Optometric Education Consultants

Ocular Biologics, Biosimilars, and Drugs for the Eye

What's the Difference and What is New

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Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

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- Envolve: PA Medical Director, Credential Committee
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- Has not received any assistance from any commercial interest in the development of this course

Text me your comments and questions

814-931-2030

Greg Caldwell, OD, FAAO

Your favor drink?

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

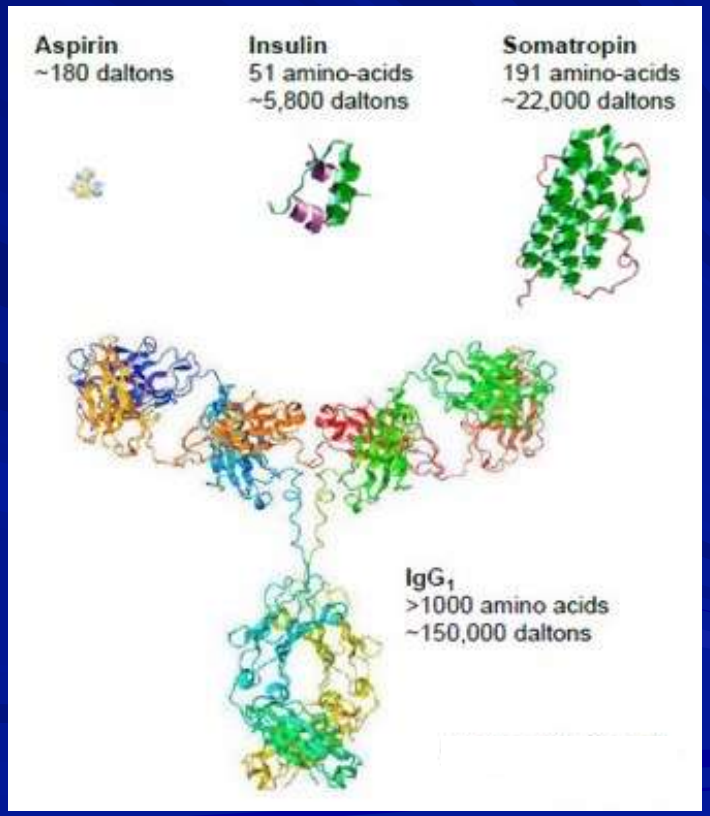
- Biologic therapies
  - Cannot be made using a simple chemical reaction
    - Mixing ingredients together in a laboratory, the way conventional drugs are made
  - Are made using living organisms

