Pharmaceutical Update 20/20

New Drugs and Indications

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Greg Caldwell, OD, FAAO
Optometric Education Consultants

Disclosure Statement
(next slide)

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Disclosures- Greg Caldwell, OD, FAAO

- Will mention many products, instruments and companies during our discussion
  - I don't have any financial interest in any of these products, instruments or companies
- Pennsylvania Optometric Association –President 2010
  - POA Board of Directors 2006-2011
- American Optometric Association, Trustee 2013-2016
- I never used or will use my volunteer positions to further my lecturing career
- Lectured for: Aerie, Alcon, Allergan, BioTissue, OptoVue
- Advisory Board: Allergan, Maculogix, Sight Sciences, Sun, Takeda
- Envolve: PA Medical Director, Credential Committee
- Optometric Education Consultants- Scottsdale, St. Paul, Quebec City, Nashville, and Orlando/Disney OCT Users meeting; Owner

2

Disclosures- Tracy Offerdahl, Bpharm, PharmD

- Boiron: honorarium, webinar/speaker
- Has not received any assistance from any commercial interest in the development of this course

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Course Description

- Every year the FDA approves numerous pharmaceuticals (AKA "Legend Drugs") for the management of diseases in many therapeutic categories
- This course will review recently approved pharmaceuticals that are pertinent to optometric patient care
- This course will review systemic and ocular complications of select pharmaceuticals

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Text Questions or Comments to:

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Small Molecule Drugs First

Biologic Drugs Second

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Vyzulta™ (latanoprostene Bunod) Ophthalmic Solution 0.024%

- Bausch & Lomb
  - previously Vesneo™
- November 2, 2017: approved
- Indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
- Once daily monotherapy
- Dual mechanism of action
  - Uveoscleral pathway to increase aqueous humor outflow
  - Butanediol mononitrate, which releases NO to increase outflow through the trabecular meshwork and Schlemm's canal.
- Ocular adverse events
  - Conjunctival hyperemia, eye irritation, eye pain and instillation site pain
  - Increased pigmentation of the iris and periorbital tissue and growth of eyelashes can occur

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Xelpros™ (latanoprost ophthalmic solution 0.005%)

- Sun Pharmaceuticals
- Approved September 2018
- Dosage: QD
- Reduce IOP in open-angle glaucoma and ocular hypertension
- Xelpros is the first latanoprost product not formulated with the preservative benzalkonium chloride
  - Potassium sorbate 0.47% - preservative
- Mechanism of delivery with castor oil
- Reduces IOP in patients with open-angle glaucoma and ocular hypertension
  - Up to a mean of 6 mm Hg to 8 mm Hg in randomized clinical trials

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Xelpros™ (latanoprost ophthalmic solution 0.005%)

- Not available in pharmacies
- A direct pay between patient and partnering pharmacies
  - Capstan Pharmacy
  - Transition Pharmacy
- Xelpros Xpress offers:
  - No prior authorizations
  - No coupon activation
  - No callbacks
  - Prompt fulfillment and refills
  - $55 for 30 days, $110 for 90 days

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Rhopressa™ 0.02% (netarsudil ophthalmic solution)

- Aerie Pharmaceuticals
  - Approved December 2017
  - Treatment of glaucoma or ocular hypertension
  - Rho kinase inhibitor
    - ROCK-NET Inhibitor
  - Once daily in the evening
    - Twice a day dosing is not well tolerated and is not recommended
  - Side Effects
    - Conjunctival hyperemia
    - Corneal verticillata
    - Conjunctival hemorrhage

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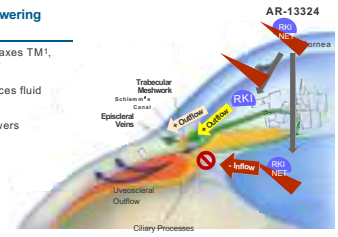
Rhopressa (ROCK-NET Inhibitor) Triple-Action

3 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)[3]



1. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014;8:883-890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma* 2015; 24(1):51-4.
3. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. *ARVO* 2014. Abstract 2900

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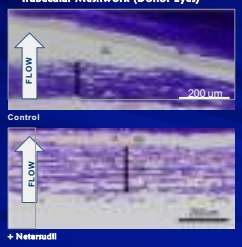
Rhopressa™ 0.02% (netarsudil)

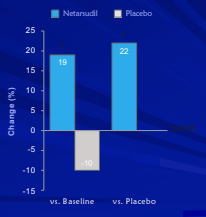
Causes Expansion of TM in Donor Eyes

Increases TM Outflow Facility in Clinic

Trabecular Meshwork (Donor Eyes)[1]



TM Outflow Facility (Healthy Volunteers)[2]



TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; EVV: Episcleral Vein

1. Ren R et al. Invest Ophthalmol Vis Sci. 2016;57(14):6197-6209. 2. Sit AJ et al. Presented at ACG 2017.

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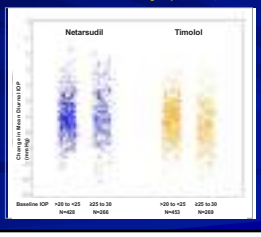
Netarsudil is Similarly Effective at Baseline IOPs <25 mmHg and ≥25 mmHg

Pooled Analysis Rocket 1, Rocket 2, Rocket 4

Day 90: Change from Baseline IOP by Baseline Subgroup (Pooled)



Baseline IOP >20 to <25 mmHg

	Netarsudil QD	Timolol BID
Median	-4.2	-4.3
Mean	-4.1	-4.3
Max	-10.7	-10.8

Baseline IOP ≥25 to <30 mmHg

	Netarsudil QD	Timolol BID
Median	-4.0	-5.3
Mean	-3.7	-5.3
Max	-12.3	-12.0

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Rhopressa™ 0.02%

- No labeled contraindications for Rhopressa™
- No clinically relevant effects on vital signs
  - Blood Pressure
    - Changes were generally small and not clinically relevant in both groups
  - Heart Rate
    - Timolol caused statistically significant reduction in the phase 3 studies by an average of 2-3 beats per month

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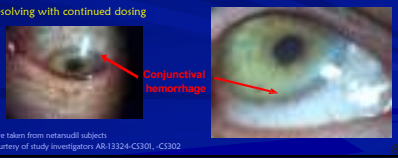
Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing

Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

Majority 92.4% (133/144) of the conjunctival hemorrhage in netarsudil QD group was mild, 6.3% (9/144) was moderate and 1.4% (2/144) was severe

Self-resolving with continued dosing



Images were taken from netarsudil subjects

Source: Courtesy of study investigators AR-13324-CS301, -CS302

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Cornea Verticillata Observed in Phase 3 Studies

- Cornea verticillata refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium
- Subjects are asymptomatic
- The onset was ~6 to 13 weeks (netarsudil QD)

AR-13324-CS302 netarsudil QD subject

AR-13324-CS302 netarsudil BID subject

Images were taken from netarsudil subjects

Source: Courtesy of study investigators AR-13324-CS302

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Cornea Verticillata Due to Phospholipidosis

Medications known to cause verticillata: amiodarone, chloroquine, naproxen, phenothiazine, ocular gentamicin and tobramycin*

Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Data on File Based on AR-13324-IPH07

* Raizman MB et al. Surv. Ophthalmol. 2017;62:286-301

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Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia	Cornea Verticillata	Conjunctival Hemorrhage
54.4% TEAE	20.9% TEAE	17.2% TEAE
Severity did not increased with continued dosing	Asymptomatic	Mild in severity and transient
Sporadic	Did not impact visual function	Self-resolving with continued dosing

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How Will I Use Netarsudil to Treat Glaucoma?

- **As a monotherapy in patients who:**
  - Have concerns about the ocular side effects of PGs
  - Are intolerant to or have inadequate efficacy with PGs
  - Need or prefer alternative to beta blockers, alpha agonists, CAIs
- **As an adjunct agent:**
  - Add to a prostaglandin
  - Add to or alternative to other adjunctive agents
- **To improve patient compliance** - fewest number of daily doses is beneficial
- **After glaucoma surgery** when desired IOP is not achieved
- **As another medical option to help delay or defer glaucoma surgery**

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Rocklatan™

(netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%

- Aerie pharmaceuticals
  - March 14, 2019
- Once-daily eye drop
- First PGA combination approved
  - Superiority versus inferiority
- Refrigeration
  - Storage and after opening
    - For now

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Bimatoprost SR

Sustained Release

- Allergan
- Phase 3 Clinical Trial Update
  - 20 month efficacy and safety study
  - 528 people with POAG or Ocular HTN
    - 30% reduced IOP over 12 week primary efficacy period
      - Met predefined criteria for noninferiority to the comparator
        - Timolol
    - These results similar to topical PGA
- Designed to lower IOP for 4 months
- Well tolerated to this point
- New drug application most likely second half of 2019

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Avaclyr™ (Acyclovir)

- Avaclyr (Acyclovir) 3% Ointment
  - Approved April 2019
    - Available in a 3.5 g tin tub (ointment)
  - Ophthalmic ointment for treatment of herpetic keratitis
    - Apply a 1 cm ribbon of ointment in the lower cul-de-sac of the affected eye
    - 5 times per day (approximately every 3 hours while awake)
      - Until the corneal ulcer heals
    - Then a 1 cm ribbon 3 times per day for 7 days
  - Comparison to Zirgan and Viroptic
  - Clinical data: Not much out there!
  - ADRs: eye pain, punctate keratitis, and follicular conjunctivitis

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Cequa™ (cyclosporine ophthalmic solution) 0.09%

- Sun Pharmaceuticals, Approved August 2018
- Dosed BID
- Single-use vials
- "New Nanomicellar Ophthalmic Solution for Treatment of Keratoconjunctivitis Sicca"
  - Formulation technology uses micelles
- Gelatinous aggregates of amphipathic molecules
  - Hydrophobic and hydrophilic molecules
  - Ease of entry into conjunctiva and cornea
    - High delivery of cyclosporine A (CsA)

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Cequa™ (cyclosporine ophthalmic solution) 0.09%
Indication and Important Safety Information

Indication:
A calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye)

Warnings and Precautions:
Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.
Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution

Adverse Reactions:
The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%)

Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection

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Cequa™ Formulation

- Novel, aqueous, nanomicellar formulation of cyclosporine A 0.09%[1-4]
- Unpreserved, isotonic, neutral pH fluid that is supplied in unit dose vials
- Well tolerated in a 12-week phase 2b/3 study[5]

1. Cholkar K et al. *Recent Pat Nanomed.* 2012;2:82-95 2. Mandal A et al. *J Control Release.* 2017;248:96-116. 3. Vaishya RD et al. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2014;6:422-437. 4. Cholkar K et al. *Trans Vis Sci Technol.* 2015;4:1-16 5. Tauber J, et al. ASCRS 2007 Paper presentation.

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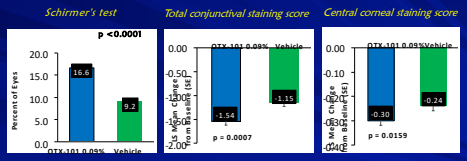
Primary Endpoints



Note: Data shown for the intent-to-treat population (subjects randomized, excluding 1 subject who was assigned to OTX-101 but not treated); missing data on day 84 were imputed by baseline values carried forward.

LS, least squares; SE, standard error.

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Cequa™ (cyclosporine ophthalmic solution) 0.09%

- Available at retail pharmacies
  - Also, available thru specialty pharmacy
    - RxCrossroads
    - Commercially insured
    - Cap the pricing and assist with prior authorizations
      - First in this class to offer capped pricing

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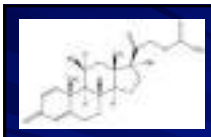
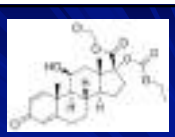


Steroids
Ketones versus Esters



- Prednisolone acetate molecule modified to undergo predictable degradation to inactive metabolites by local esterases
- Corticosteroids, C-20 ketone replaced with a C-20 ester
- C-20 ester steroids are associated with a lower incidence of IOP elevations vs. C-20 ketone steroids
  - IOP and cataracts
- Retrometabolic drug design of loteprednol aims to improve safety while maintaining efficacy

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Loteprednol Etabonate Products
Ester Steroids

- Lotemax suspension 0.5%
- Alrex suspension 0.2%
- Lotemax gel 0.5%
- Lotemax SM gel 0.38%
- Inveltys suspension 1.0%
- KPI-121 loteprednol etabonate suspension 0.25%

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Lotemax SM (loteprednol etabonate) 0.38%

