Pharmaceutical Update 20/20

New Drugs and Indications

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Disclosure Statement
(next slide)

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

Disclosures- Tracy Offerdahl, Bpharm, PharmD

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

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

Text Questions or Comments to:

814-931-2030

Small Molecule Drugs First

Biologic Drugs Second

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

Valeant Changes Name to Bausch Health Companies

- On Tuesday, Valeant announced that it will change its name to Bausch Health Companies
- Name effective July 2018
  - new logo
  - new branding
  - ticker "BHC" on the New York Stock Exchange and Toronto Stock Exchange
- Bausch + Lomb: Valeant bought in 2013 for $8.7 billion
- In 2017, Bausch + Lomb and branded generic drugs sold outside the United States made up $4.9 billion of Valeant's $8.7 billion total revenue

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

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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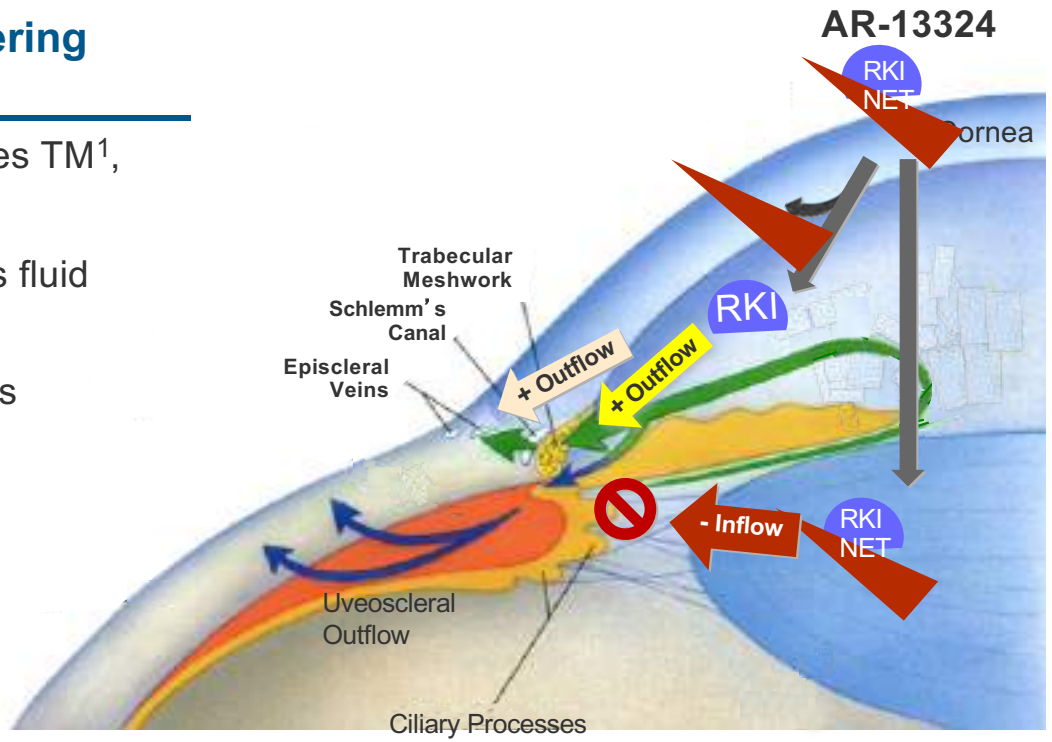
Rhopressa™ 0.02% (netarsudil ophthalmic solution)

- 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

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]



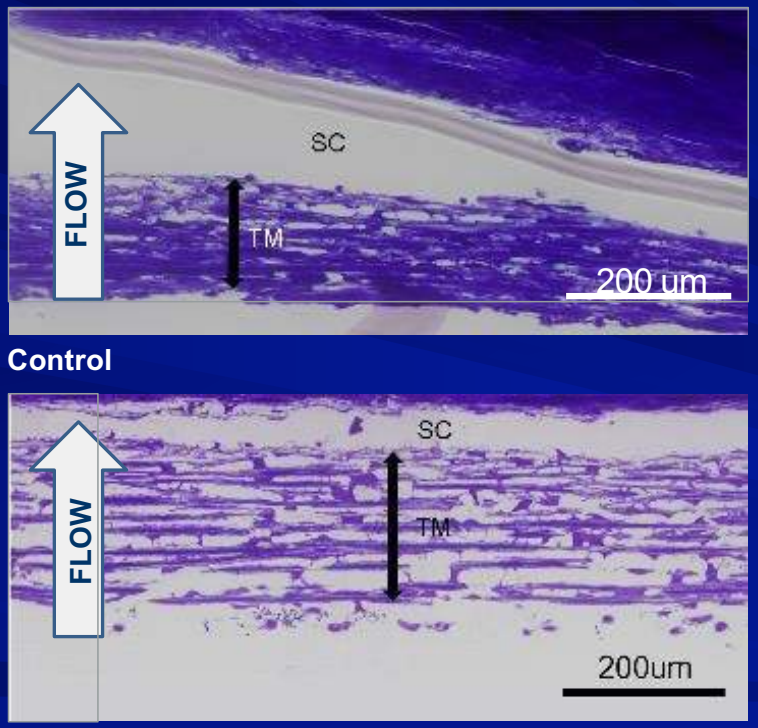
1. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014;8:883-890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *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

Rhopressa™ 0.02% (netarsudil)

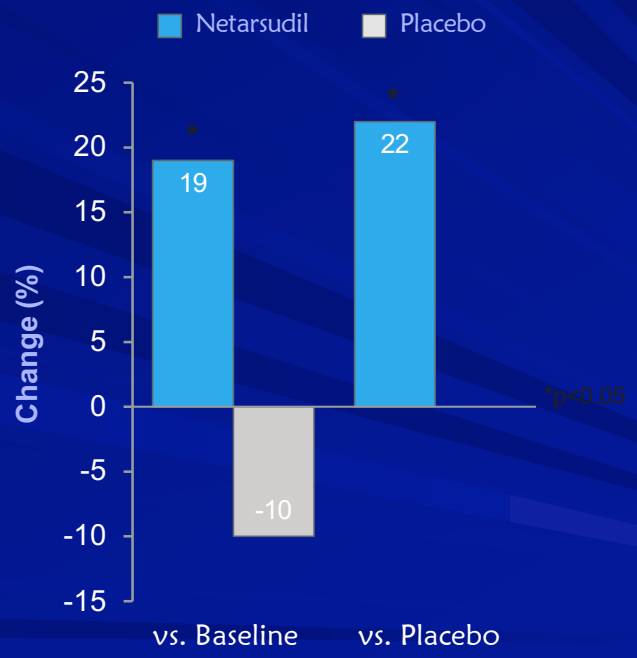
Causes Expansion of TM in Donor Eyes

Increases TM Outflow Facility in Clinic

Trabecular Meshwork (Donor Eyes)[1]



TM Outflow Facility
(Healthy Volunteers)[2]



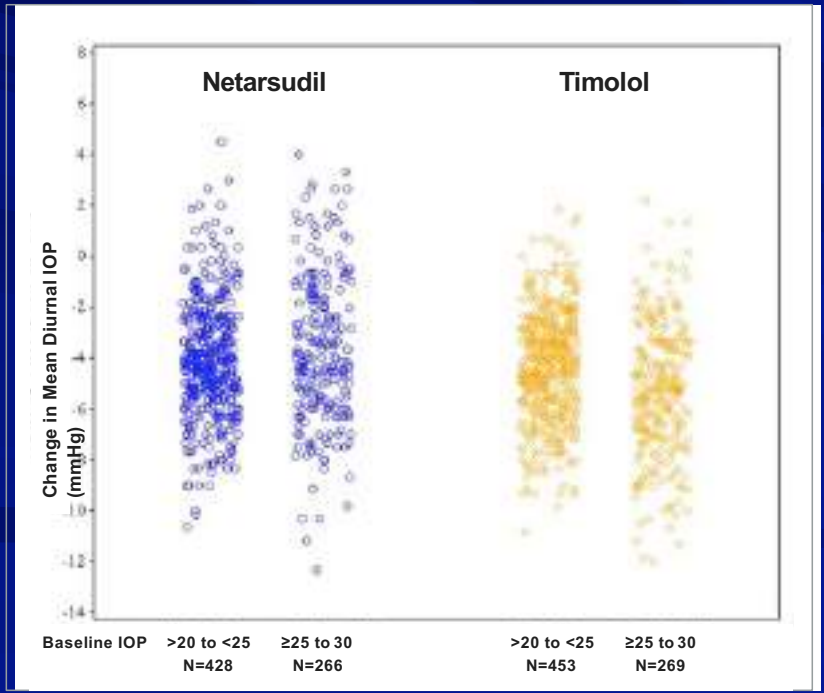
TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein

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

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

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

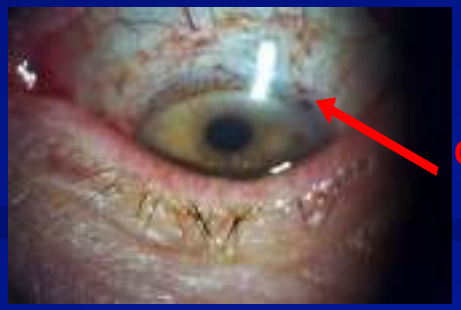
1. RHOPRESSA® (netarsudil ophthalmic solution) 0.02% Prescribing Information. 2. Khouri et al. Association for Research in Vision and Ophthalmology oral presentation 2017 [E-abstract 2461].

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

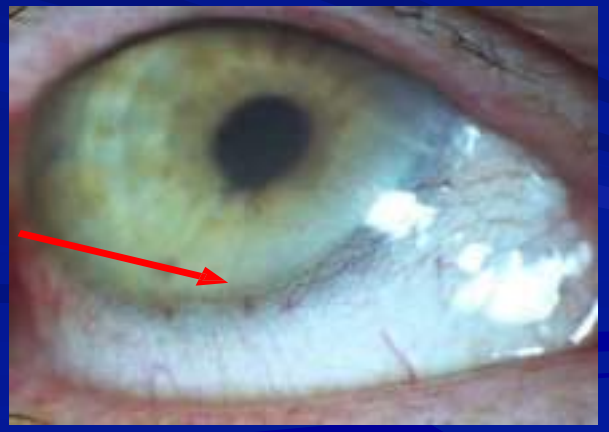
Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

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



Conjunctival hemorrhage

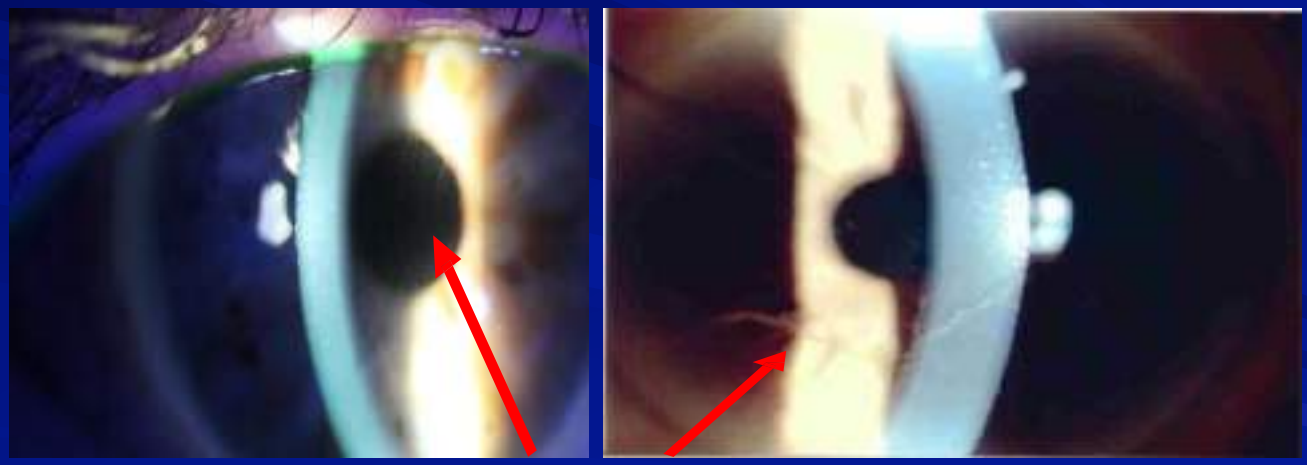


Images were taken from netarsudil subjects

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

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)