Small Molecule Drugs versus Biologics

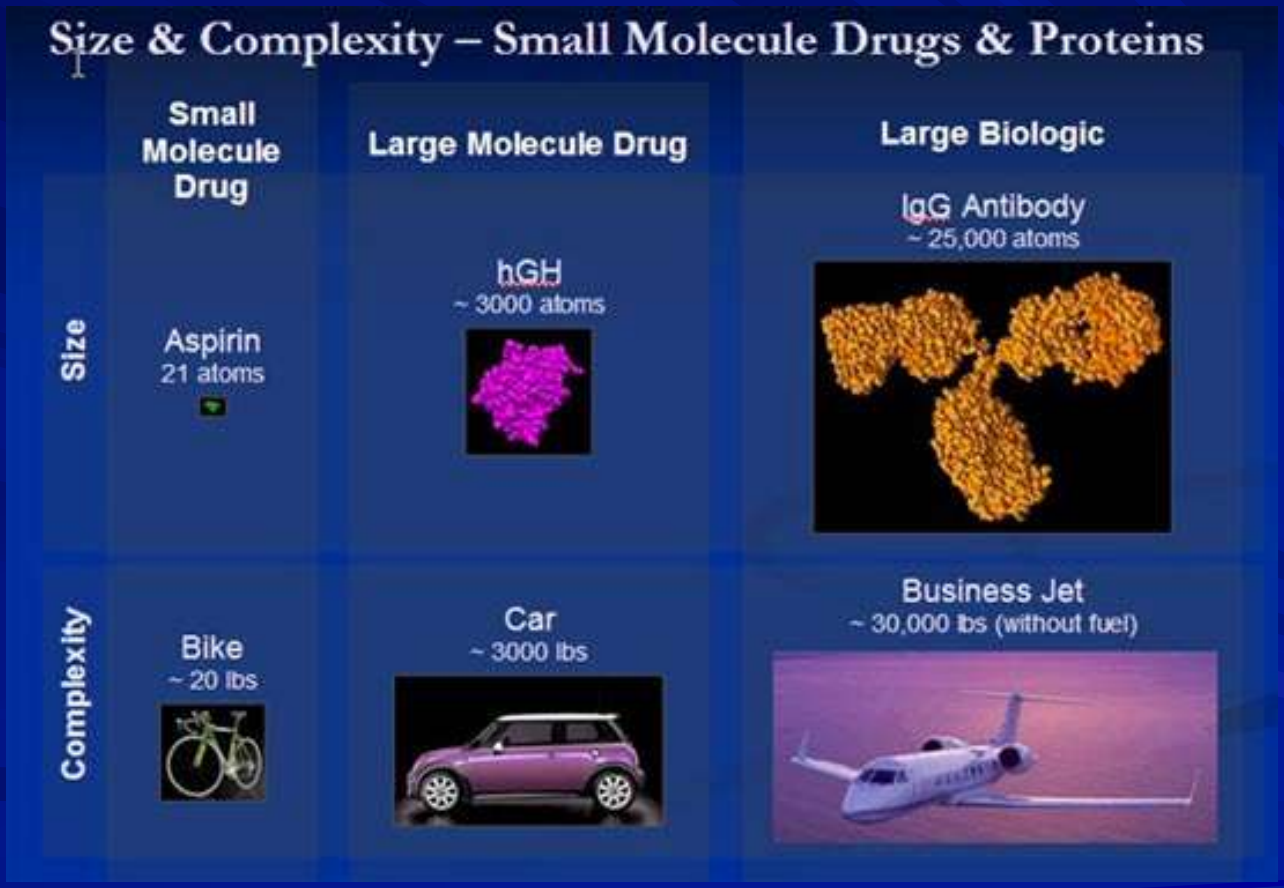
- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions
  - Organic chemistry
  - Inorganic chemistry
- Biologics are made by harvesting the substances produced and secreted by constructed cells
  - Genetic engineering – is the closet manufacturing process of a biologic drug

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

And there is MORE!

- Biologic (AKA "reference" or "innovator")
  - ✶ Clinically validated target and therapy/treatment
- Biosimilar
  - ✶ NO INNOVATION from "Biologic" (AKA "reference" or "innovator")
  - ✶ Some call these "Biogenerics"
  - ✶ Takes ~ ½ the time to make, ~ 1/10 of the price
- "Biosuperior" or "Biobetter"
  - ✶ Innovation in the original therapy (the "Biologic")
  - ✶ New lead, function, drug conjugate, size of molecule
  - ✶ Improved protein engineering

    = enhanced, therapeutically beneficial mechanism of action; increases in potency, bioavailability, half-life, efficacy, and safety

It's all in the name…

- Biologics
  - Infli***xi***mab (Remicade) – "1st generation"
    - Chimeric molecule – mouse and human protein
    - Very active in suppressing the immune system via inhibition of INF-alpha
  - Adali***mu***mab (Humira)
    - Fully human protein, less hypersensitivity
    - Anti-TNF (RA and Crohn's Disease, etc.)
  - Tocili***zu***mab (Actemra)
    - Humanized
    - Interleukin inhibitor (GCA, PMR, RA, Crohn's, etc.)

- Immunomodulary
  - Teprotu***mu***mab (Tepezza)
    - Full humanized monoclonal antibody
      - All the proteins are human – less to no sensitivity – more focused effect
    - IGF-1R inhibitor

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

Treatments for Choroidal Neovascularization (CNV)