- Indicated for the treatment of post-operative inflammation and pain following ocular surgery
- SubMicron - *Particle size* reduced to facilitate ocular penetration
  - Allowing for a decrease in drug concentration and dosing frequency (TID)
  - Increase intraocular penetration
  - Median particle diameter size reduced 5 to 12.5-fold:
    - LE gel 0.38% = 0.4-0.6 µm
    - Lotemax gel 0.5% = 3-5 µm
  - Potential for a ~10-fold increase in rate of drug dissolution
    - Based on a 10-fold increase in relative surface area with smaller particles

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Lotemax SM (loteprednol etabonate) 0.38%

- Increased concentrations demonstrated in ocular tissues
  - Cornea and aqueous humor
  - Following single topical ocular instillation of Lotemax SM 0.38% vs Lotemax gel 0.5% in rabbits
- Compared to Lotemax Gel 0.5%
  - Single topical instillation of Lotemax SM 0.38% were greater in the aqueous humor and cornea
  - Concentrations in the conjunctiva remain the highest out of the ocular tissues, with ample drug to mediate anti-inflammatory effects at the ocular surface
- Formulation advancement while maintaining a low BAK
  - Lowest concentration of BAK, 0.003% among the commercially available corticosteroid ocular drops
    - Inveltys is 0.01%

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Lotemax SM (loteprednol etabonate) 0.38%

- **Submicron formulation is designed to reduce the Lotemax Gel drug concentration 0.38% vs. 0.5%)**
- **Dosing frequency TID vs. QID**
- **Formulation builds on the heritage and advantages of Lotemax gel 0.5%:**
- **Retrometabolically designed corticosteroid**
  - Retains potent anti-inflammatory activity
  - Minimal potential for class Aes
- **Mucoadhesive, non-settling, shear-thinning gel**
  - A gel in the bottle; transitions to a liquid upon instillation
  - Becomes mucoadhesive liquid on dilution with tears
  - No need to shake - uniform dosing
  - Non-blurring

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Inveltys ™ - loteprednol etabonate suspension 1.0%

- Kala (ka-la) Pharmaceuticals
- August 2018
- Now in distribution centers and pharmacies
- Nanoparticle-based Mucus Penetrating Particles (MPP)
  - "Amplified Technology"
  - MOD
  - Allows drug to penetrate through tear mucins
    - Increased penetration into tissues, 3-fold to other loteprednol
- 1.0% post-operative inflammation and pain after ocular surgery
  - Dosage BID
    - First ocular corticosteroid to be BID

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KPI-121 loteprednol etabonate suspension 0.25%

Stay Tuned

- Kala (ka-la) Pharmaceuticals
- First product indicated for the temporary relief of signs and symptoms of dry eye disease
- Phase 2 and Phase 3 efficacy and safety trials
  - STRIDE- Short Term Relief in Dry Eye
    - Over 2000 patients with dry eye disease
- PDUFA date: August 15, 2019
  - Recruiting more people
  - Strict inclusion and exclusion criteria

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Biologic Drugs

- Biologic therapies include wide range of medical products
  - First-generation biologic therapies
    - Vaccines
    - Blood products
    - Stem cell injections
- Today, when people talk about "biologics" they usually mean the second-generation biologic therapy drugs
  - Humira, Remicade, Enbrel
- Biologic therapies
  - Cannot be made using a simple chemical reaction
    - Mixing ingredients together in a laboratory, the way conventional drugs are made
  - Are made using living organisms

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Small Molecule Drugs versus Biologics

- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions (i.e. organic chemistry)
- Biologics are made by harvesting the substances produced and secreted by constructed cells (i.e. genetic engineering)

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Size and Complexity of Biologic Drugs

- Small molecule drugs can be taken orally
  - Tend to work in the body within cells
- Biologics are significantly larger in size
  - Typically injected and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells
- Small molecule drugs
  - Such as aspirin
  - Composed of only 20 to 100 atoms
- Small biologics
  - Such as hormones
  - Composed of 200 to 3000 atoms
- Large biologics
  - Such as antibodies
  - Composed of 5000 to 50,000 atoms

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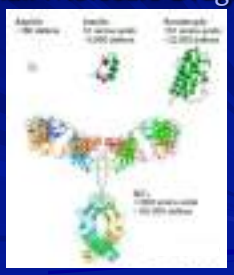
Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs
  - Larger, complex, dynamic structures
  - Diverse populations of molecules
    - Not easily characterized
  - Complicated manufacturing
  - Example: Teprotumumab (Tepezza)
- Small Molecule Drugs
  - Synthetic
  - Manufactured using a defined chemical process
  - Smaller and simpler
  - Example: Aspirin



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Size and Complexity of Biologic Drugs

https://www.asbio.org/small-molecules-large-biologics-and-the-biosimilar-debate

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Making Biologics

A piece of DNA is inserted into a living cell— yeast, bacterial, viral, or mammalian cell

↓

Cell then produces a large amount of a specific molecule (e.g. protein)

↓

Desired molecular isolation (living cells/material removed - only the desired molecules are left)

↓

The isolated molecules become the active ingredient in a biologic drug

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Making Biologics

- The molecules in a biologic drug are different from the molecules in most other pharmaceutical products because of their **large size, lack of uniformity,** and **weak chemical bonds.**
  - Large size and lack of uniformity
    - The molecules that make up a biologic drug are not uniformly the same, and each molecule typically has tens of thousands atoms
  - **Weak chemical bonds**
    - The chemical bonds that hold these molecules together are relatively weak
    - The molecules can degrade if they are exposed to rapid temperature changes and other factors (percussion)
- Because the molecules that make up biologics are so **sensitive**, manufacturers must follow specific steps to make and package a biologic product
- Even small differences in the manufacturing and packaging process—as well as storage and administration—of a biologic can affect a drug's ability to work
- So where do biosimilars fit in?!?

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What is a Biologic versus Biosimilar?

