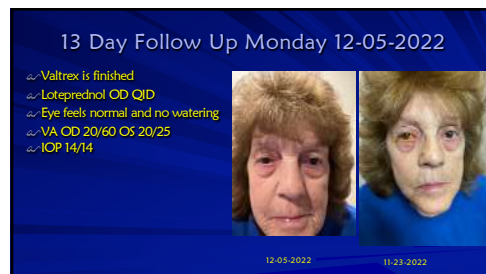
24



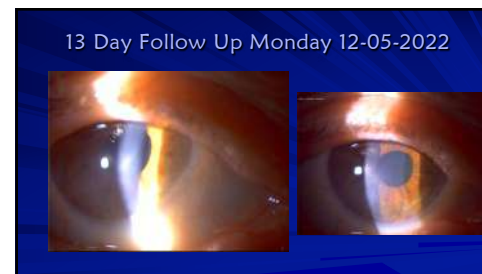
25



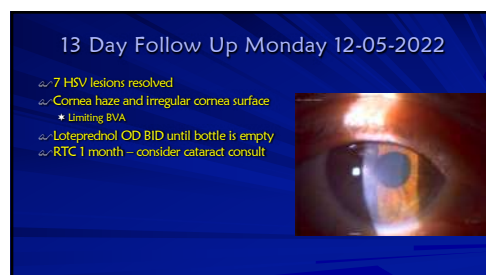
26



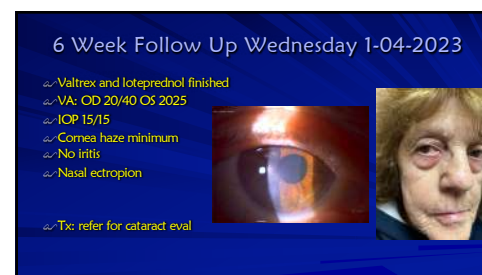
27



28



29



30

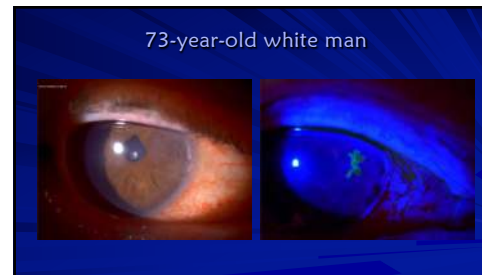
### 72-year-old white man

- First saw patient 6-26-2017
- History of herpes viral keratitis and cataract OD
- Wants opinion on keratitis and cataract
- VA: OD 20/100 OS Prosthetic
- Saw at age 2 to OS
- Valtrex PO 500 mg
- Timolol OD QD
- Prednisolone OD QD
- IOP OD 18

**Diagnosis: Monocular patient**

- Ocular HTN/Steroid responder
  - Good IOP
- Recurrent HSV keratitis
  - Quiet
- Iritis
  - Quiet
- Cataract
  - Refer for cataract surgery west ready
  - Will increase Valtrex PO
- Cataract surgery 1-18-2018
  - Increased Valtrex pre and post op
  - VA: OD 20/25

31



32



33



34

### 54-year-old white woman

- Review of records of ECP: 12-30-2021 OD red, itchy, - especially the inner corner
- PCP - ophthalmic 2 drops every 4 hours
  - Used for 2 days, no improvement
- Hurts into cheekbone
- Do: cornea abrasion
- Tx: Maxitrol OD TID, check 1 week

January 3, 2022 - patient wants 3<sup>rd</sup> opinion

- Eye started to improve over weekend, now redness and irritation is back
  - Not as itchy
  - Pressure when closes eyes