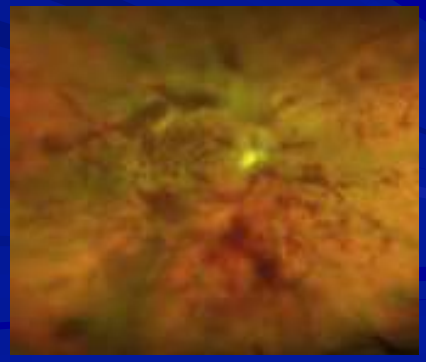
- Where is all started in the eye
- Disorders of the blood vessels in the retina are responsible for some of the most common causes of blindness in the world
  - Retinopathy of prematurity
    - Important cause of blindness in children in middle-income countries
  - Diabetic retinopathy
    - Common 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

Beovu (brolucizumab)

- Indication: injection is used for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD)
  - Offers a 3-month dosing schedule in the first year of treatment
- Warning issued by the American Society of Retinal Specialists about a series of intraocular inflammation events—some of which led to severe vision loss
- On April 8, 2020, Novartis announced its completion of the review, which included an assessment by an external, independent Safety Review Committee
- Complications: n=1098
  - Intraocular inflammation (IOI) - 4.6% (n=50)
  - IOI + retinal vasculitis – 3.3% (n=36)
  - IOI + retinal vasculitis –retinal (artery) vascular occlusion – 2.1% (n=23)
  - Vision loss of 15 letters or more - <1%

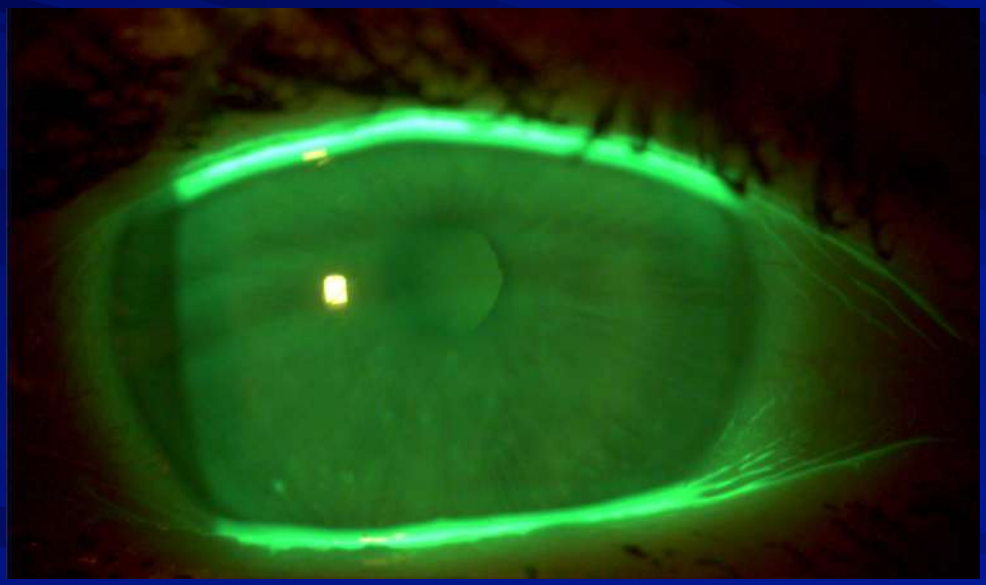


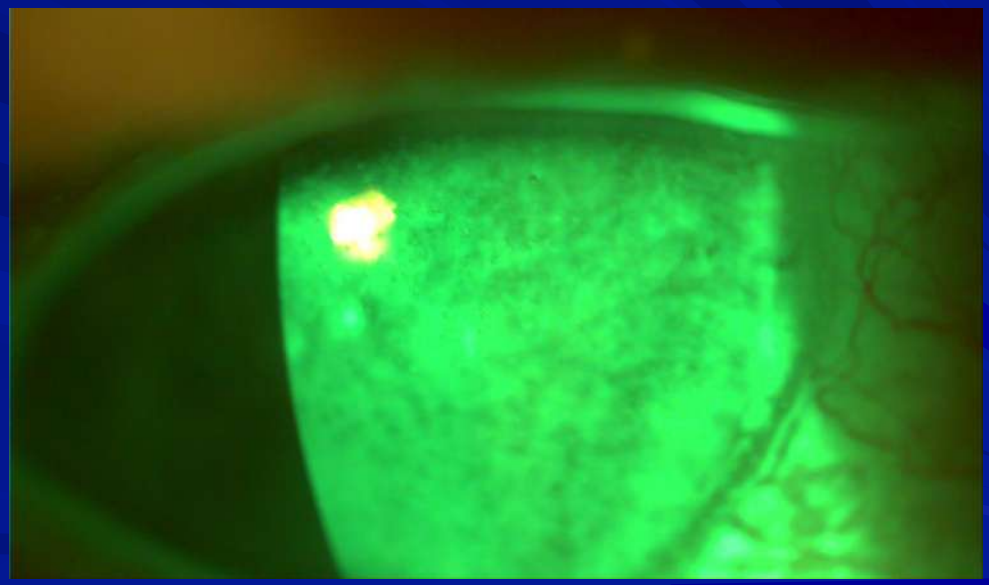
Byooviz™ (ranibizumab-nuna)