- **Biologics**
  - Isolated from natural sources - human, animal, or microorganism
  - "High-tech" treatments; AKA "biotechnology"
  - Difference between "regular/chemical drugs" and "biologics"…
    - "**Regular/Chemical drugs**" – generally synthesized with known chemical structures
      - Can be made easily into oral products, topical products, etc.
    - "**Biologics**" - very complex mixtures that are NOT easy to identify
      - Very sensitive and easily made unstable; earliest products were only available as an injection, but newer products are ocular preps and oral formulations
      - AKA "reference product", "innovator product"
    - May be used to treat a variety of medical conditions for which **NO OTHER** treatments are available
      - The downside?!? COST

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Biosimilars

- "Highly similar" to the "reference product" (ie. The biologic/reference or innovator product)
- FDA's approach: The biosimilar company's research is to PROVE "biosimilarity" between the proposed biosimilar product and the reference product…NOT to independently establish the safety and effectiveness of the proposed product
- There are no clinically meaningful differences in terms of:
  - Safety
  - Purity
  - Potency
- Why is there no such thing as a GENERIC biologic medication?
  - Biologics come from LIVING "things", so it is not likely to be EXACTLY the same as the reference product! USUALLY differs in terms of inactive ingredients
  - Generic medications are chemically synthesized so that the active ingredient is IDENTICAL to the brand name medication

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Biologic versus Biosimilar

tldrpharmacy.com

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Monitoring Parameters Biologics

- Biologics are Immunomodulating/Immunosuppressive medications!
  - HIGH immunogenicity potential because they "tinker" with the immune system & come from nature
  - Small molecule drugs have LOW immunogenicity because they are synthetic
- Many of the systemic agents for autoimmune disease can cause significant morbidity and mortality!
  - Must place PPD before initiating = if PPD+, then initiation of a biologic may convert latent TB to ACTIVE tuberculosis
  - Once a biologic is initiated, watch for any signs or symptoms of infection
    - If the patient has a "cold", "flu", or is taking antibiotics
    - Then biologic dose must be HELD until the patient is healthy
  - FULL work-up for signs/symptoms of infection!
  - ASK your patients about meds!
  - We will look at the diversity of the side effects with these newer biologics

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Ocular Biologics

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Treatments for Choroidal Neovascularization (CNV)

- Where is all started in the eye
- Disorders of the blood vessels in the retina are responsible for some of the most common causes of blindness in the world
  - Retinopathy of prematurity
    - Important cause of blindness in children in middle-income countries
  - Diabetic retinopathy
    - Common cause of blindness in the working-age population of industrialized countries
  - Age-related macular degeneration
    - A common cause of blindness in the world
- These conditions are caused partly by over-production of a protein called vascular endothelial growth factor (VEGF)
- VEGF was discovered in the 1980s and is important in the growth and development of blood vessel in tumor growth
  - 1994 it was proven that retinal hypoxia produces VEGF

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Treatments for Choroidal Neovascularization (CNV)

- Current Anti-VEGF treatments
  - Pegaptanib (Macugen)
    - First FDA Approved December 2004
    - RNA aptamer
    - AMD
  - Bevacizumab (Avastin)
    - Humanized full length monoclonal antibody - 2005
    - AMD
  - Ranibizumab (Lucentis)
    - Humanized monoclonal antibody fragment – 2006
    - AMD, DME, DR, RVO
  - Aflibercept (Eylea)
    - Fusion protein – 2011
    - AMD, DME, DR
  - Brolucizumab-dbll (Beovu)
    - Humanized single-chain antibody fragment - 10-8-2019
    - Up to 3 months dosing intervals, most are 4-6 weeks
      - 50% remained 3 months after 1 year

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Oxervate™ (cenegermin-bkbj)

- Approved 2018 (August 28, 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
  - Used as eye drop
    - Not infused or injected
- 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
- Contraindications
  - None

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Escherichia Coli

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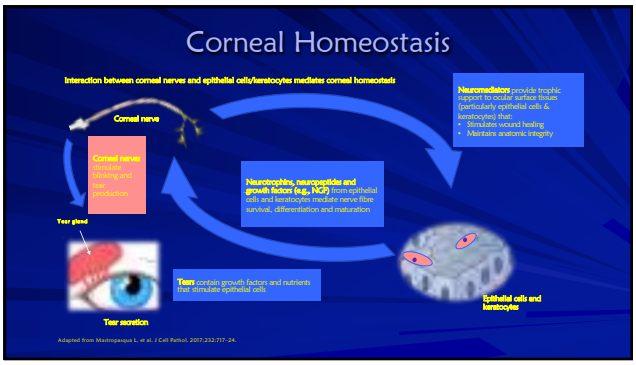
Corneal Homeostasis



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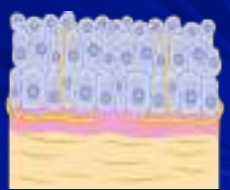
Pathophysiology of NK[1]

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



1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521-42.

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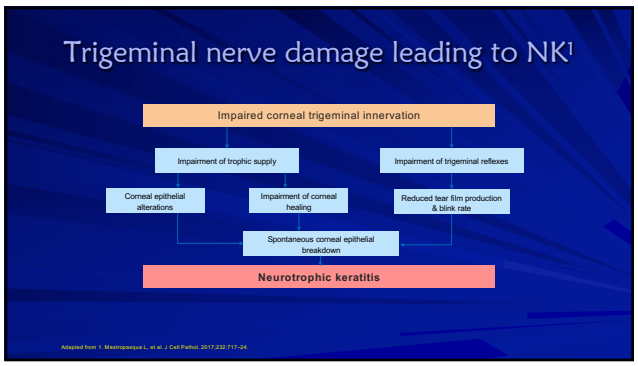

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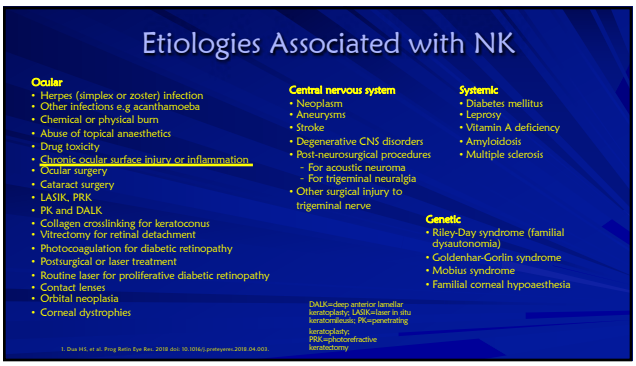