Cornea verticillata

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

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

Summary of the Most Common Netarsudil Ocular TEAEs

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

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

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

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)

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

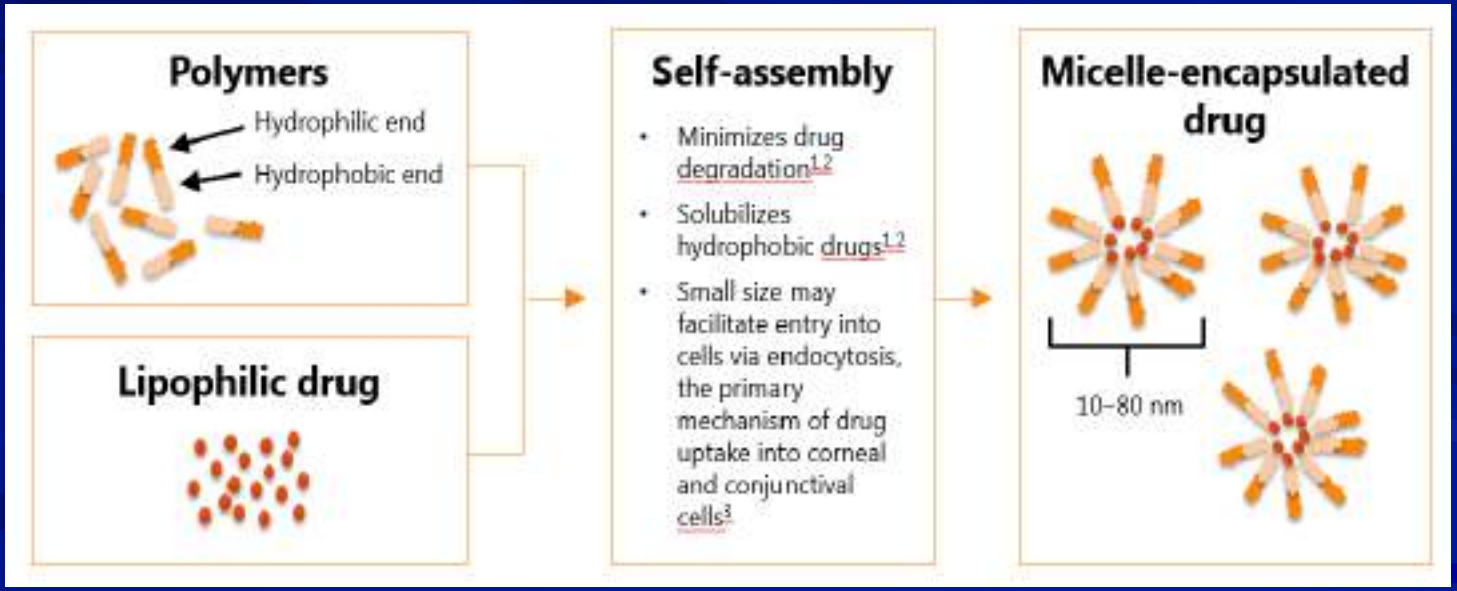
Adverse Reactions:

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

Cequa™ Formulation

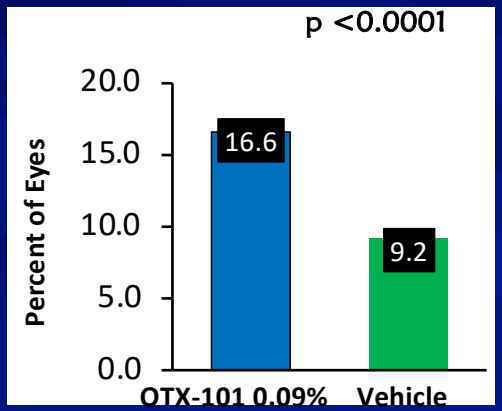
- Novel, aqueous, nanomicellar formulation of cyclosporine A 0.09%[1–4]
- Unpreserved, isotonic, neutral pH fluid that is supplied in unit dose vials
- Well tolerated in a 12-week phase 2b/3 study[5]



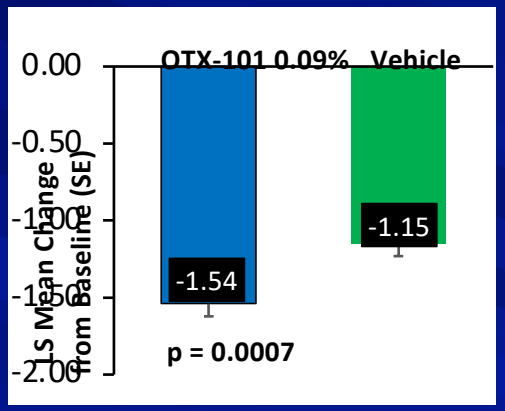
1. Cholkar K et al. *Recent Pat Nanomed.* 2012;2:82-95 2. Mandal A et al. *J Control Release.* 2017;248:96-116. 3. Vaishya RD et al. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2014;6:422-437. 4. Cholkar K et al. *Transl Vis Sci Technol.* 2015;4:1-16 5. Tauber J, et al. ASCRS 2017 Paper presentation.

Primary Endpoints

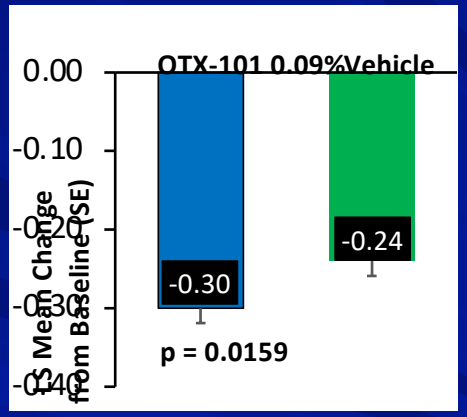
Schirmer's test



Total conjunctival staining score



Central corneal staining score



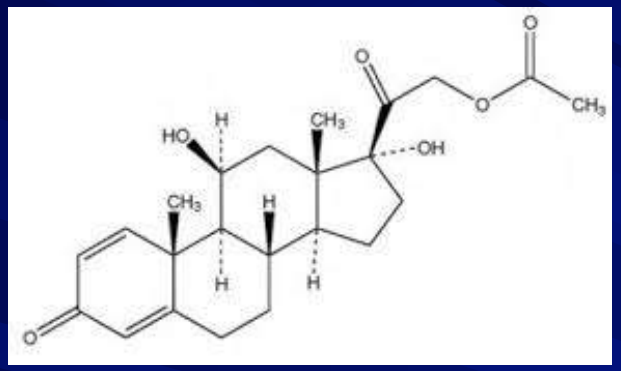
Note: Data shown for the intent-to-treat population (subjects randomized, excluding 1 subject who was assigned to OTX-101 but not treated); missing data on day 84 were imputed by baseline values carried forward.

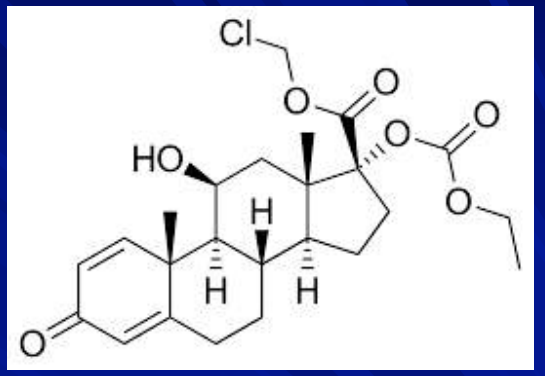
LS, least squares; SE, standard error.
OTX-101-2016-001 study report; data on file.

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

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

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%

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

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%

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

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

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

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)

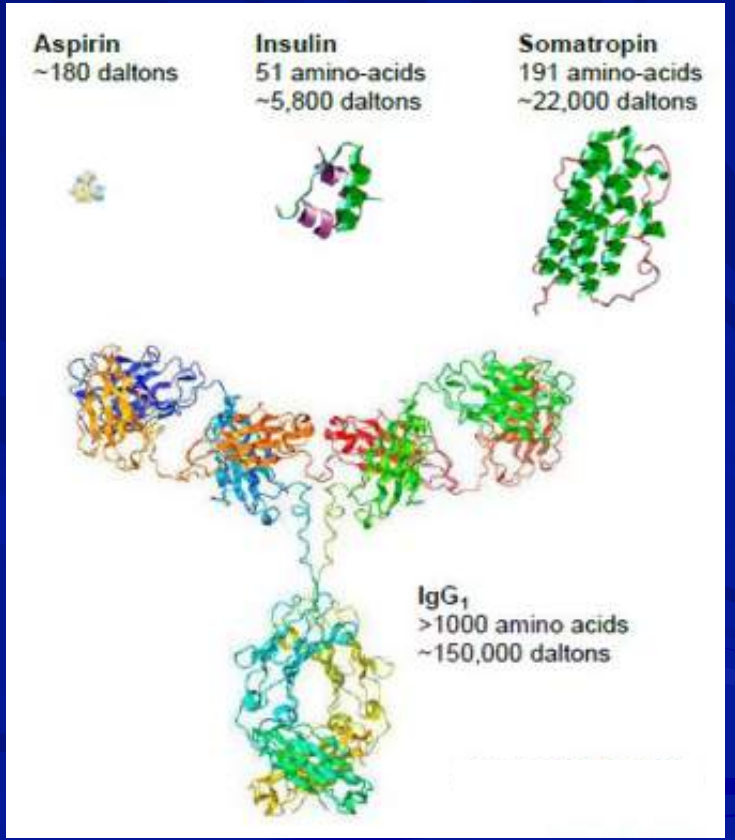
- Biologics are made by harvesting the substances produced and secreted by constructed cells (i.e. genetic engineering)

Size and Complexity of Biologic Drugs

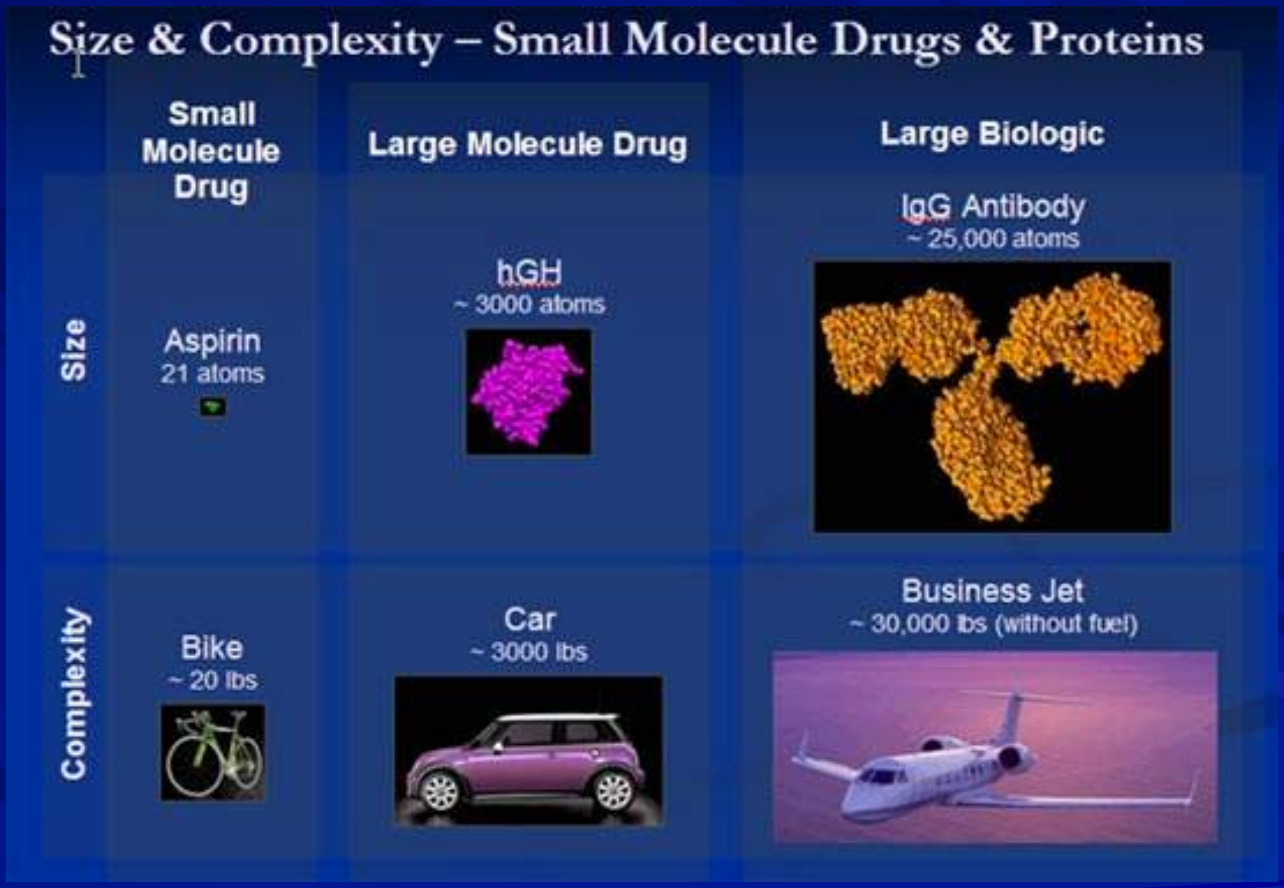
- Small molecule drugs can be taken orally
  - Tend to work in the body within cells
- Biologics are significantly larger in size
  - Typically injected and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells
- Small molecule drugs
  - Such as aspirin
  - 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