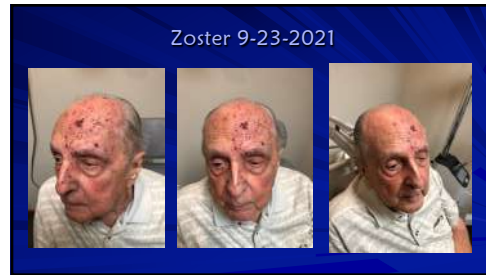
35



36



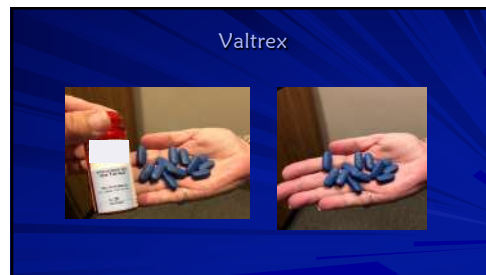




43



44



45



46



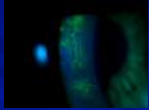
47



48

24-48 hours before Zirgan arrives


- ~ Zirgan
- ~ Viroptic
- ~ Orals only
- ~ Orals and Amniotic Membrane



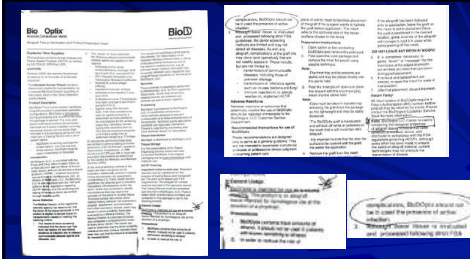
49

Herpes Simplex Virus Keratitis

- ~ Infectious epithelial keratitis
- ~ Stromal keratitis
- ~ Endotheliitis
- ~ Neurotrophic keratopathy



51



52

Cryopreserved

Indications:

- PROKERA is intended for use in eyes in which ocular surface cells are damaged or underlying stroma is inflamed or scarred. Acting as a self-adhering biological contact bandage, PROKERA effectively treats superficial corneal surface diseases by increasing inflammation and related pain, promoting epithelial healing, and avoiding haze.
- PROKERA is inserted between the eyelid and the eyeball to maintain space in the orbital cavity and to prevent closure or adhesions. Placement of the conformer also enables application of the cryopreserved amniotic membrane to the ocular surface without the need for sutures.
- PROKERA is for single-use only in one patient by an ophthalmologist or ophthalmic nurse.

Contraindications:

- PROKERA should not be used in eyes with glaucoma drainage devices or filtering blebs.

Precautions:

Storage & Temperature	Use After Placement
<p>Unopened PROKERA should be stored at 2-8°C (36-46°F).</p> <p>DO NOT use if the expiration date has expired.</p>	<p>After the conformer is placed on the eye, PROKERA should be used within 14 days.</p> <p>DO NOT use if the expiration date has expired.</p>

53



55

37-year-old woman  
OD red and painful

Va 20 / 30  
cc 20

Current Correction  
R -2.50-1.00 x 180  
L -3.25-1.00 x 180

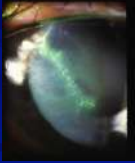
EOMs: full, unrestricted  
CT: ortho D/N

PERRL (-)APD  
CF: full by FC OU

56




### Slit Lamp Evaluation



- ~ Diagnosis
- ~ Ocular history
  - First episode
- ~ Treatment
- ~ Maintenance of oral antiviral?

57

### 4 weeks later



- ~ Resolved
- ~ Chance of occurring again within 12 months?
  - 25%

58


### Cranium Keeper

~ Viroptic (trifluridine solution) should be used for how long?

- One drop every 2 hours while awake (up to 9 drops per day)
- 21 days via package insert/instructions

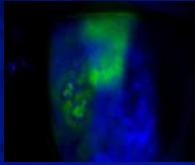
~ Zirgan (ganciclovir ophthalmic gel) 0.15%

- One drop five times per day until the corneal ulcer heals
- Then one drop three times per day for seven days



59

### Slit Lamp Evaluation



- ~ 5 months later
- ~ Treatment
- ~ Maintenance of oral antiviral?
  - Education patient on treatment options
  - 43% occurring again

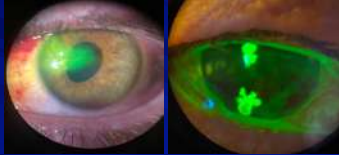
60

### 4 Months Later



- ~ Ocular history
  - Third episode
- ~ Treatment
- ~ Oral antiviral maintenance?
  - What dosage?
    - Short term
    - Long term