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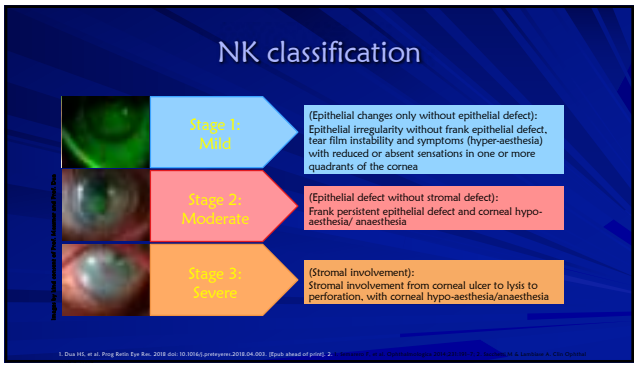

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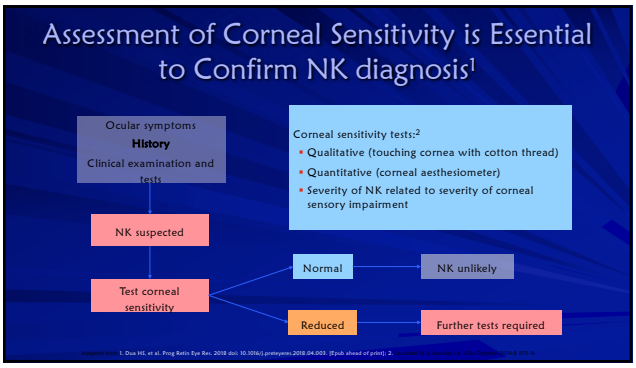

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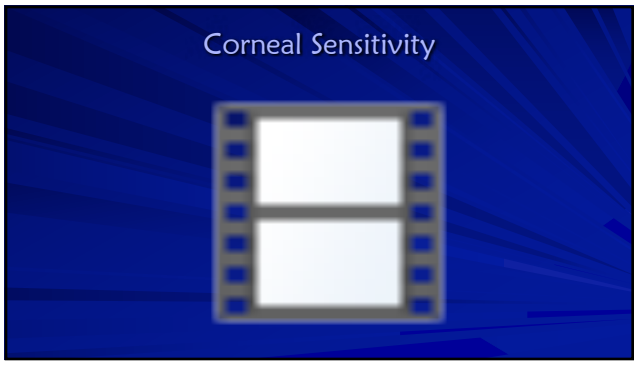

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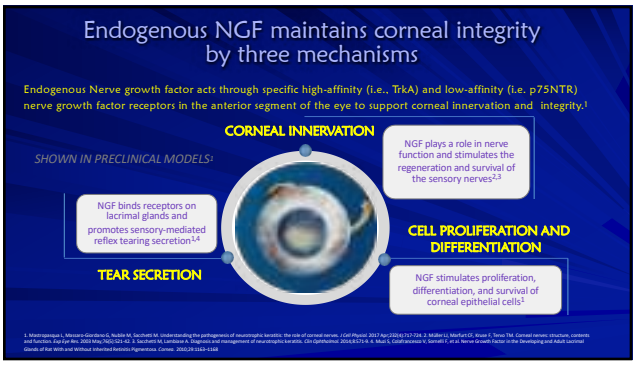

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Active ingredient structurally identical to human nerve growth factor produced in ocular tissues

- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons[1]
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s[1]
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein[2]

1. Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 1998;338:1174-80. 2. Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA 2018;320(13):1309.

61

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

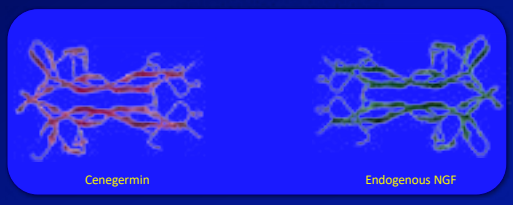
- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares

- **Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

62

Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues



Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Dosing and Administration

Instill 1 drop of OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

2 — Every 2 hours

6 — Apply 6 times daily

8 — Continue for 8 weeks

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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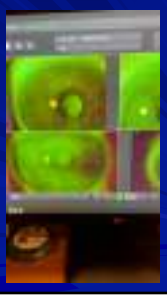
Let's Hear From a Patient

April 7, 2020 - After 1 week

April 21, 2020 - After 3 weeks

May 12, 2020 - After 6 weeks



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Study Conclusions

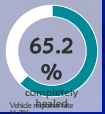
After 8 weeks of treatment, 6 times daily

In the majority of patients across two clinical studies OXERVATE™ (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

50 clinical trial sites in Europe and the U.S.

Study NGF0212 (REPARO) (N=52 per group)
European patients with NK in one eye
NCT01756456

Study NGF0214 (N=24 per group)
U.S patients with NK in one or both eyes
NCT02227147



Of patients who healed after one 8-week course of treatment…

80% Remained healed for one year*

**Based on REPARO, the study with longer follow-up*

Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing*

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. 3. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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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.

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Thyroid Disease and Thyroid Eye Disease

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Normal Thyroid Function

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Thyroid Dysfunction

- What is the most common cause of thyroid dysfunction?
  - A. Cancer
  - B. Surgically induced
  - C. Medication toxicity or side effect
  - D. Pregnancy
  - E. Autoimmune disease
- In autoimmune disease the body typically produces _____ that attacks itself, this can be systemic or organ specific
  - Antibodies, immunoglobulins

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Antibodies of Thyroid Dysfunction

- TSH Receptor Antibodies
  - Stimulating TSH receptor antibody
    - Thyroid Stimulating Immunoglobulin (TSI)
  - Thyroid blocking antibody (TBAb)
- Thyroid Peroxidase Antibodies (TPOAb)
  - TPO is found in thyroid follicle cells where it converts the thyroid hormone T4 to T3
  - TPOAb contributes to thyroid cellular destruction
- Most autoimmune thyroid dysfunctions have a combination of thyroid antibodies, however depending on which AB is more abundant results in the outcome of the disease

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Thyroid Dysfunction

Hyperthyroidism
(Thyrotoxicosis)

- Primary-autoimmune
  - Graves
    - Graves-Basedow or von Basedow' s
- Secondary/Tertiary
  - Excess thyroid medication for treatment of hypo or goiter
  - Toxic multinodular goiter
  - Toxic adenoma
  - Excess iodine
  - Thyroiditis (inflammatory induced)
  - Excess hormone production ectopic tissue
  - Thyroid carcinoma

Hypothyroidism
(most common organ-specific autoimmune disorder)

- Primary-autoimmune
  - Chronic autoimmune thyroiditis
    - Hashimoto's thyroiditis
  - Autoimmune atrophic thyroiditis
    - Primary myxedema
    - Opposite of Graves disease
  - Postpartum thyroiditis
- Secondary/Tertiary
  - Lithium medication
  - Pregnancy
  - Surgically induced
  - Disorders of the pituitary gland or hypothalamus