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



Size and Complexity of Biologic Drugs



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

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

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?!?

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

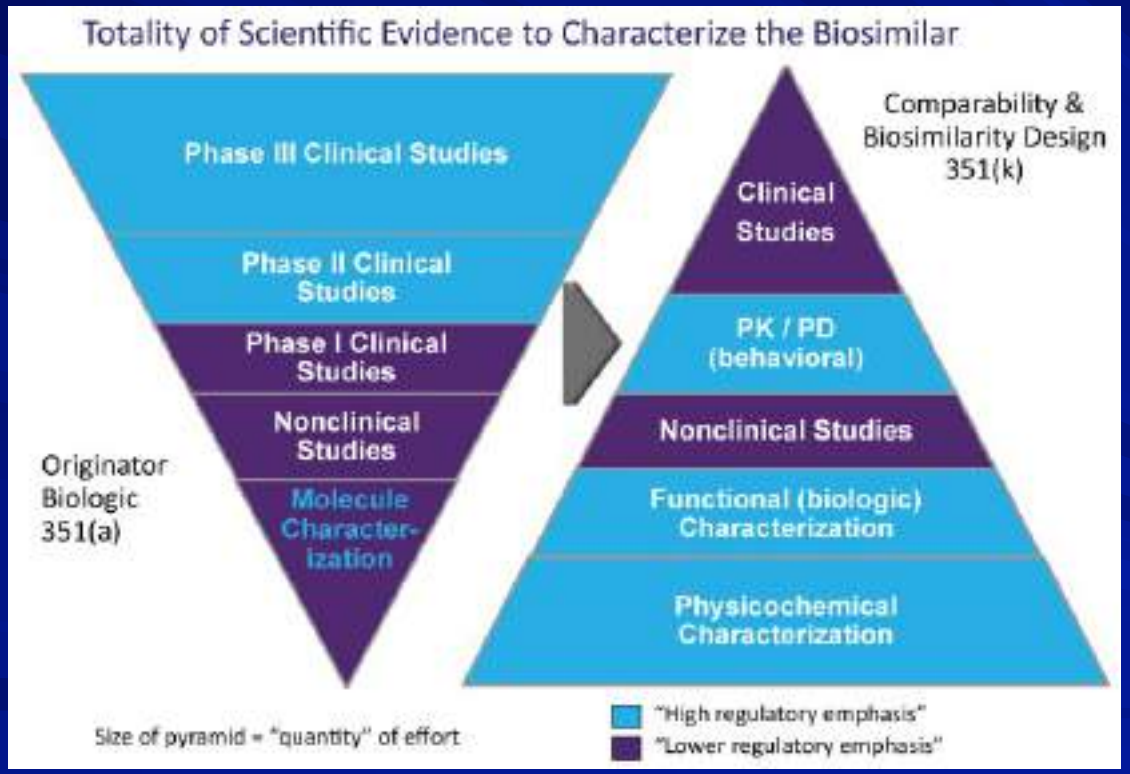
Biosimilars

- "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

Biologic versus Biosimilar



tldrpharmacy.com

Biosimilars

FDA U.S. FOOD & DRUG ADMINISTRATION

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

Ocular Biologics

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

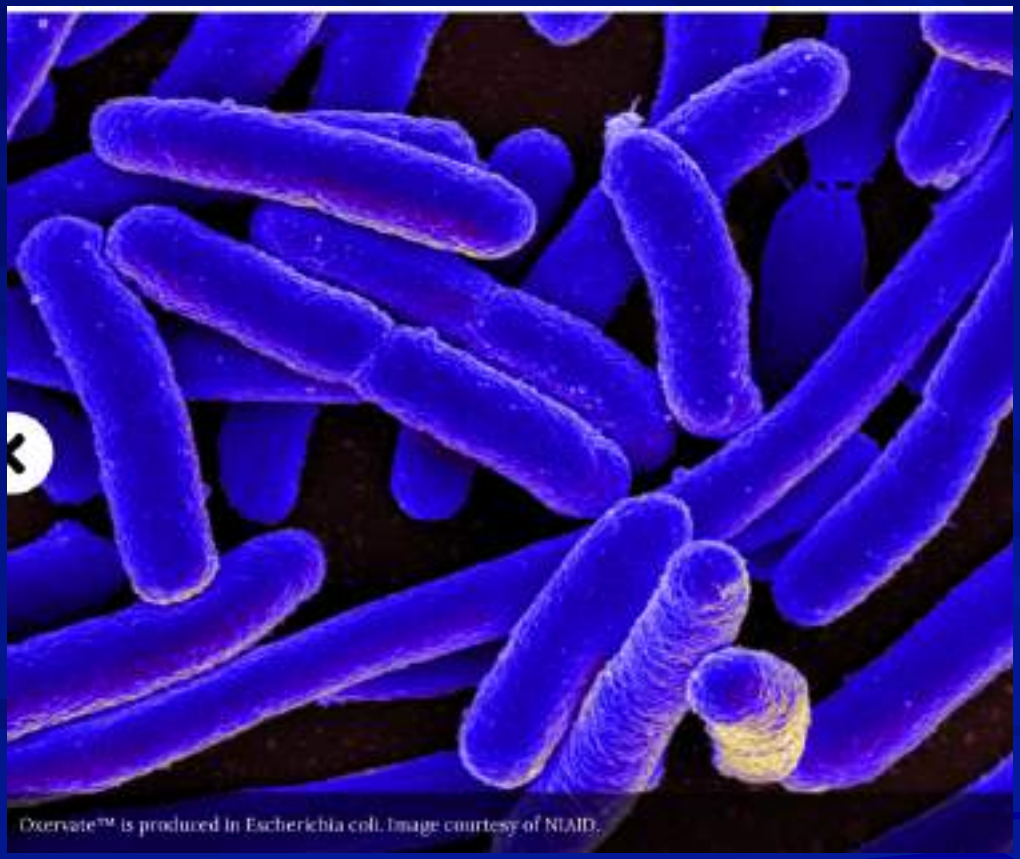
Treatments for Choroidal Neovascularization (CNV)

- 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

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

Escherichia Coli



Corneal Homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis

Corneal nerves stimulate blinking and tear production

Neuromediators provide trophic support to ocular surface tissues (particularly epithelial cells & keratocytes) that:

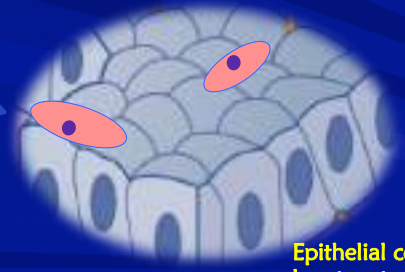
- Stimulates wound healing
- Maintains anatomic integrity

Neurotrophins, neuropeptides and growth factors (e.g., NGF) from epithelial cells and keratocytes mediate nerve fibre survival, differentiation and maturation

Tear gland

Tear secretion

Tears contain growth factors and nutrients that stimulate epithelial cells

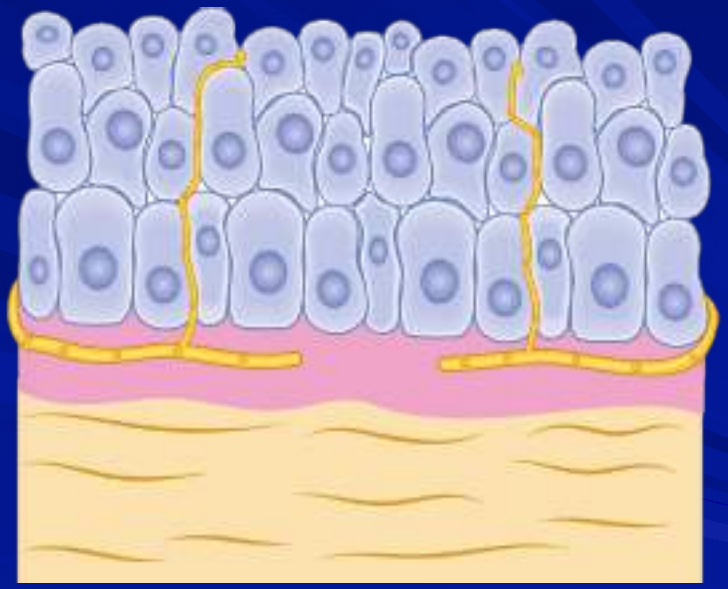


Epithelial cells and keratocytes

Adapted from Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

Pathophysiology of NK[1]

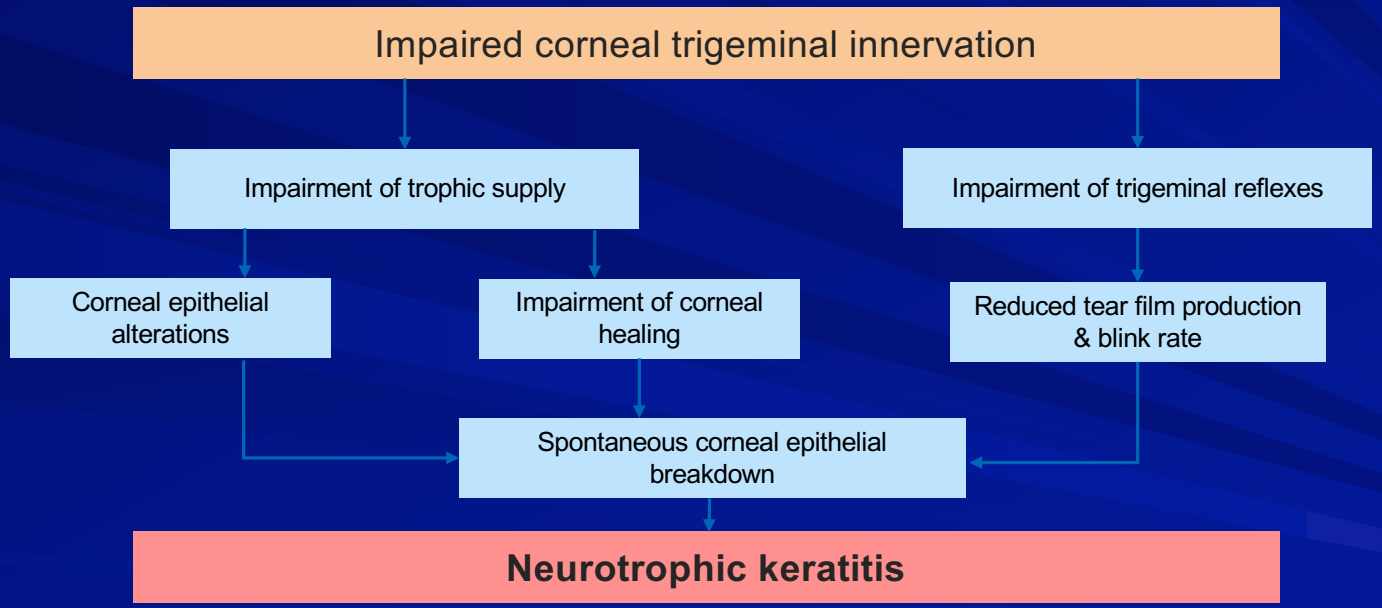
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production 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