61



63

## Herpetic Eye Disease Study

- HEDS I
  - Benefit from steroids in stromal keratitis
  - No benefit from oral Acyclovir in stromal keratitis
  - Benefit from steroids if iritis present
- HEDS II
  - No benefit from Acyclovir to stop progression to stromal or iridocyclitis
  - Maintenance dose 400 mg BID, decreases recurrence by 41% within 1st year

64

## Recurrent Herpes Simplex Keratitis

- Treatment
  - Topical antiviral
  - Oral antiviral
- Remember to check for?
  - Patient is allergic to Penicillin and Keflex
  - Patient is also 2 months pregnant



65

## Medical History

- Before we Rx any medications we take a thorough **medical** history which includes:
  - CC
  - HPI
  - ROS
    - Kidney disease, liver disease, dialysis
  - PFS History
  - Current Medications
  - Allergies...Adverse Reactions/Allergies
  - Pregnancy...any chance you might be pregnant?

66

## FDA Pregnancy Categories

- Category A- studies in pregnant women...no risk
- Category B- animal studies no risk but human not adequate...or...animal toxicity but human studies no risk...safe
- Category C- animal studies show toxicity human studies inadequate but benefit of use may exceed risk...OR...there are no adequate studies in animals or humans...avoid (MOST new drugs are here)
- Category D- evidence of human risk but benefits may outweigh risks...avoid
- Category X- fetal abnormalities, risk>benefits...avoid

67

Pregnancy and Lactation Labeling Rule-FDA  
December 4, 2014 Final Rule

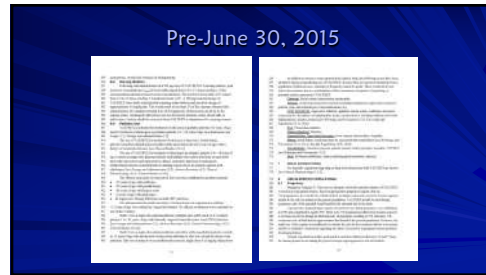
- **Effective June 30, 2015**
  - Effective now for new medications and a 3-5 year phase in period (application)
- Labeling for human prescription drugs and biological products will include:
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
- Pregnancy (8.1)
  - Pregnancy Exposure Registry - omit if not applicable
  - Risk Summary - required subheading
  - Clinical Considerations- omit if none of the headings are applicable
    - Disease-associated maternal and/or embryofetal risk - omit if not applicable
    - Dose adjustments during pregnancy and the postpartum period - omit if not applicable
    - Maternal adverse reactions - omit if not applicable
    - Fetal/neonatal adverse reactions - omit if not applicable
    - Labor or delivery - omit if not applicable
  - Data - omit if none of the headings are applicable
    - Human Data - omit if not applicable
    - Animal Data - omit if not applicable

68

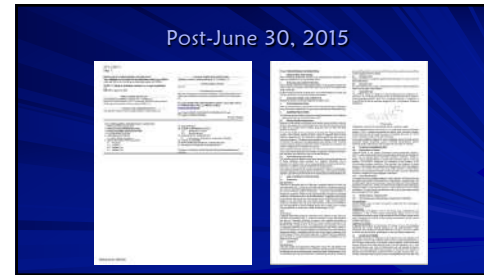
Pregnancy and Lactation Labeling Rule-FDA  
December 4, 2014 Final Rule

- Lactation (8.2)
  - Risk Summary- required subheading
  - Clinical Considerations- omit if not applicable
  - Data- omit if not applicable
- Females and Males of Reproductive Potential (8.3) - omit if none of the headings are applicable
  - Pregnancy testing- omit if not applicable
  - Contraception- omit if not applicable
  - Infertility - omit if not applicable

69



70



71

### Renal Impairment

- Identify patients on hemodialysis
- Adjustment made by patient's creatinine clearance (CrCl)...ml/min
  - ★ Work with patient's PCP/Internist

72

### Oral Anti-Virals

- 3rd generation, go into every cell but only activate in viral infected cells
  - ★ (1st generation=mutagenic)
- Use prophylactically prior to PKP, LASIK and PTK

73

### Zovirax (acyclovir)

- Good for simplex and zoster
- Available in 200, 400 and 800 mg, IV
- Dosage: 800 mg/5 times/day (4 grams daily)
- Poor GI absorption
- Maintenance dose: 200-400 mg bid
- Caution if impaired renal function
  - ★ Excreted by kidneys
- Category B

75


### Off-Label

- Valtrex and Famvir used for the eye
  - ★ Off label
  - ★ Only approved for genital herpes
  - ★ Won't find dosage in PDR for ocular usage


76



Is there a difference in efficacy between topical and orals in the various forms of ocular herpes?