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Thyroid Eye Disease

- Thyroid Eye Disease has 2 phases
  - A phase secondary to abnormal thyroid hormone levels
    - Increased or decreased FT3 and FT4 levels
    - Once these levels are normalized, ocular symptoms will resolve
  - Congestive Autoimmune form of Thyroid Eye Disease
    - Active phase-stimulating or blocking TRAb are causing ocular activity
    - Plateau phase-reduced activity
    - Resolution phase-symptoms regress and eyes return to normal

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Phase secondary to abnormal thyroid hormone levels (T_3/T_4)
(Thyroid Eye Disease)

- Hyperthyroidism eye symptoms
  - Excess hormone acting on the nerves that supply the eye
  - Usually spastic and include staring
  - Dryness
  - Eyelid retraction
- Hypothyroidism eye symptoms
  - Deficient hormone causing venous congestion, impaired circulation and fluid stagnation
  - Periorbital edema

- This form of TED resolves within a few weeks after thyroid hormone levels (FT4 and FT3) are corrected and brought back into the normal range
- The pituitary hormone TSH can stay low or suppressed for many months during the course of treatment for hyperthyroidism and doesn't mean that the patient is still hyperthyroid
- TSH also lags at least 6 weeks behind thyroid hormone levels and often remains elevated longer in people who have been hypothyroid
- Relying on the TSH level can be misleading and in treating TED

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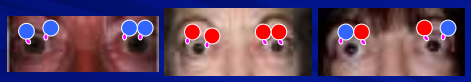
Congestive Autoimmune form of Thyroid Eye Disease
(Active phase, Plateau phase, Resolution phase)

- Caused by both stimulating and blocking TSH receptor antibodies (TRAb) and also immune system chemicals known as cytokines
- Secondary targets appear to be TSH receptor antigens (epitopes) located on orbital fibroblasts as well as dermal fibroblasts
- Active "inflammatory" phase of TED varies
  - Symptoms resolve quickly although on average the active phase lasts about 12-18 months
  - TRAb levels are high, patients are smokers, nutrient deficiencies are present, or the patient continues to be exposed to environmental triggers such as excess dietary iodine, the active phase can last as long as 5 years
  - Avoid any lid, muscle or orbital surgery
- Plateau phase and Resolution "Passive" phase
  - An individual may be left with structural changes, such as eye protrusion, eyelid retraction, and in some cases, double vision
  - There are corrective procedures that can be performed to address these problems

75

Similar receptors are found in the skin, fat and muscle of the orbit



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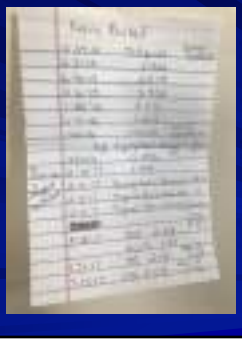


You're in the Know

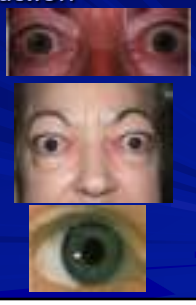
Normal Values
Thyroglobulin 20 IU/ml
Peroidase <35 IU/ml
TSI 1.75 IU/ml

It does work!

77

Lid Retraction

- Scleral show in primary gaze
- Occurs in ~90% of Grave's patients
  - Excess stimulation of Muller's muscle
  - Fibrotic inferior rectus
  - Mechanical restriction or infiltration of levator
  - Increased orbital volume causes exophthalmos
- Normal Lid Position
  - Upper lid intersects cornea at the 2 and 10 o'clock positions
    - ~2 mm below the limbus
  - Lower lid coincident or 1-2mm below the limbus



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Eyelid Lag: von Graefe's Sign

- Immobility or lagging of upper eyelid on downward gaze
- Fibrosis of the inferior rectus muscle may induce lower lid retraction

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Conjunctiva

- Conjunctival and episcleral injection
  - Especially near the horizontal recti insertions
- Chemosis
  - Edema of the conjunctiva and caruncle
- Superior Limbic Keratoconjunctivitis
  - 65% correlation between SLK and systemic thyroid disease
  - Rheumatoid arthritis
  - Sjögren's syndrome

80

Periorbital Edema

- Inflammation of the subcutaneous connective tissue
- May be first sign of thyroid eye disease
- Greatest in the morning

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Infiltrative Orbitopathy (Exophthalmos/Proptosis)

- Thyroid Eye Disease is most common cause of unilateral and bilateral exophthalmos
- The term exophthalmos is reserved for prominence of the eye secondary to thyroid disease
- May need MRI to determine or obvious exophthalmos may be present
- It is permanent in 70% of cases
- Caused by increased volume of the extra ocular muscles
  - Lymphocytic infiltration
  - Proliferation of fibroblasts
  - Edema within the interstitial tissue of the muscle

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Infiltrative Orbitopathy (Exophthalmos/Proptosis)

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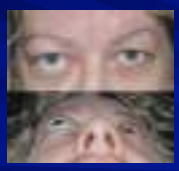
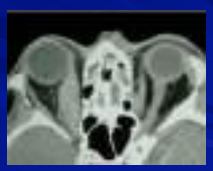
Infiltrative Orbitopathy (Exophthalmos/Proptosis)





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Treatment of Thyroid Eye Disease

- Palliative (hormone imbalance, active, passive)
  - Lubricants
  - Topical anti- inflammatory (Lotemax/Restasis)
  - Prisms
- Steroids (active phase)
  - Orals
  - Peri-ocular injections
  - IV with oral steroid taper
- Orbital radiotherapy (active phase)
- Orbital Decompression (passive phase)
  - Fat removal orbital decompression (FROD)
    - Large orbits
  - Bone removal orbital decompression (BROD)
    - Small orbits
  - Both FROD and BROD

Smoking causes the thyroid eye disease to be more severe
Smoking causes treatments to be less effective

86

Lid Retraction, Eyelid Lag, Lagophthalmos

- Must treat underlying thyroid dysfunction
- Abnormal hormone level and Active phase
  - Treat the exposure keratitis with lubricants
  - Tape eyelids shut at night
  - Lid weight
  - Moisture chamber at night
  - Antibiotic ointments
- Passive Phase
  - Surgical Management
  - Inferior rectus recession
  - Mullerotomy
  - Recession of lower lid retractors