Penetration of nerves into the epithelium

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

Trigeminal nerve damage leading to NK[1]



Adapted from 1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

Etiologies Associated with NK

Ocular
- Herpes (simplex or zoster) infection
- Other infections e.g acanthamoeba
- Chemical or physical burn
- Abuse of topical anaesthetics
- Drug toxicity
- Chronic ocular surface injury or inflammation
- Ocular surgery
- Cataract surgery
- LASIK, PRK
- PK and DALK
- Collagen crosslinking for keratoconus
- Vitrectomy for retinal detachment
- Photocoagulation for diabetic retinopathy
- Postsurgical or laser treatment
- Routine laser for proliferative diabetic retinopathy
- Contact lenses
- Orbital neoplasia
- Corneal dystrophies

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures
  - For acoustic neuroma
  - For trigeminal neuralgia
- Other surgical injury to trigeminal nerve

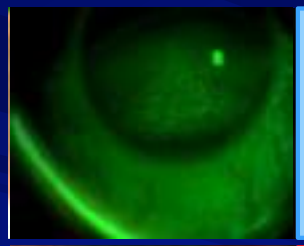
Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

Genetic
- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoaesthesia

DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

NK classification

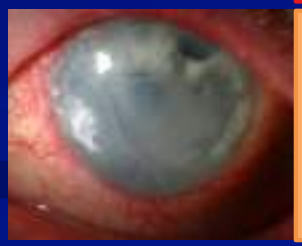


Stage 1: Mild

(Epithelial changes only without epithelial defect): Epithelial irregularity without frank epithelial defect, tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea

Stage 2: Moderate

(Epithelial defect without stromal defect): Frank persistent epithelial defect and corneal hypo-aesthesia/ anaesthesia



Stage 3: Severe

(Stromal involvement): Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/anaesthesia

Images by kind consent of Prof. Messmer and Prof. Dua

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]. 2. 1. Semarero F, et al. Ophthalmologica 2014;231:191-7; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis[1]

Ocular symptoms

History

Clinical examination and tests

NK suspected

Test corneal sensitivity

Normal → NK unlikely

Reduced → Further tests required

Corneal sensitivity tests:[2]

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

Corneal Sensitivity

Endogenous NGF maintains corneal integrity by three mechanisms

Endogenous Nerve growth factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e. p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.[1]

SHOWN IN PRECLINICAL MODELS[1]

CORNEAL INNERVATION

NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves[2,3]

NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]

TEAR SECRETION

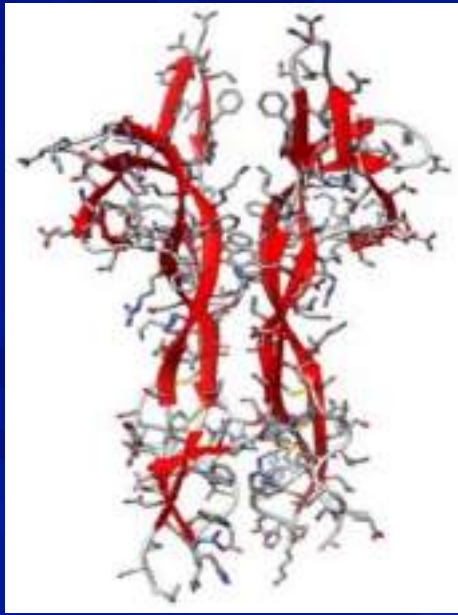
CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017 Apr;232(4):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003 May;76(5):521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-9. 4. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2010;29:1163–1168

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.

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

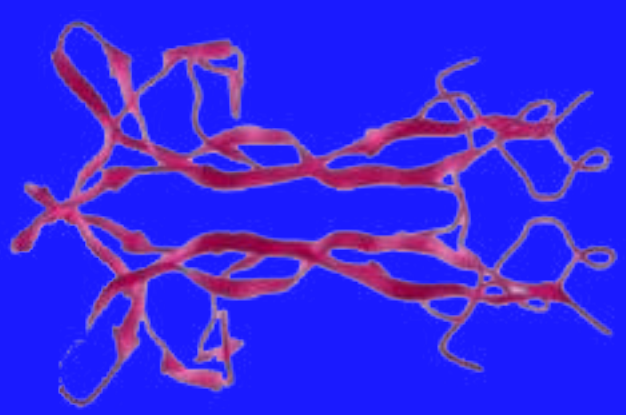
The Delivery System Kit Contains:

- 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

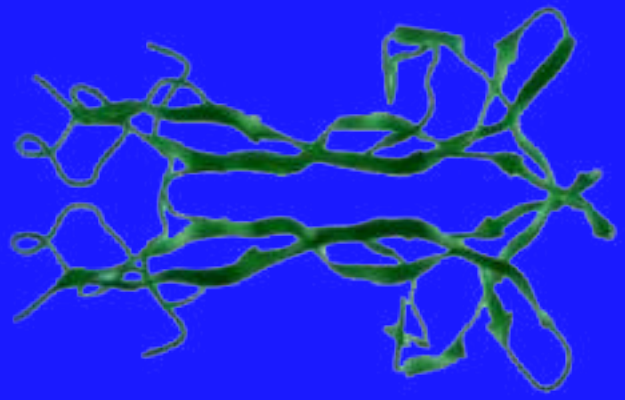
- **Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

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

Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues



Cenegermin



Endogenous NGF

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.

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)

Every 2 hours

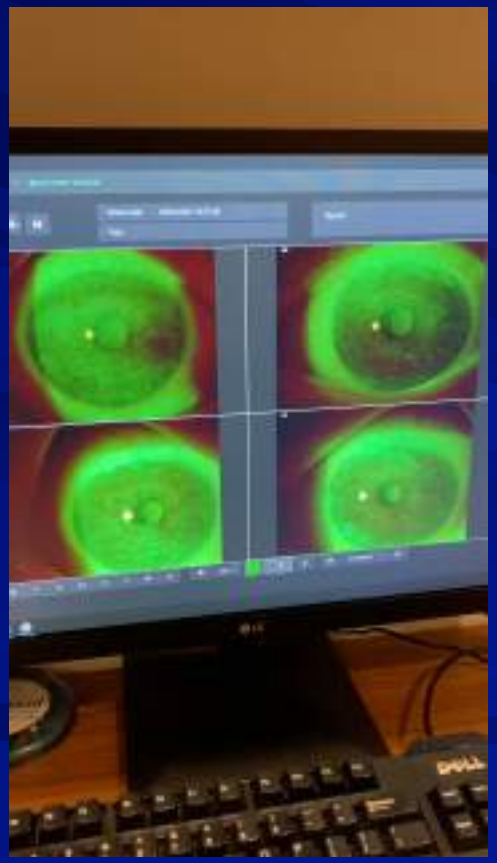
Apply 6 times daily

Continue for 8 weeks

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

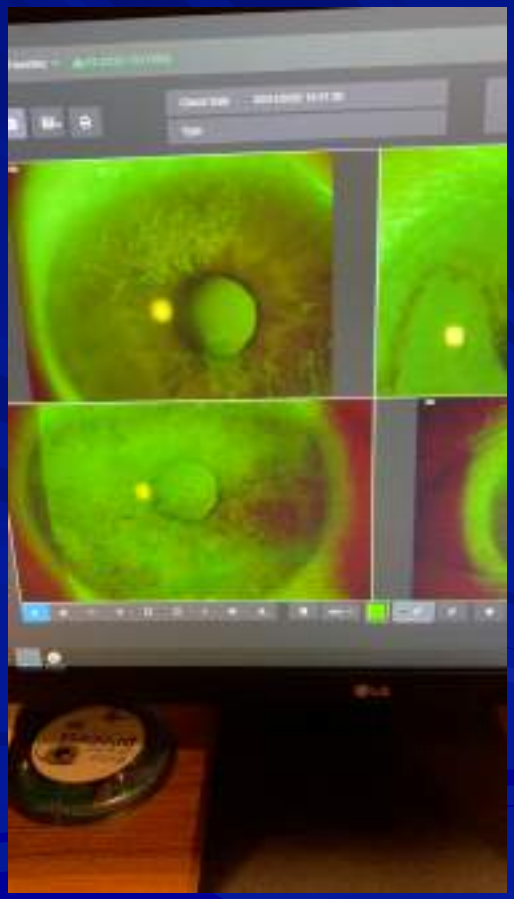
Let's Hear From a Patient

April 7, 2020 - After 1 week



April 21, 2020 - After 3 weeks

May 12, 2020 - After 6 weeks



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.

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

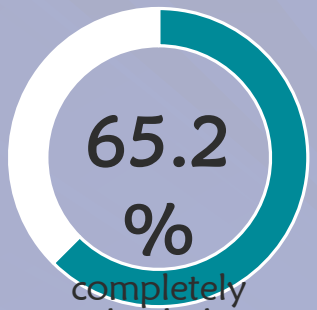
NCT01756456

Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



Vehicle response rate 16.7%

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[3]

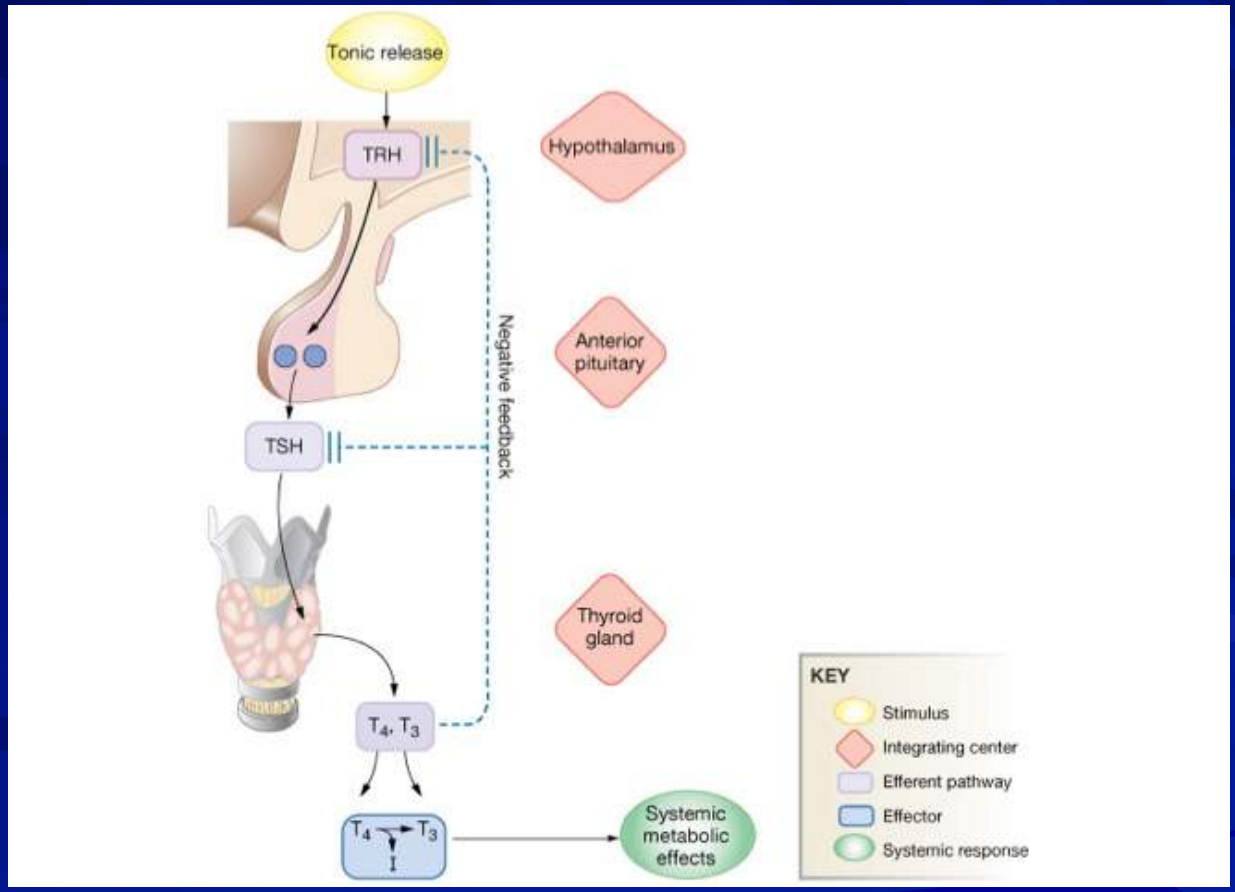
1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. Chao W, J. BOC, R. D. et al. Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017. 3. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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.