- Reference drug Ranibizumab (Lucentis™)
  - Ten manufacturers are working on Ranibizumab biosimilar (as of 2021)
- Samsung Bioepis, South Korea
  - First ophthalmology biosimilar approved by US-FDA in September 2021
    - Others have been approved around the world
  - Treat wet AMD, Macular Edema following RVO, and myopic CNVM,
  - A randomized phase 3 multicenter, parallel-group double-masked study compared efficacy, safety, pharmacokinetics & Immunogenicity of Byooviz with the reference Ranibizumab in patients of nAMD.
  - 705 patients were enrolled and randomized (1:1) to receive Byooviz or reference Ranibizumab every 4 weeks through week 48.
  - The safety and immunogenicity profile of SB11 and reference ranibizumab were comparable at all points up to week 52

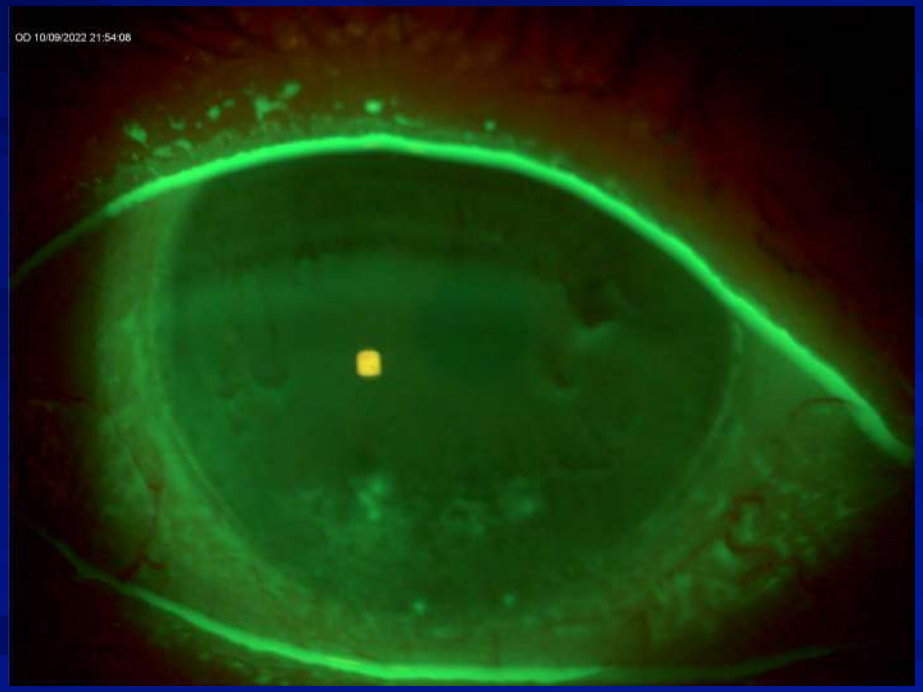
Stain Without Pain!