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Lid Retractor Surgery

88

Conjunctiva, Periorbital edema

- Topical lubricants
  - Artificial tears
  - Ointments at night
  - Topical steroids
  - Restasis?
- Tape eyelids closed at night or use mask
- Elevate head at night to decrease lid edema
- Oral diuretics Acetazolamide
- Oral steroids
  - 60-80mg/day for 3 months
- IV steroids
- Periorbital steroids
  - Kenalog last 1 month

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Infiltrative Orbitopathy (Exophthalmos/Proptosis)

- Orbital Disease Consult
  - Systemic steroids to reduce inflammation
  - Low dose radiotherapy
  - Surgical orbital decompression

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Restrictive Myopathy

- Non-surgical (while waiting for stability)
  - Teach proper head position to alleviate diplopia
  - Prism in spectacle correction (Fresnel or ground in)
  - Oral steroids
  - Botulinum toxin injection
- Surgical Consult
  - Recession of the rectus muscle/s involved
  - Diplopia in primary gaze, reading gaze or both
  - Stable angle of deviation for at least 6 months
  - No evidence of active disease
  - Binocular vision in at least primary and reading positions

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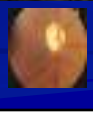
Optic Neuropathy

- Systemic Steroids
  - If rapidly progressive and painful in the early stage of the disease
  - Only if no contraindications
  - Prednisolone 80-100mg, expect results within 48hrs. Taper dose and d/c within 3 mo
- IV Methylprednisolone
- Radiotherapy: if contraindication to steroid
- Orbital decompression



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Orbital Decompression

- Not effective if no medical treatment
  - Two-wall decompression
    - 3-6 mm retro-placement of the globe
  - Three-wall decompression
    - 6-10mm retro-placement
  - Four-wall decompression
    - 10-16mm retro-placement

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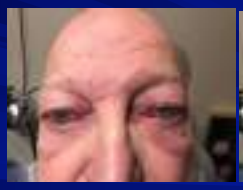
February 25, 2019
"Nothing Else Can Be Done"



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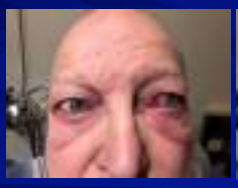
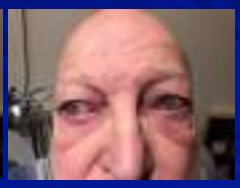
February 25, 2019
"Nothing Else Can Be Done"





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March 1, 2019 (4 days later)
Oral and Topical Steroids

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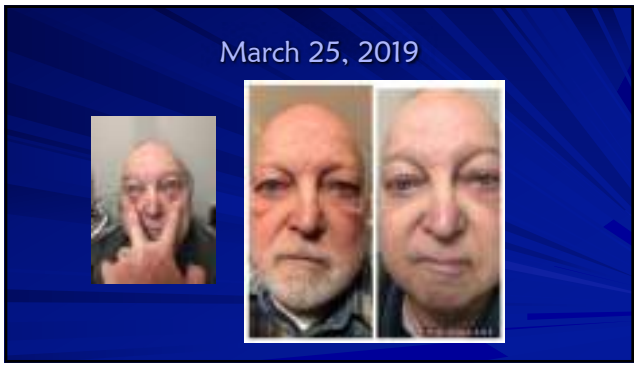

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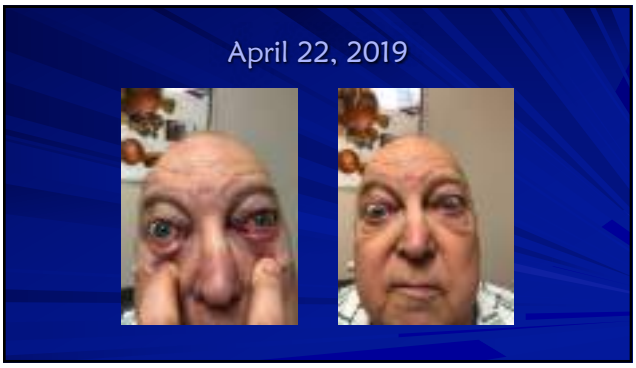

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Teprotumumab-trbw (Tepezza)

- Horizon Therapeutics – HQ Dublin, Ireland and US based Chicago
- Biologic pharmaceutical
  - Chinese Hamster Ovary
  - Infusion, 8 total, every 3 weeks
- Thyroid eye disease
  - IGR-1 (Insulin like growth factor 1) and TSH receptors are over expressed
- IGF-1 receptor inhibitor monoclonal antibody
  - On the orbital fibroblasts
    - Inhibiting downstream inflammatory cascade
      - Cytokines, hyaluran, leukotriene
      - Differentiation into adipocytes and myofibroblasts
- Phase 2 and published in New England Journal of Medicine
- Phase 3 completed
  - Not published
- PDUFA- March 2020, was approved early in 2020

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Teprotumumab-trbw (Tepezza)

https://www.tepezza.com/hcp/tepezza-moa/

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Teprotumumab-trbw (Tepezza)

- Optics and Optic-X Studies
  - 8 infusions, every 3 weeks, 24 weeks
  - Optics – acute, less than 9 months of disease
  - Optics X – chronic, 12-16 months disease
- Clinical Activity Score
  - Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
  - Scale of 7, needed 4 to be in the study
- Proptosis
  - Improvement of 2 mm or better
- Diplopia
  - Scale of 0, 1, 2, or 3
- Grave's Ophthalmopathy -Quality of Life Score
  - Scale 0-100

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Teprotumumab-trbw (Tepezza)

- Clinical Activity Score
  - Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
  - Scale of 7, needed 4 to be in the study
    - 78% improved to 0 or 1, 7% improved 0 or 1 with placebo
- Proptosis
  - Improvement of 2 mm or better
    - 83% had 2 mm or better, 10% with placebo
    - Average was 3.2 mm at week 24
- Diplopia
  - Scale of 0, 1, 2, or 3
    - 68% improved 1 point, 29% with placebo
- Grave's Ophthalmopathy -Quality of Life Score
  - Scale 0-100
    - 17.28 point improved, 1.80 with placebo

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Teprotumumab-trbw (Tepezza)

- **Adverse Reactions**
  - **Very well tolerated**
  - The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

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Teprotumumab-trbw (Tepezza)

- **Infusion Reactions (mild/moderate):** approximately 4% of patients
  - transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain
  - consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate.
- **Hyperglycemia:** Increased blood glucose or hyperglycemia
  - In clinical trials, 10% of patients experienced hyperglycemia
  - Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with teprotumumab
  - Patients with preexisting diabetes should be euglycemic before beginning treatment

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Teprotumumab-trbw (Tepezza)

- Infusion center
  - Go to Horizon website
  - Contact Us
  - Type in your question
    - Looking for infusion center

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Humira™ (adalimumab)

- Company: Abbvie
  - Approved July 2016
  - Indication: uveitis
    - Specifically indicated for the treatment of non-infectious intermediate, posterior and panuveitis
  - Dosage: subcutaneous injection
    - Recommended dose is 80 mg initial dose
    - Followed by 40 mg every other week starting one week after initial dose
  - The significance of this FDA approval is important! Many insurance companies (ex. Medicare) will not pay for "off-label" uses.