Thyroid Disease
and
Thyroid Eye Disease

Normal Thyroid Function



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

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

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

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

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

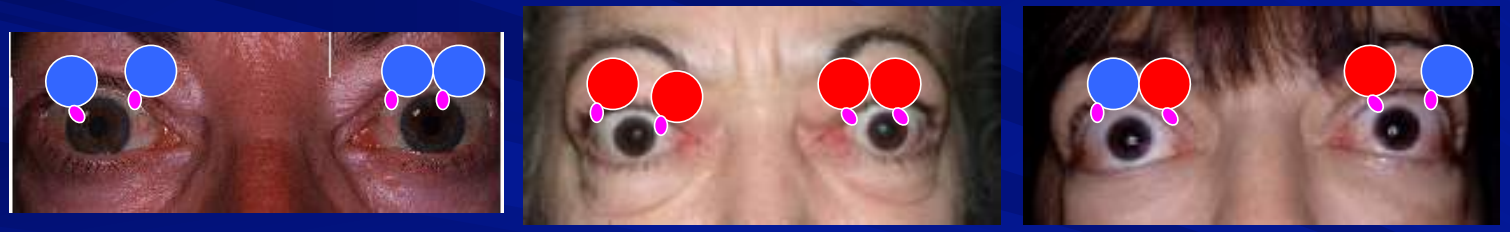
- Hyperthyroidism eye symptoms
  - Excess hormone acting on the nerves that supply the eye
  - Usually spastic and include staring
  - Dryness
  - Eyelid retraction
- Hypothyroidism eye symptoms
  - Deficient hormone causing venous congestion, impaired circulation and fluid stagnation
  - Periorbital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

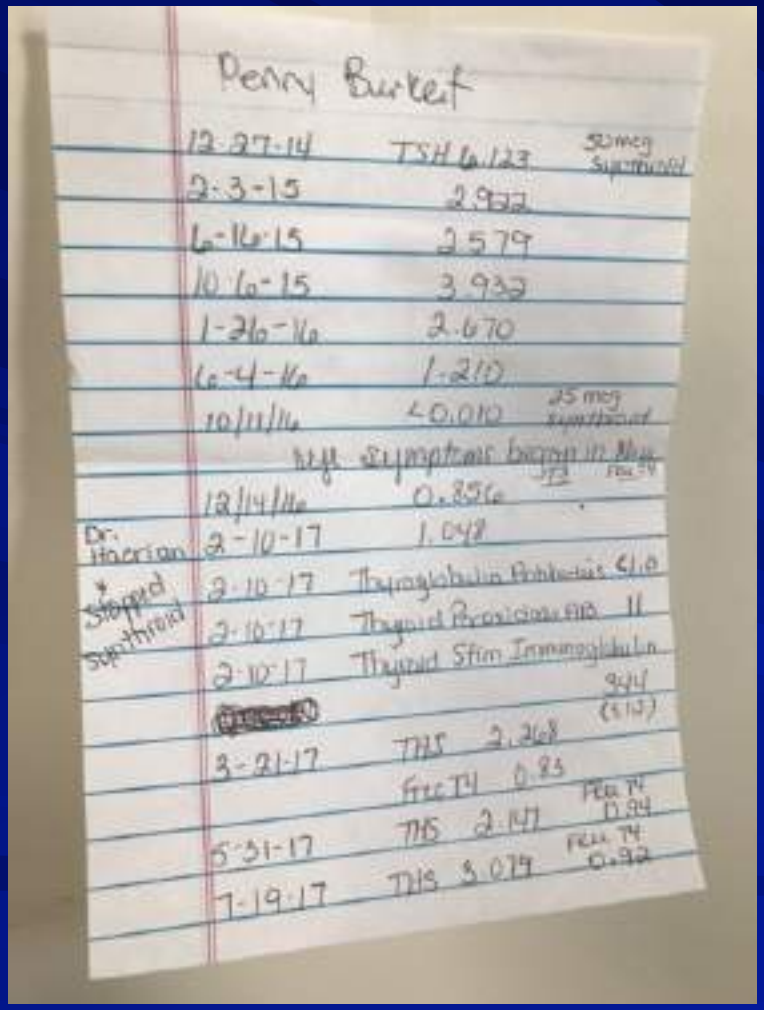
- This form of TED resolves within a few weeks after thyroid hormone levels (FT4 and FT3) are corrected and brought back into the normal range
- The pituitary hormone TSH can stay low or suppressed for many months during the course of treatment for hyperthyroidism and doesn't mean that the patient is 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

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

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





You're in the Know

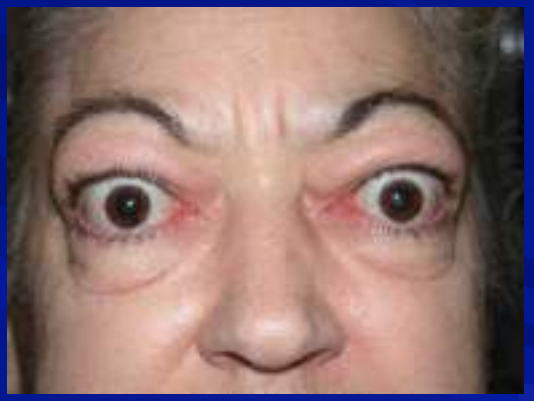
Normal Values
Thyroglobulin 20 IU/ml
Peroidase <35 IU/ml
TSI 1.75 IU/ml

It does work!

Lid Retraction

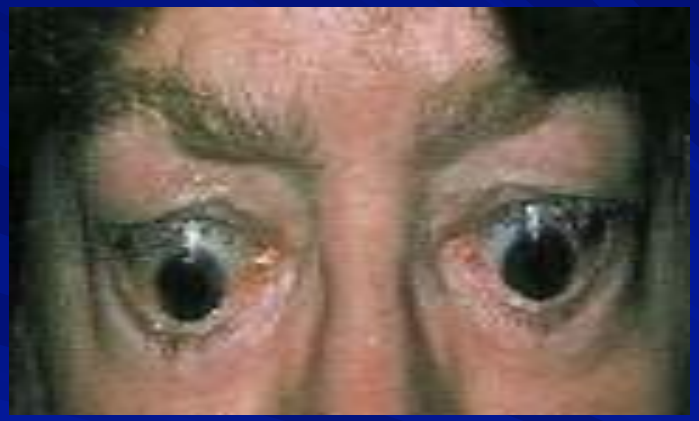
- Scleral show in primary gaze
- Occurs in ~90% of Grave's patients
  - Excess stimulation of Muller's muscle
  - Fibrotic inferior rectus
  - Mechanical restriction or infiltration of levator
  - Increased orbital volume causes exophthalmos

- 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



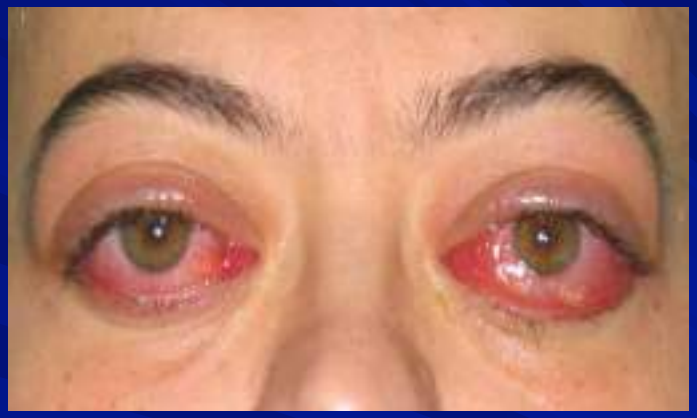
Eyelid Lag: von Graefe's Sign

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



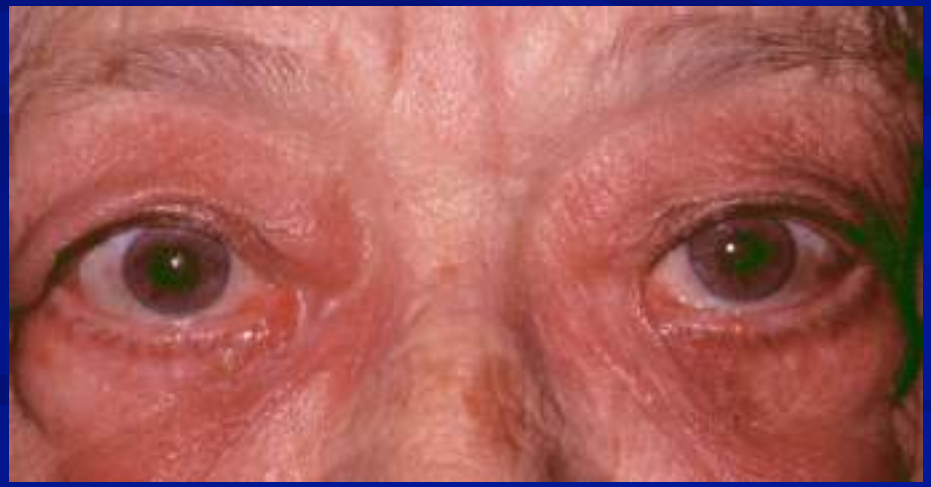
Conjunctiva

- 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



Periorbital Edema

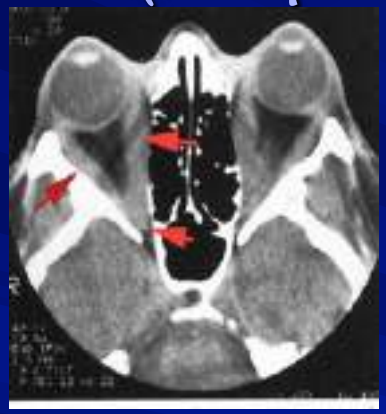
- Inflammation of the subcutaneous connective tissue
- May be first sign of thyroid eye disease
- Greatest in the morning



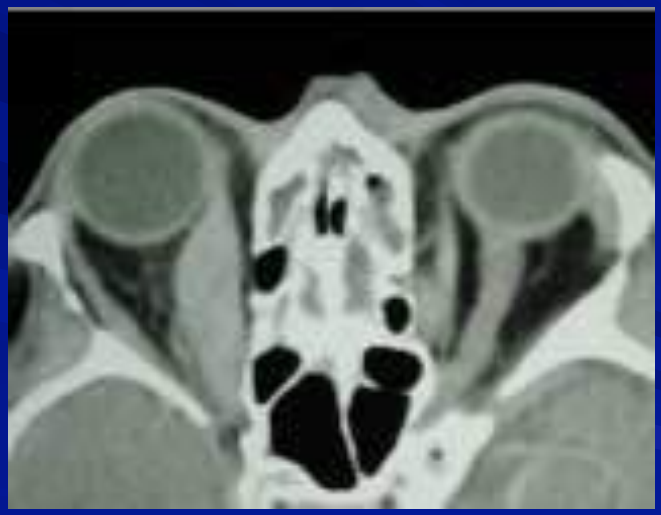
Infiltrative Orbitopathy
(Exophthalmos/Proptosis)