Ganciclovir ophthalmic gel




Oral antivirals

- Acyclovir
- Valacyclovir
- Famciclovir

83

The deeper the involvement, the more efficacious orals become. But what about epithelial keratitis?...There seems to be equivalence




Oral acyclovir (Zovirax) in herpes simplex dendritic ulceration (keratitis)

60 patients with HSV dendritic ulceration included (small number with direct involvement keratitis)

randomized to oral vs. topical acyclovir

No statistically significant difference in time to resolution (mean = 5 days)



Oral acyclovir alone appeared as effective a topical antiviral therapy in the treatment of herpes epithelial keratitis

Oral delivery appears to get to corneal target even though it is an aqueous fluid

Guidelines Database Sept-Dec 2010-01/2011-1-199

84

### Lysine or L-Lysine

- ~ An essential amino acid
- ~ It is necessary for human health
- ~ But the body can't manufacture it
- ~ You have to get lysine from food or supplements
- ~ Amino acids like lysine are the building blocks of protein
  - ★ Lysine is important for proper growth

85

### Lysine and Herpes

- ~ Some studies have found that taking lysine on a regular basis may help prevent outbreaks of cold sores and genital herpes
- ~ Lysine has antiviral effects by blocking the activity of arginine
  - ★ Which promotes HSV replication
- ~ One review found that oral lysine is more effective for preventing an HSV outbreak than it is at reducing the severity and duration of an outbreak
- ~ One study found that taking lysine at the beginning of a herpes outbreak did not reduce symptoms
- ~ Typically comes in 500 mg
  - 2000-3000 mg while active or infectious
  - 1000 mg as maintenance

86

### Cranium Keeper

- ~ Percentages in HSV keratitis
  - ★ 25%
  - ★ 43%
  - ★ 41%

87

### Vaccines

- ~ Zostavax™ – live vacciner, 60 years and older
  - ★ "the only game in town..."
  - 50-100% effective; 1 dose
  - Efficacy wanes after 4-5 years
- ~ Shingrix™ – has replaced Zostavax™
  - ★ We are moving in the right direction!
  - ★ Recommended for 50 years and older
    - 90-10% effective; 2 doses; IM; recombinant vaccine
    - Efficacy seems solid up to 7-8 years

88

### Prevention Through Vaccination

How effective are today's vaccines?

**Zostavax (Merck)- subcutaneous injection**

- Does not confer life-long immunity ... effect wanes after 5 years with booster suggested at 10 years
- 38-70% reduction in risk of shingles after vaccination
- 60-70% reduction in occurrence of PHN
- Not recommended for patients with post-HZV1 corneal or intraocular infection
- Patients with previous shingles may experience ocular, dermatologic, or disseminated disease

**Shingrix- Subunit Vaccine HZ/su (GSK)- Intramuscular 2 injections**

- Recombinant VZV glycoprotein E with AS01B adjuvant system
- Primary vaccine with boost 2 months later
- ZOE-50 trial reduced risk of shingles by 97% (Cunningham, et al NEJM 2016)
- ZOE-70 trial reduced risk of shingles by 90% (Cunningham, et al NEJM 2016)
- Pooled data demonstrated HZ/su associated risk reduction of PHN by 89%
- Potentially beneficial for immunocompromised individuals