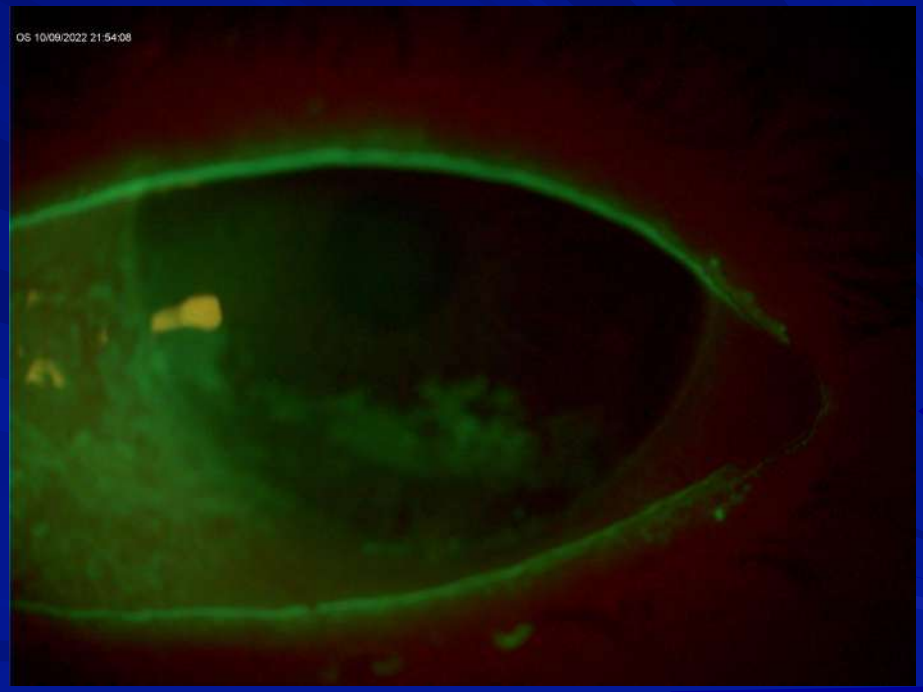
Actually, the OS is More Comfortable – What?