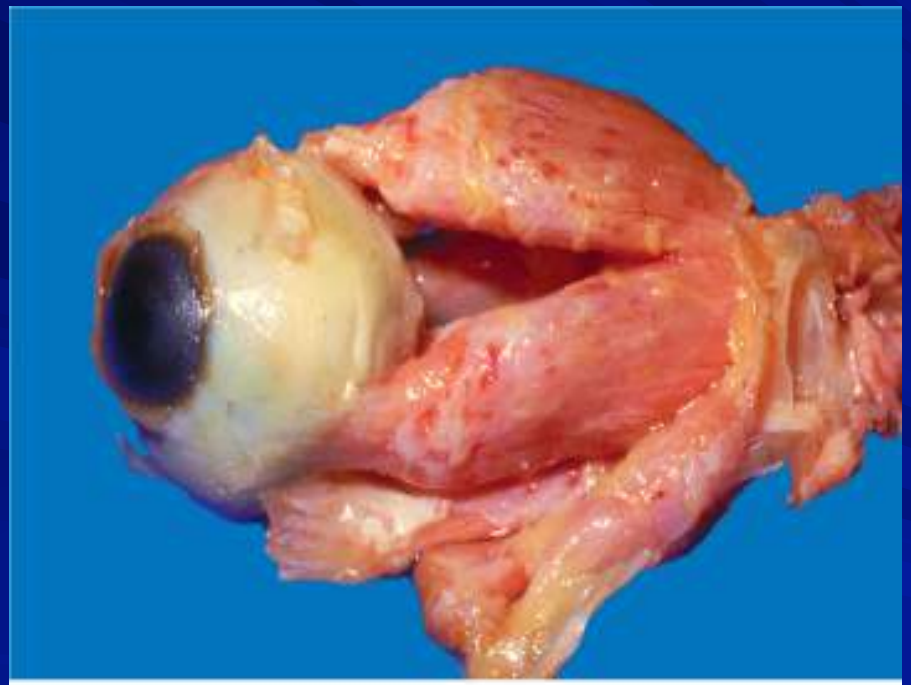
- Thyroid Eye Disease is most common cause of unilateral and bilateral exophthalmos
- The term exophthalmos is reserved for prominence of the eye secondary to thyroid disease
- May need MRI to determine or obvious exophthalmos may be present
- It is permanent in 70% of cases
- Caused by increased volume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

Infiltrative Orbitopathy
(Exophthalmos/Proptosis)



Infiltrative Orbitopathy
(Exophthalmos/Proptosis)





Treatment of Thyroid Eye Disease

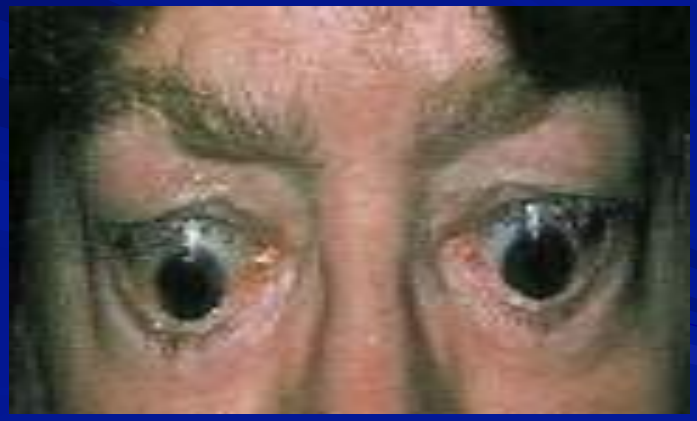
- Palliative (hormone imbalance, active, passive)
  - Lubricants
  - Topical anti- inflammatory (Lotemax/Restasis)
  - Prisms
- Steroids (active phase)
  - Orals
  - Peri-ocular injections
  - IV with oral steroid taper
- Orbital radiotherapy (active phase)
- Orbital Decompression (passive phase)
  - 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

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



Lid Retractor Surgery

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

Infiltrative Orbitopathy
(Exophthalmos/Proptosis)

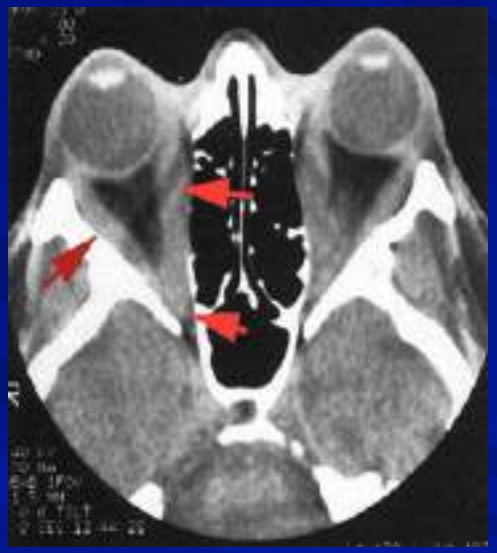
- Orbital Disease Consult
  - Systemic steroids to reduce inflammation
  - Low dose radiotherapy
  - Surgical orbital decompression

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

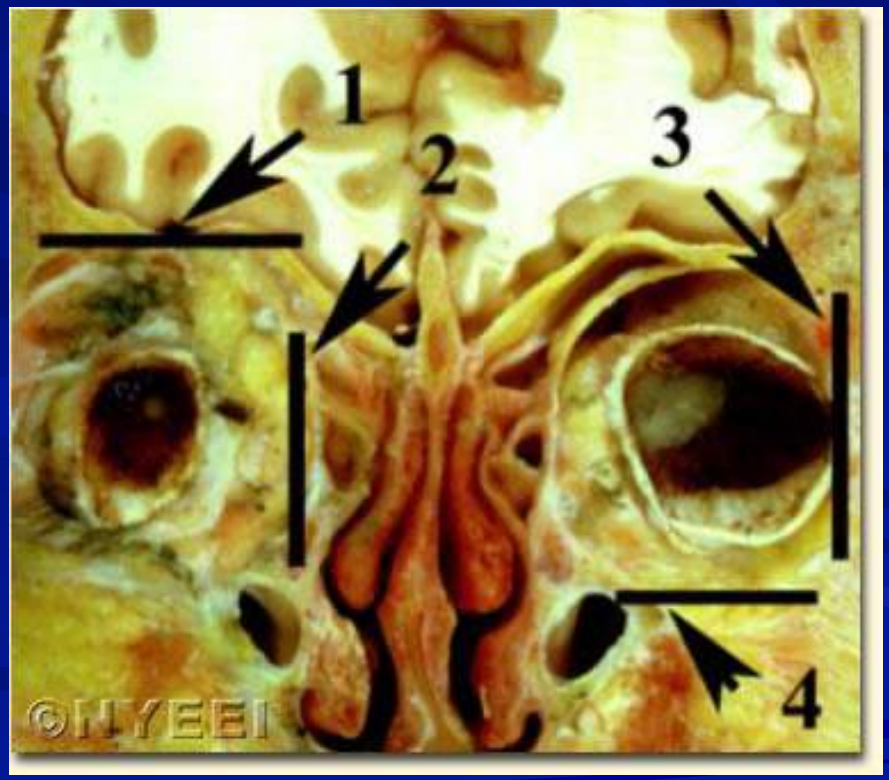
Optic Neuropathy

- 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



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



February 25, 2019

"Nothing Else Can Be Done"

February 25, 2019

"Nothing Else Can Be Done"

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

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

March 25, 2019

March 25, 2019

April 22, 2019

MEETING NEWS

Thyroid eye disease therapy shows promise

Primary Care Optometry News, December 2018

CHICAGO — Teprotumumab, an IGF-1 receptor antagonist antibody, demonstrated improvement of double vision in patients with thyroid eye disease, according to a study presented here.

If approved by the FDA, teprotumumab (Horizon Pharma) would be the first drug with an indication for thyroid eye disease, **Raymond S. Douglas, MD, PhD,** said at the American Academy of Ophthalmology annual meeting.

COMMENT

SAVE

If approved by the FDA, teprotumumab (Horizon Pharma) would be the first drug with an indication for thyroid eye disease, **Raymond S. Douglas, MD, PhD,** said at the American Academy of Ophthalmology annual meeting.

In the phase 2 trial, 42 patients were treated with the study drug and 45 patients made up the placebo control arm. At week 24, which marked the end of the controlled trial, statistically significantly more patients taking the study drug achieved the primary endpoint of improvement in clinical activity score and reduction of proptosis ($P < .001$). Diplopia improvement was "impressive" at week 24, and of the patients with diplopia at baseline who did improve, 70% continued to have that improvement 48 weeks later, Douglas said.

The most reported adverse event was hyperglycemia, which returned to normal after discontinuation of the drug, he said.

"Teprotumumab ... appears to have stable improvement and durability of improving the double vision, proptosis and clinical activity in these patients and appears to reverse the effects of thyroid eye disease," Douglas said. "The phase 3 trial will also have the added benefit of having a crossover group who will receive open-label therapy if [patients are] nonresponders at week 24, which ... may make this even more universally applicable to patients with long-standing disease." – *by Patricia Nale, ELS*

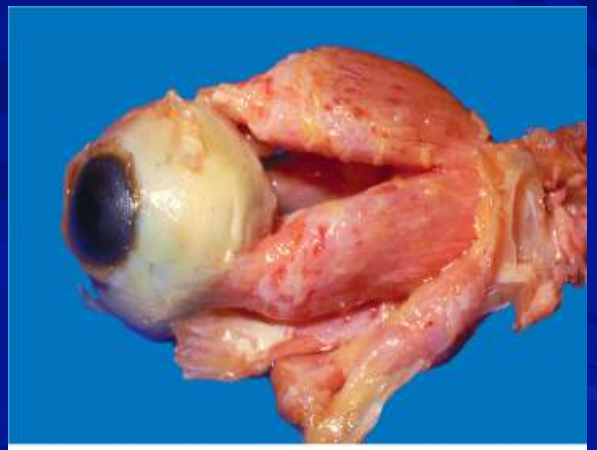
Reference:

Douglas RS. Diplopia response in a controlled trial with teprotumumab, an IGF-1 receptor antagonist antibody for thyroid eye disease. Presented at: American Academy of Ophthalmology annual meeting; Oct. 27-30, 2018; Chicago.

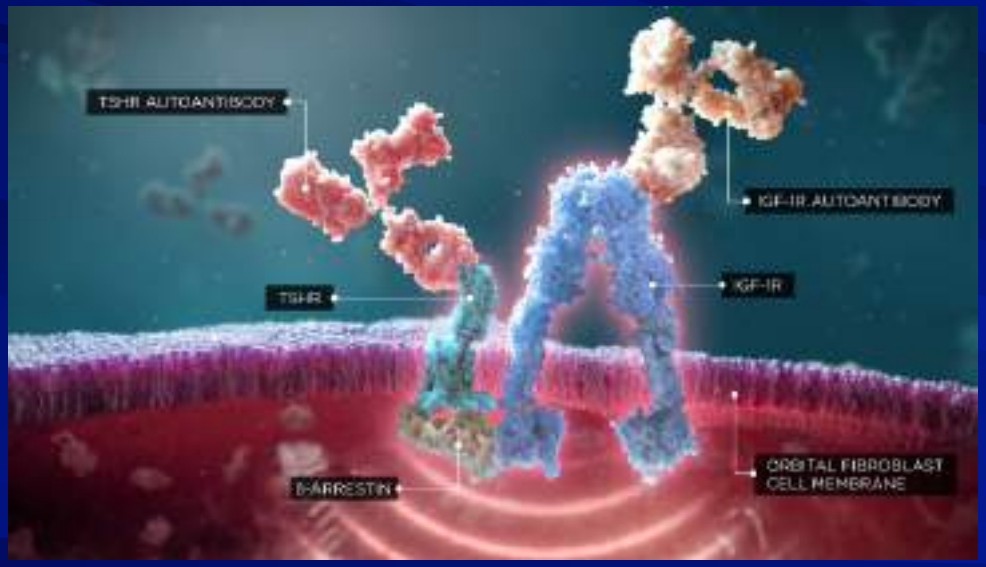
Disclosure: Douglas reports no relevant financial disclosures.