89

### Serious Complications of Herpetic Eye Disease

- Neurotrophic States
- Acute Retinal Necrosis
- Post Herpetic Neuralgia

90

### Post Herpetic Neuralgia

#### How To Treat and Possibly Avoid It

91

### Post Herpetic Neuralgia (PHN)

- Patients with PHN report decreased quality of life and interference with activities of daily living
- Approximately 1 million cases of herpes zoster occur annually in the US
  - One in every three people develops herpes zoster during their lifetime
- PHN is a frequent complication occurring in 5% to 15% of cases
  - Causing moderate to severe neuropathic pain
- PHN is a neuropathic pain syndrome characterized by pain that persists for months to years after resolution of the herpes zoster rash
- Neuropathic pain
  - Does not respond consistently to classic non-opioid analgesic drugs
  - Better treated with antidepressant, anticonvulsant drugs and topical agents
- Neuropathic pain is a major public health problem worldwide
  - Unclear mechanism
  - Treatment is one of the most difficult medical problems

92

### Post Herpetic Neuralgia (PHN)

#### Treatment

- Approaches to management of post herpetic neuralgia include
  - Preventing herpes zoster through vaccination and/or antiviral treatment
  - Administering specific medications to treat pain
- First-line drugs
  - Anti-convulsant -neuropathic pain
    - Calcium channel  $\alpha_2\delta$  ligands
    - gabapentin (Neurontin) and pregabalin (Lyrica)
  - Tricyclic antidepressants
    - amitriptyline, nortriptyline, desipramine
  - Topical lidocaine patches
    - While treating PHN is a peripheral neuropathy
    - Radicular pain** is a type of **pain** that radiates into the lower extremity directly along the course of a spinal nerve root (topical lidocaine not effective)

93

### Lyrica - pregabalin

#### Neurontin - gabapentin

- Does Duration of Neuropathic Pain Impact the Effectiveness of Pregabalin?
  - Patients with chronic pain conditions such as neuropathic pain frequently experience delays in diagnosis and treatment
  - Pregabalin significantly improves pain irrespective of the length of time since onset of neuropathic pain

94



### Neurotropic Cornea Ulcer

- Difficult to manage due to:
  - Decreased ocular innervation
  - Decreased tear production
- Medications to avoid
  - Topical corticosteroids
    - May increase collagenase activity and promote stromal melting
  - Topical NSAIDs
    - No shown benefit in wound healing
    - Can decrease corneal sensitivity

95

### Neurotropic Cornea Ulcer

- Traditional Treatments**
  - Preservative-free artificial tears, gels, and ointments
  - Discontinuation of any topical ocular therapies
    - Those that can decrease corneal sensitivity
      - timolol, betaxolol, sulfacetamide, diclofenac, ketorolac
    - Those that contain preservatives
  - Punctal occlusion
  - Doxycycline 100 mg PO qd/qod; anti-inflammatory properties
  - Autologous blood serum
- Alternative to traditional treatments**
  - Scleral contact lens
  - Amniotic Membrane

96

### Oxervate™ (cenegermin-bkbi)

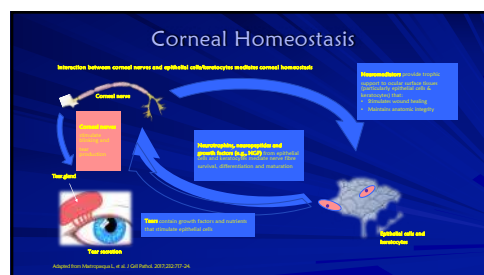
- Approved 2018 (August 28, 2018)
- Dompe pharmaceutical SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
  - Used as eye drop
    - Not infused or injected
- Storage issues: in the freezer at the pharmacy
  - Patient keeps the individual vial in the fridge -- once "actively ready" for use, then it is only stable for 12 hours
- Contraindications
  - None

98

### Escherichia Coli



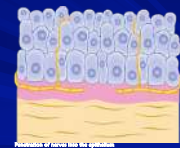
99



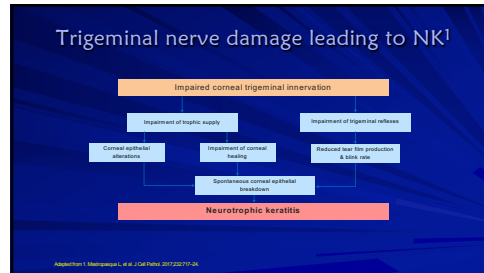
100

### Pathophysiology of NKI

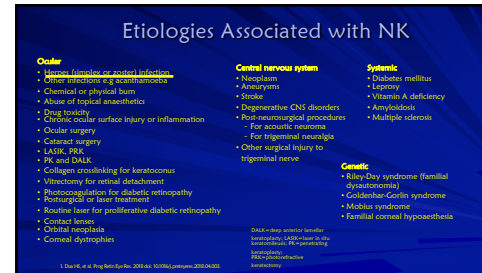
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neurotrophins that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomical integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal preservation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NKI