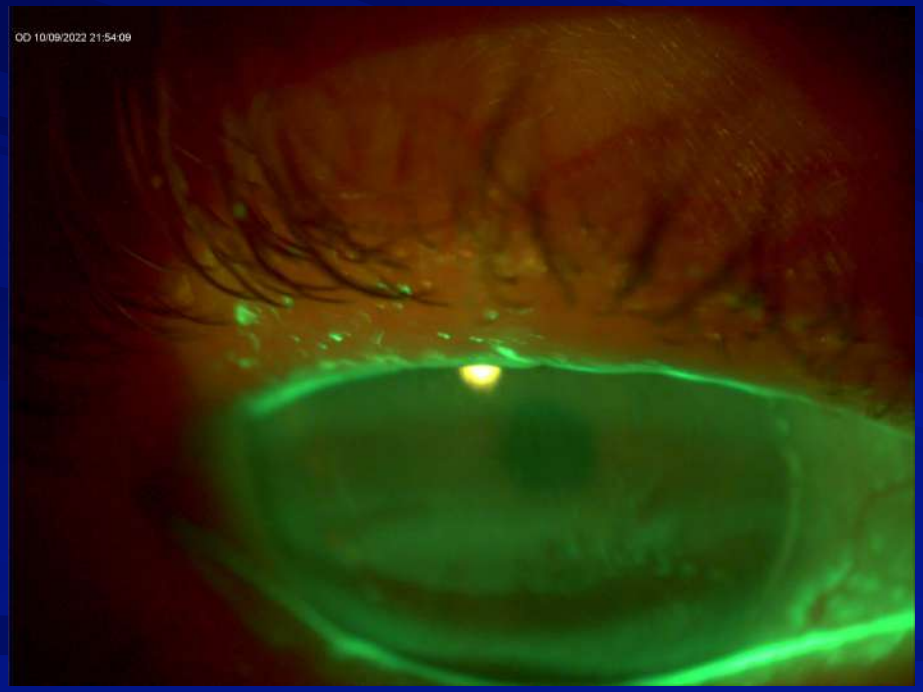


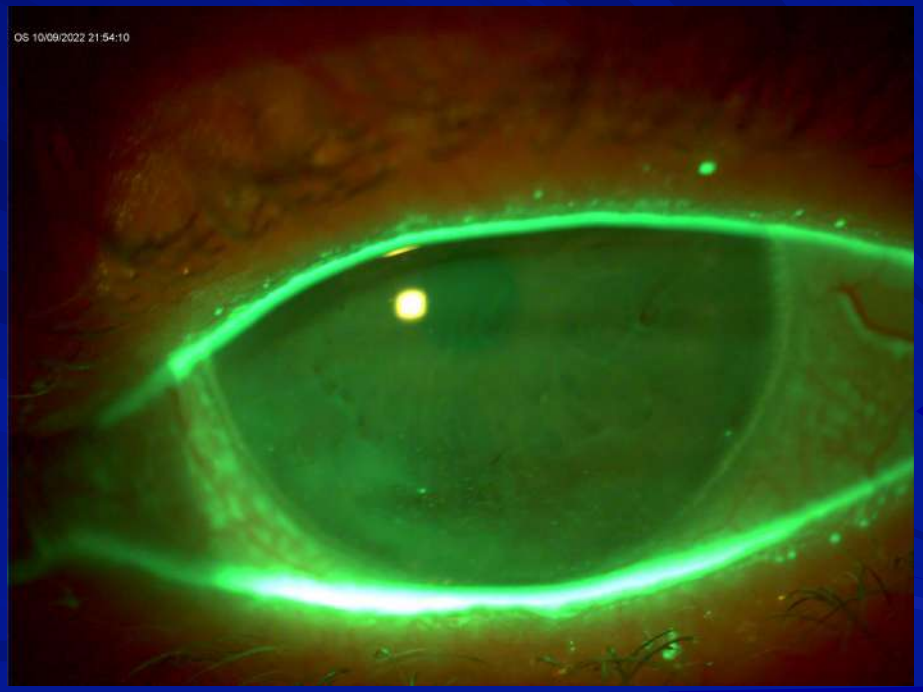
Before Oxervate™ (cenegermin-bkbj) Treatment





After Oxervate™ (cenegermin-bkbj) Treatment





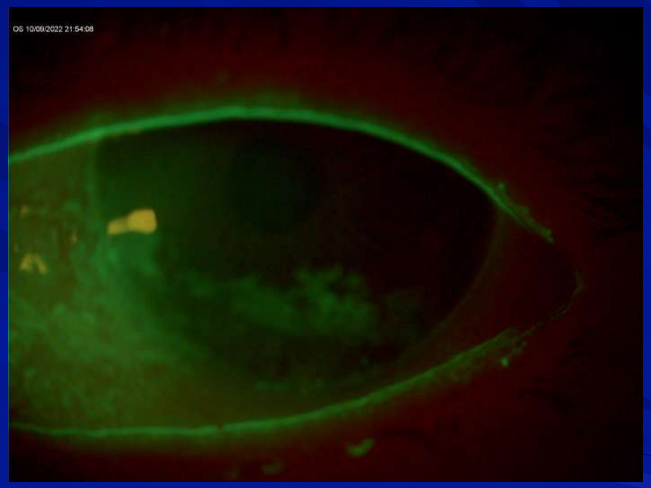
Corneal Sensitivity

Oxervate™ (cenegermin-bkbj)