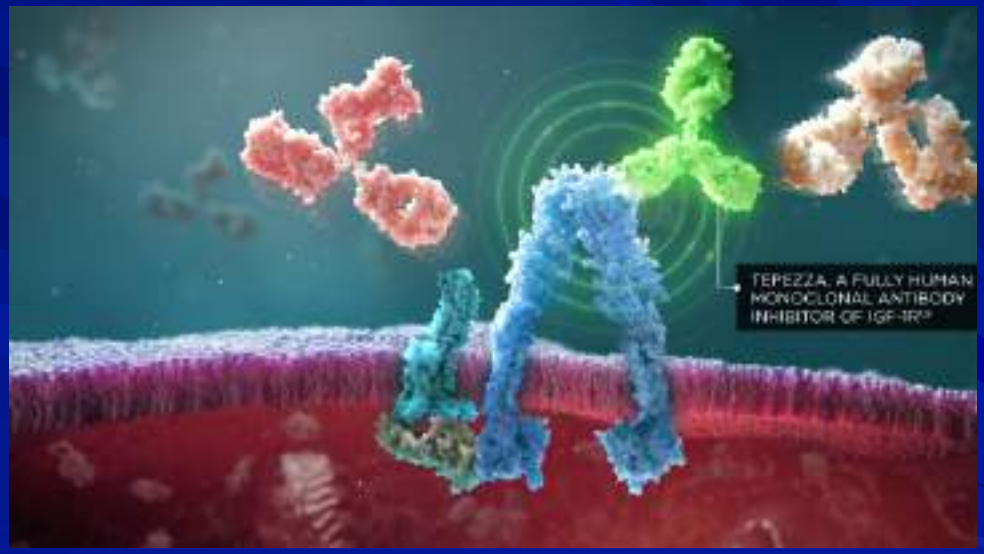
Teprotumumab-trbw (Tepezza)

- 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



Teprotumumab-trbw (Tepezza)





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

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

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

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.

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

Teprotumumab-trbw (Tepezza)

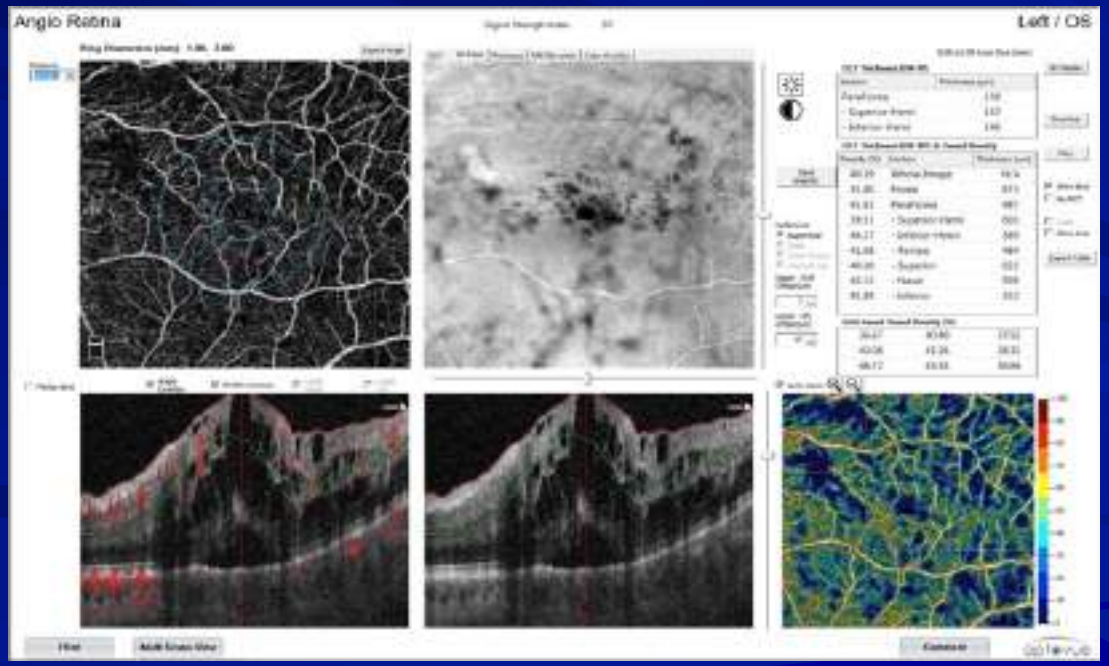
- Infusion center
  - Go to Horizon website
  - Contact Us
  - Type in your question
    - Looking for infusion center

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.

Humira™ (adalimumab)

- Non-infectious intermediate, posterior and panuveitis
  - Reason for reduced acuity?



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.

Hadlima™ (adalimumab-bwwd)

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

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

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCY (5.2):

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

Actemra™ (tocilizumab)

INDICATIONS

ACTEMRA is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

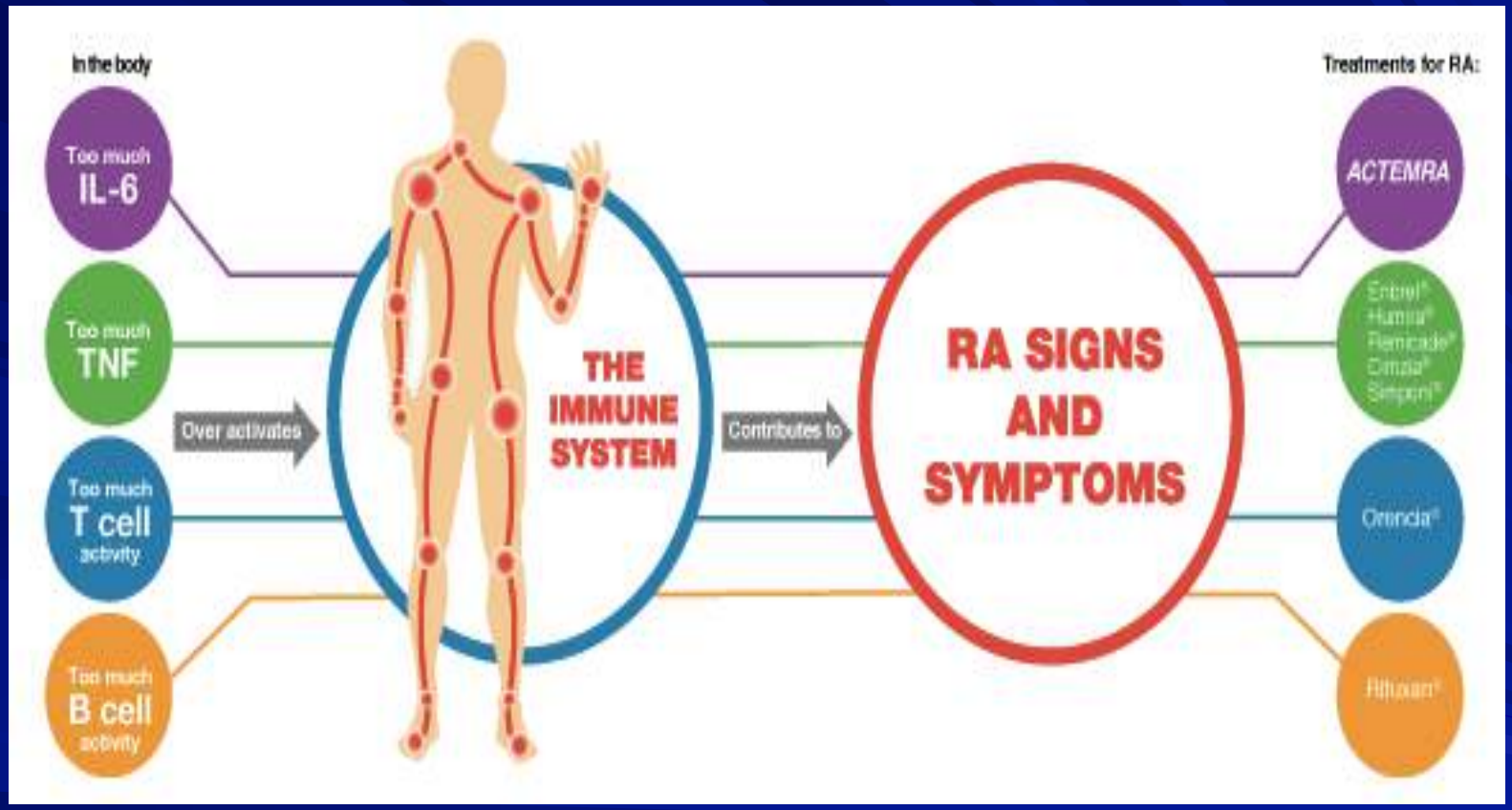
ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

ACTEMRA is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

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

Let's qualify this statement



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

NDC 50242-137-01

Actemra®

(tocilizumab)

Injection

400 mg/20 mL

(20 mg/mL)

For Intravenous Infusion only after dilution.

Single-Use Vial; Discard unused portion

ATTENTION PROVIDER: Each patient is required to receive the enclosed Medication Guide

No Preservative

℞ only

Genentech

10175060

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

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

Tocilizumab

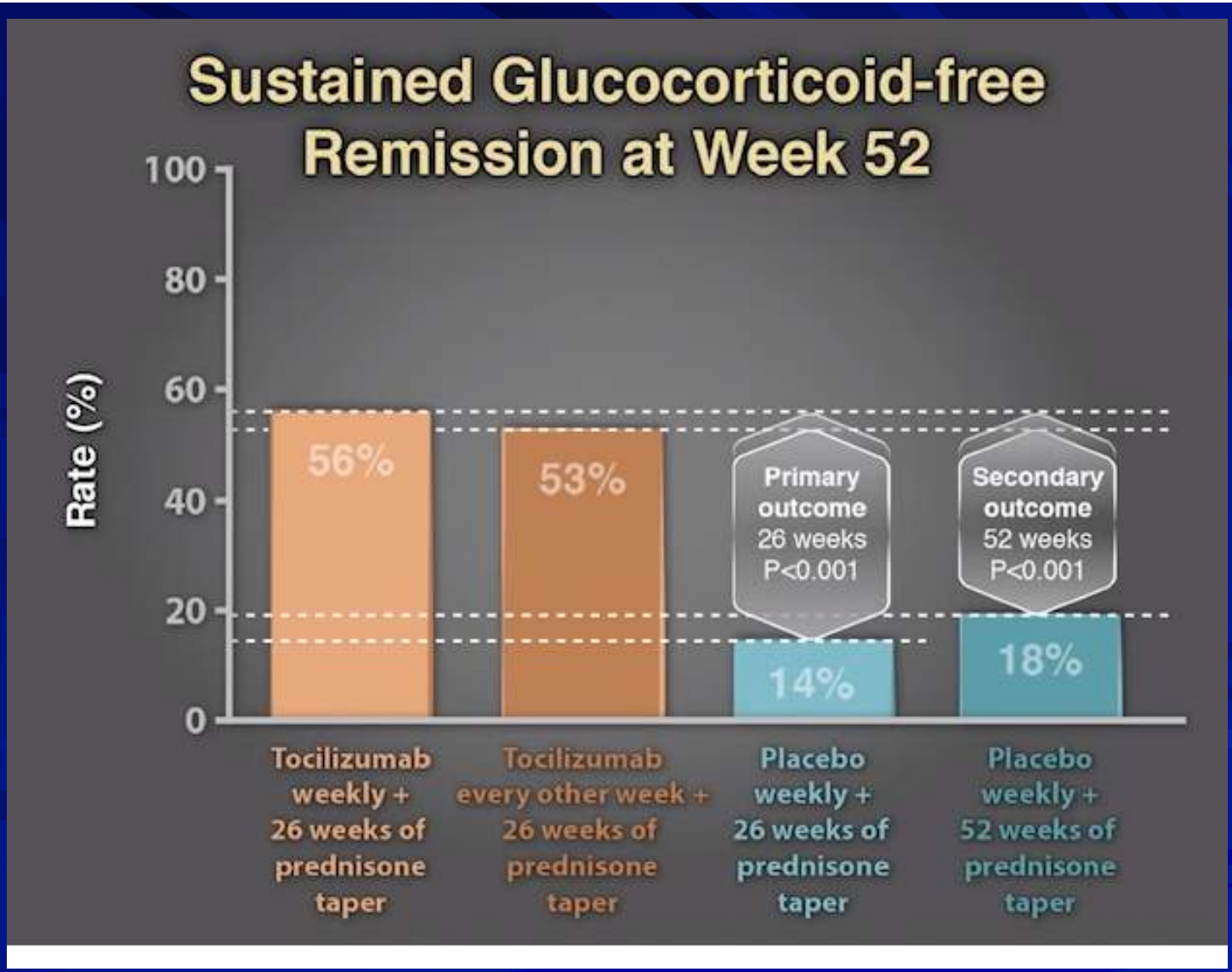
Tocilizumab weekly
+ 26 weeks of
prednisone taper
(N=100)