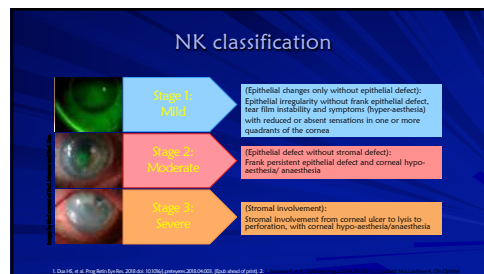
101



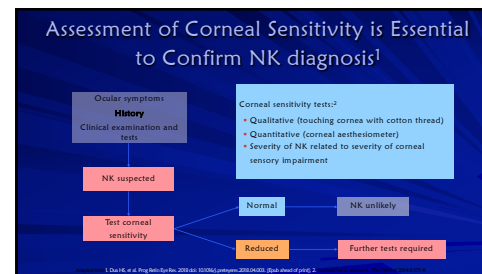
102



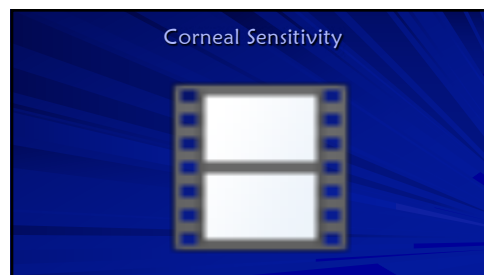
103



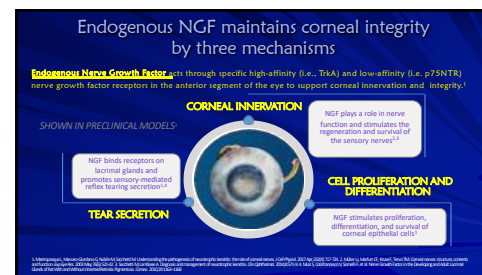
104



105



106



107

108

109

110

111

112

113

### OXERVATE™ (cenegermin-bkbj)

- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
  - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying cenegermin
  - presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion
  - Lenses may be reinserted 15 minutes after administration.

114


### Oxervate™ (cenegermin-bkbj)

- Approved 2018
- Dompe Farmaceutici SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2 hour intervals) for 8 weeks
- Storage issues: in the freezer at the pharmacy; patient keeps the individual vials in the fridge – once “actively ready” for use, then it is only stable for 12 hours
- ADRs: eye pain, inflammation, corneal deposits

115

### Sutureless Amniotic Membrane

- Amniotic membrane is the innermost lining of the placenta (amnion)
  - Shares the same cell origin as the fetus
  - Stem Cell behavior
- Regenerative platform that possesses natural growth factors and scaffolding properties that are
  - Anti-inflammatory
  - Anti-scarring
  - Anti-angiogenic
- Therapeutic action
  - Promotes Stem Cell Expansion
  - Suppresses pain
  - Promotes cellular migration
  - Expedites recovery



116

### Cryopreserved and Dehydrated

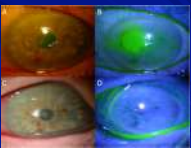


- Cryopreserved
  - PROKERA- Biotissue
- Dehydrated
  - AmbioDik - IOP Ophthalmics
  - BioDOptix – BioD
- Taped tarsorrhaphy/tapesorrhaphy

117

### 67-year-old woman with a history of recurrent HSV keratitis and dry eye

- She presented with mild ocular discomfort (cornea hypoesthesia) and progressive decrease of vision (20/400) for several weeks
- Examination revealed a central corneal epithelial defect surrounded by a rim of loose epithelium, stromal edema, and anterior chamber inflammatory reaction (Fig. A, B)
- Neurotrophic keratitis



- PROKERA was placed along with punctal plug, tarsorrhaphy, and oral Acyclovir
- Complete healing occurred within one week, resulting in clear vision, 20/20 vision, and improved tear meniscus (Fig. C, D).