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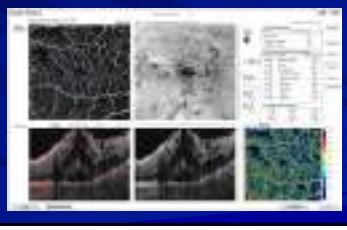
Humira™ (adalimumab)

- Non-infectious intermediate, posterior and panuveitis

Reason for reduced acuity?



111

Humira™ (adalimumab)

- Monitoring parameters:
  - Must place PPD before initiating = if PPD+, then initiation of Humira may convert latent TB to ACTIVE tuberculosis
  - Once Humira is initiated, watch for any signs or symptoms of infection…if the patient has a "cold", "flu", or is taking antibiotics, then Humira dose must be HELD until the patient is healthy.

112

Hadlima™ (adalimumab-bwwd)

- Biosimilars
  - Hadlima (Adalimumab-bwwd)
    - Biologic agent SIMILAR to Humira
    - What is a "biosimilar"agent?
      - Remember what the FDA say about "biosimilars"

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Humira™ (adalimumab)
Hadlima™ (adalimumab-bwwd)

114

Actemra™ (tocilizumab)

ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

Let's qualify this statement

115

From: http://www.actemra.com/actemra/rheumatoid-arthritis/ra.html

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Actemra™ (tocilizumab)

- Actemra™ (tocilizumab)- Genetec
  - First innovative therapy for GCA in more than 50 years
  - Design to speed the development for treatments of serious diseases such as GCA and certain cancers

118

Actemra™ (tocilizumab)

- Patients were randomized to receive tocilizumab 162 mg weekly injections plus a 6-month and 12-month prednisone-taper compared to controls receiving placebo plus similar steroid taper
- The preliminary results indicate that patients receiving high dose tocilizumab had superior disease remission at 1 year compared to the steroid-only taper
- Further investigation from this study will attempt to identify the lowest therapeutic dose of prednisone that can be used in patients also using tocilizumab, the amount of tocilizumab needed to induce remission, and how long patients stay in remission on this therapy

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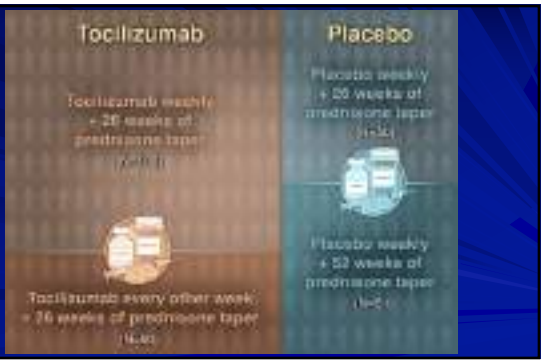

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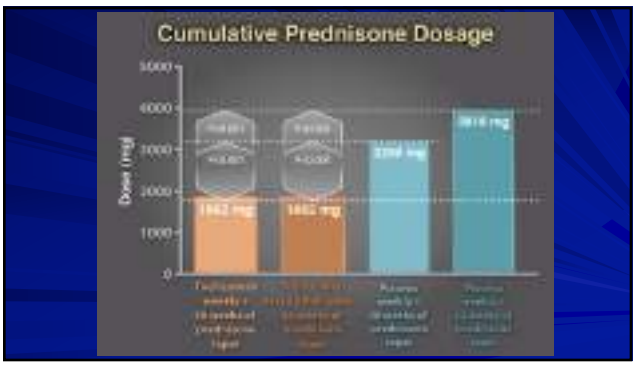
121



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Actemra™ (tocilizumab)

- Tocilizumab does ~~not~~ directly treat GCA
  - Reduces steroid load after disease has been adequately treated by steroids and enhances disease remission
- Steroids are main therapy
- Studies are ongoing to see:
  - What is the lowest steroid tapering dose that can be used with tocilizumab
  - Future studies may show tocilizumab as steroid replacement

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Tocilizumab (Actemra)

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)
- If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

124

Biologics

No ocular indication

125

Olumiant™ (baricitinib) and Rinvoq™ (upadacitinib)

- Janus Kinase inhibitors – approved 2018 and 2019
  - Indicated for the treatment of adult patients with moderate/severe active rheumatoid arthritis
    - Must have failed 1 or more TNF-alpha inhibitors (e.g. Remicade, Humira)
- THE HUB-BUB? It is an orally administered medication, as opposed to MOST of the others that are injectables!
  - Known as "un-jections"

126

Family Medicine

- Aimovig™ (erenumab-aooe)
- Ajovy ™ (fremanezumab-vfrm)
  - Approved 2018
  - Indicated for the PREVENTIVE treatment of migraine in adult patients
  - Calcitonin gene-related receptor antagonist
    - SQ injection
    - Once per month for either product
    - Once every three months for Ajovy™
- ADRs: constipation, injection site reactions

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Erenumab (Aimovig)

128

Biologics

In Studies with the Potential for Eye Care

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Galimedix Therapeutics

- Galimedix Therapeutics is a Phase 2 neuropharmaceutical company developing novel first-in-class drugs with ground-breaking potential to slow or stop the progression of neurodegeneration and to improve function in glaucoma and dry AMD – leading causes of blindness – and also in Alzheimer's disease.

https://www.galimedix.com/

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Galimedix Therapeutics – Glaucoma and AMD

https://www.galimedix.com/technology/mechanism-of-action

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Thank You!

Questions?

Tracy and Greg

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