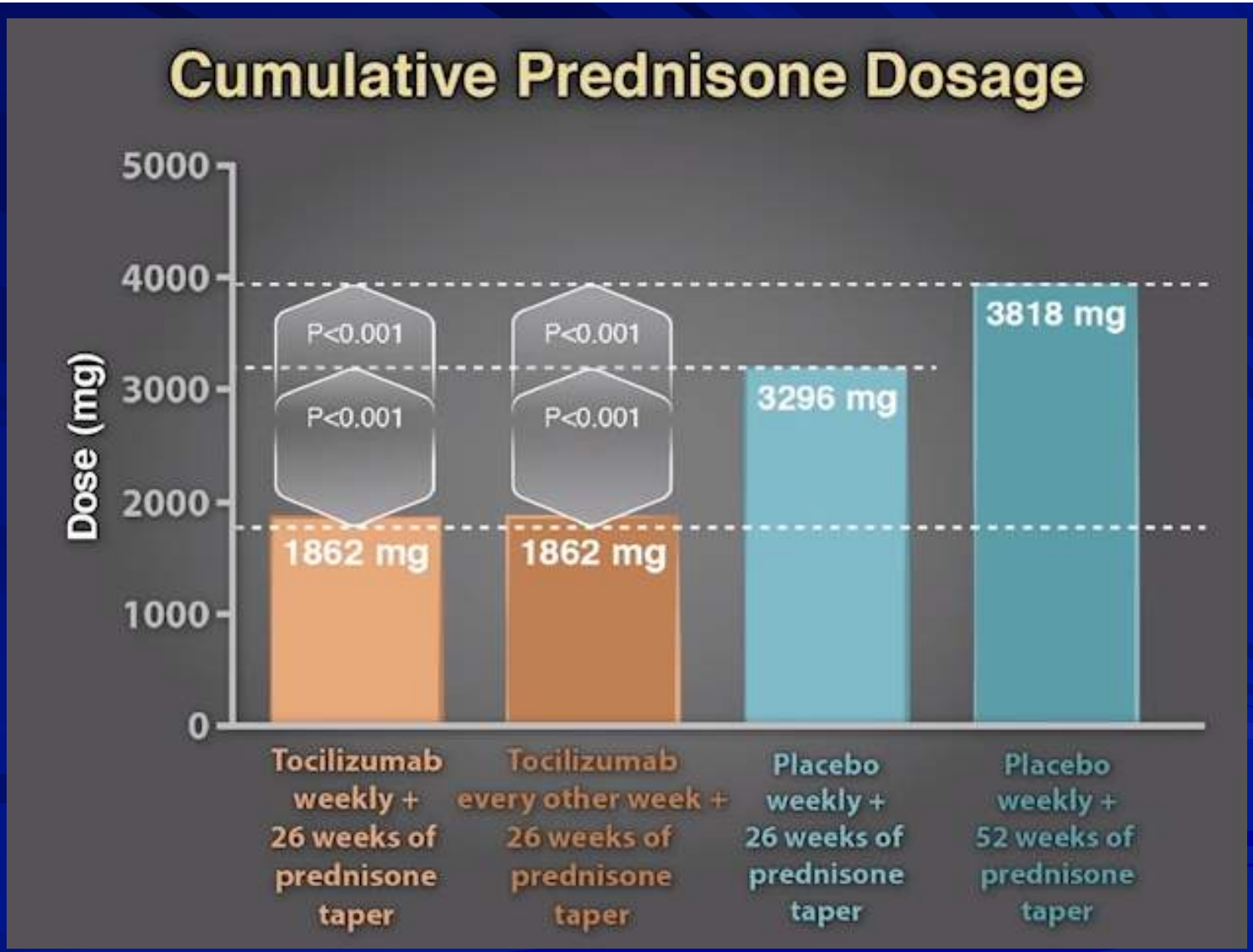
Tocilizumab every other week
+ 26 weeks of prednisone taper
(N=50)

Placebo

Placebo weekly
+ 26 weeks of
prednisone taper
(N=50)

Placebo weekly
+ 52 weeks of
prednisone taper
(N=51)


Sustained Glucocorticoid-free Remission at Week 52
Rate (%)
100
80
60
40
20
0
56%
53%
14%
18%
Primary outcome 26 weeks P<0.001
Secondary outcome 52 weeks P<0.001
Tocilizumab weekly + 26 weeks of prednisone taper
Tocilizumab every other week + 26 weeks of prednisone taper
Placebo weekly + 26 weeks of prednisone taper
Placebo weekly + 52 weeks of prednisone taper


Cumulative Prednisone Dosage
Dose (mg)
5000
4000
3000
2000
1000
0
P<0.001
P<0.001
P<0.001
P<0.001
1862 mg
1862 mg
3296 mg
3818 mg
Tocilizumab weekly + 26 weeks of prednisone taper
Tocilizumab every other week + 26 weeks of prednisone taper
Placebo weekly + 26 weeks of prednisone taper
Placebo weekly + 52 weeks of prednisone taper

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

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)**

Biologics

No ocular indication

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"

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

Erenumab (Aimovig)

5.2 Constipation with Serious Complications

Constipation with serious complications has been reported following the use of AIMOVIG in the postmarketing setting. There were cases that required hospitalization, including cases where surgery was necessary. In a majority of these cases, the onset of constipation was reported after the first dose of AIMOVIG; however, patients have also presented with constipation later on in treatment. AIMOVIG was discontinued in most reported cases of constipation with serious complications. Constipation was one of the most common (up to 3%) adverse reactions reported in clinical studies *[see Adverse Reactions (6.1)]*.

Monitor patients treated with AIMOVIG for severe constipation and manage as clinically appropriate *[see Patient Counseling Information (17)]*. The concurrent use of medications associated with decreased gastrointestinal motility may increase the risk for more severe constipation and the potential for constipation-related complications.

5.3 Hypertension

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of AIMOVIG in the postmarketing setting. Many of the patients had pre-existing hypertension or risk factors for hypertension. There were cases requiring pharmacological treatment and, in some cases, hospitalization. Hypertension may occur at any time during treatment but was most frequently reported within seven days of dose administration. In the majority of the cases, the onset or worsening of hypertension was reported after the first dose. AIMOVIG was discontinued in many of the reported cases.

Monitor patients treated with AIMOVIG for new-onset hypertension, or worsening of pre-existing hypertension, and consider whether discontinuation of AIMOVIG is warranted if evaluation fails to establish an alternative etiology.

Biologics

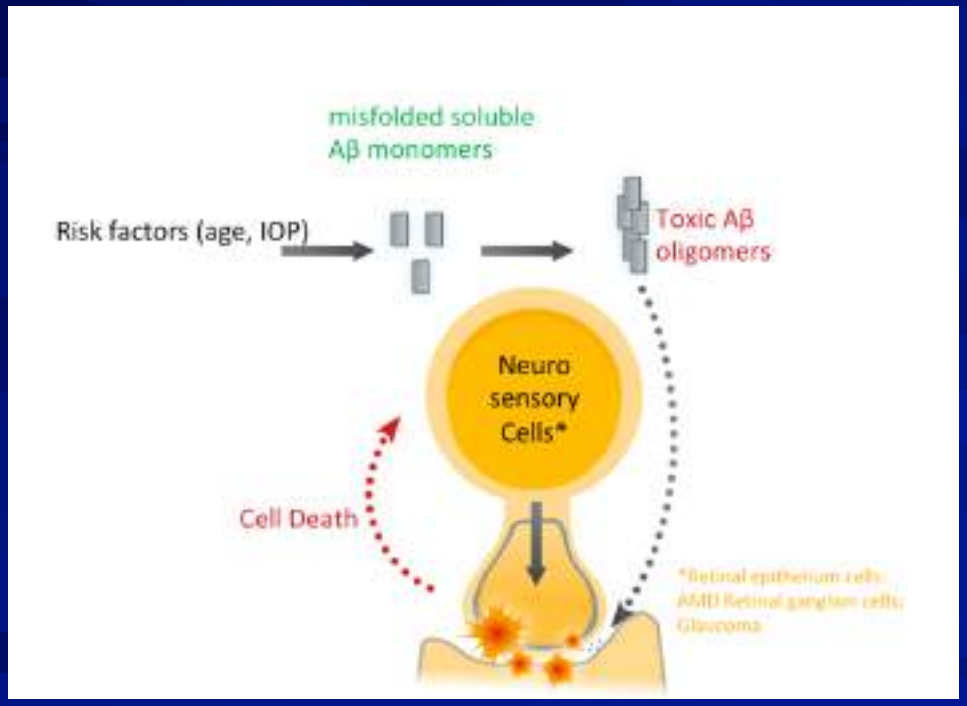
In Studies with the Potential for Eye Care

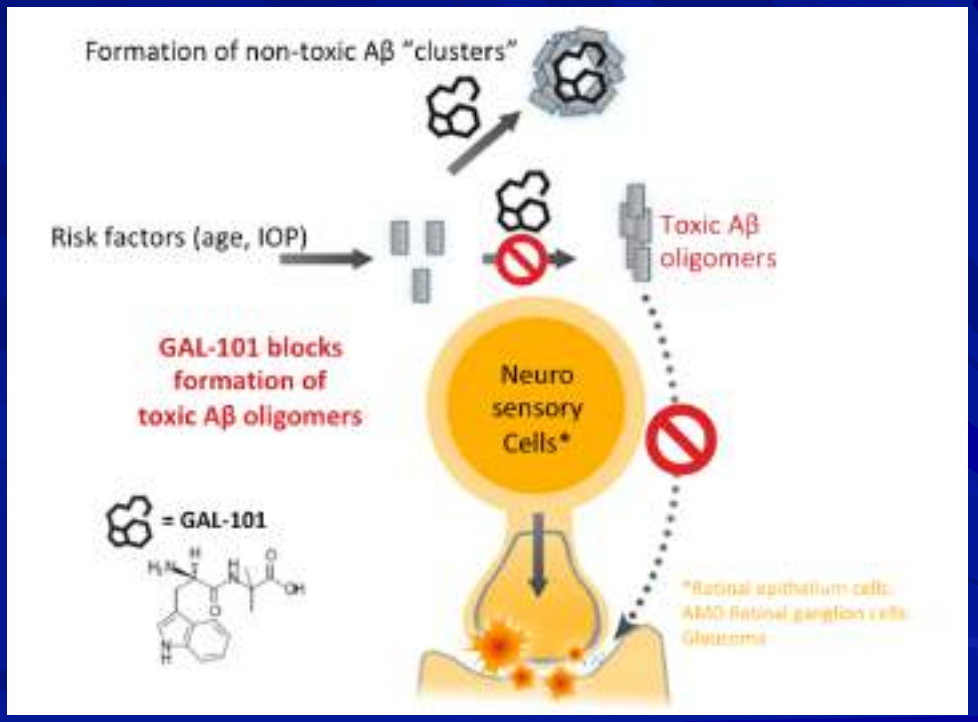
Galimedix Therapeutics

- 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/

Galimedix Therapeutics – Glaucoma and AMD





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

Thank You!

Questions?

Tracy and Greg