Early intervention with PROKERA promotes regenerative healing and prevents haze

118

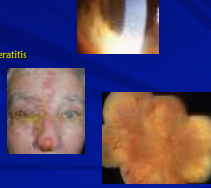
### Severe Neurotrophic Keratopathy

- May need surgical repair
  - Lamellar keratoplasty
  - Penetrating keratoplasty
  - Sutured multilayer amniotic membrane transplantation
    - Used in defects as deep as 90% of the depth of the stroma
  - Cyanoacrylate glue with a soft bandage contact lens
    - Defects smaller than 2 mm

119

### Ocular Findings Associated with Herpes Family

- ~ Epideritis
- ~ Scleritis
- ~ SPK
- ~ Pseudodendritic keratitis
- ~ Stromal keratitis
- ~ Uveitis
- ~ Iris atrophy
- ~ Glaucoma
- ~ Vitritis
- ~ Retinitis
- ~ Choroiditis
- ~ Optic neuritis
- ~ CN palsy



120


### Acute Retinal Necrosis (ARN)

- ~ A rare presentation of herpetic or other viral disease
  - Varicella zoster is most common cause
  - HSV1/2, CMV, EBV infections
- ~ Characterized by large areas of retinal whitening and necrosis that spreads centripetally with a high rate of accompanying detachment and vascular occlusion
- ~ Historically, ARN was believed to affect healthy adults
  - Increasing evidence suggests that patients who develop ARN have underlying immune dysfunction
- ~ Polymerase chain reaction-based (PCR) analysis of the intraocular fluid is valuable in diagnosis of infectious retinitis
  - Aqueous or vitreal fluid
  - Small sample volume from the anterior chamber is usually sufficient to detect copies of VZV, HSV, CMV, or Toxoplasma gondii DNA in patients with infectious retinitis
  - Results within 1 week

121

### Acute Retinal Necrosis (ARN)


- ~ HIV uninfected patients
  - VZV greater than 50%
  - HSV-1 and HSV-2
  - CMV, less common
- ~ Patient with HIV
  - VZV 33%
  - CMV then HSV-1/HSV-2



122

### PORN

- ~ Progressive Outer Retina Necrosis (PORN)
  - Starting in posterior pole then outer retina
    - ARN emphasis is peripheral retina
  - Severely immunosuppressed patient
  - HIV positive patient
  - Minimal vitreous involvement despite extensive retina involvement
- ~ It is documented herpetic retinitis can affect any part of the retina
  - Regardless of immune status



123

### Treatment

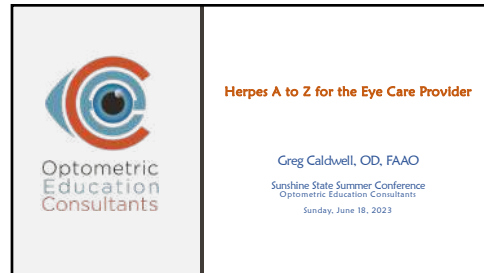
- ~ Oral valacyclovir at 2 g TID can achieve systemic levels similar to intravenous acyclovir
- ~ Intravenous acyclovir 10-15mg/kg TID for 5-10 days followed by oral regimen for 6-12 weeks
- ~ Intra-vitreal injection of foscarnet or ganciclovir can be considered
- ~ Laser photocoagulation is controversial
- ~ Management of the retina detachment is both tractional and rhegmatogenous
  - Vitreous condensation and inflammation
  - PVR occurs in up to 75% of patients with ARN

124

### Differential Diagnosis

- ~ Necrotizing retinitis is typically from Herpes Family of viruses but keep in mind:
  - Syphilitic retinitis
  - Toxoplasmic retinochoroiditis
  - Primary vitreo-retinal lymphoma
  - Sarcoidosis
  - Tuberculosis
  - Toxocariasis
  - Fungal or bacterial retinitis/endophthalmitis
  - Behçet's disease

125



127