- Grading corneal sensitivity: (Cotton Tip)
  - Normal
  - Reduced
  - Absent

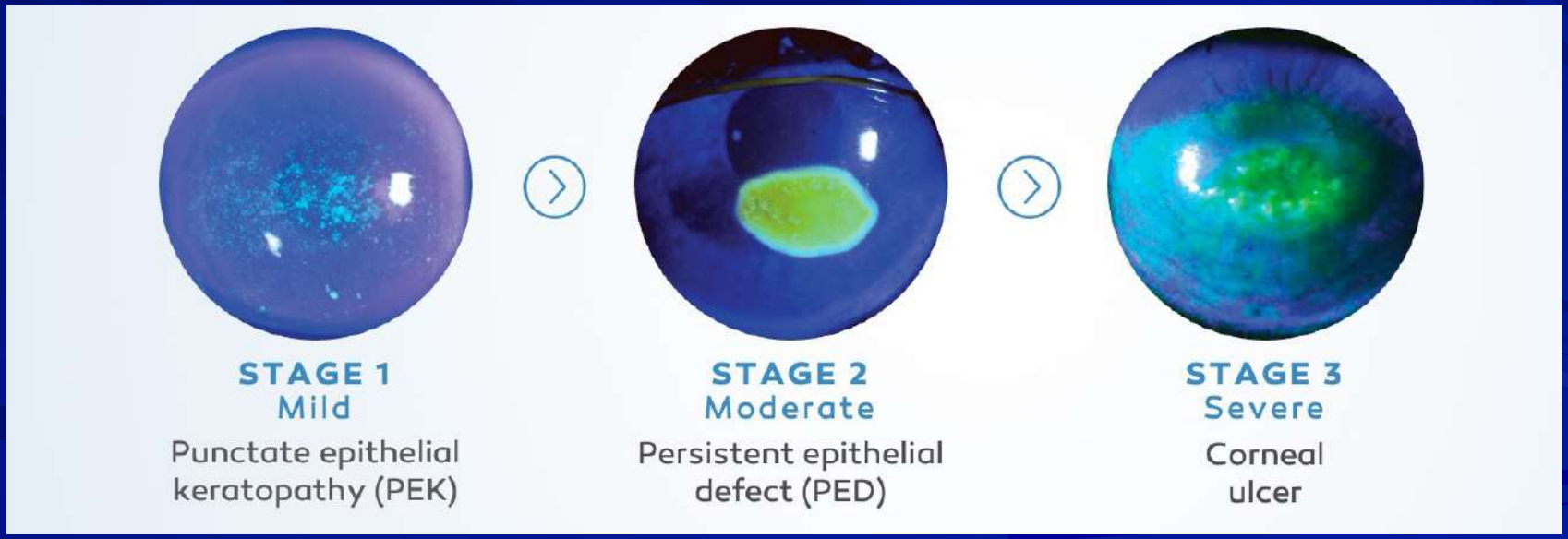
  - Reduced in all quadrants and centrally
  - Absent inferior quadrant, reduced everywhere else

- Neurotrophic Keratitis: (Staining)
  - Mild – Stage 1
  - Moderate – Stage 2
  - Severe – Stage 3



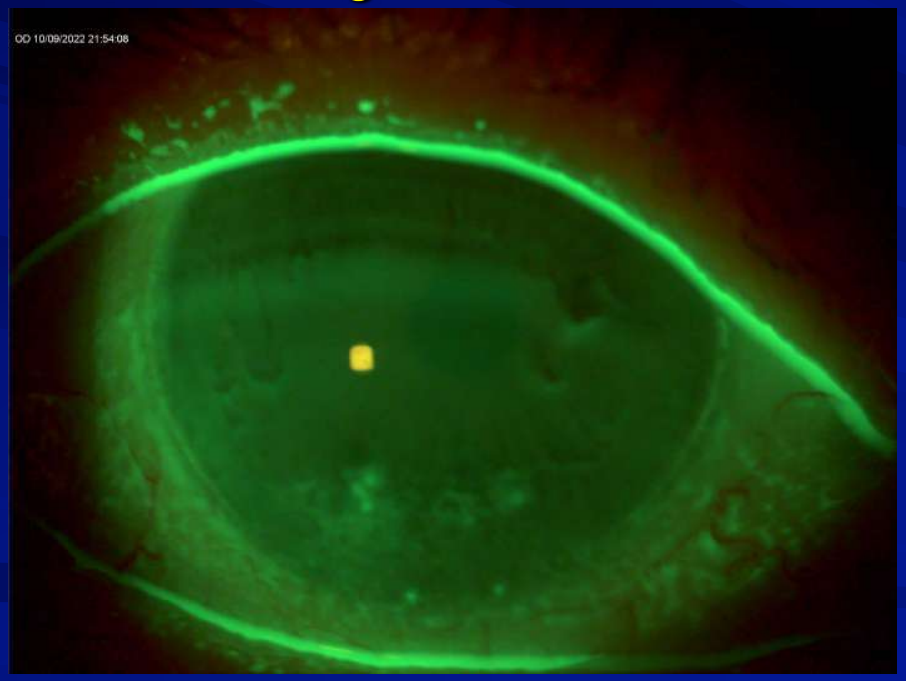
Neurotrophic Keratitis is a Degenerative Disease

- The Mackie classification represents one way to assess or grade NK – stage or progression

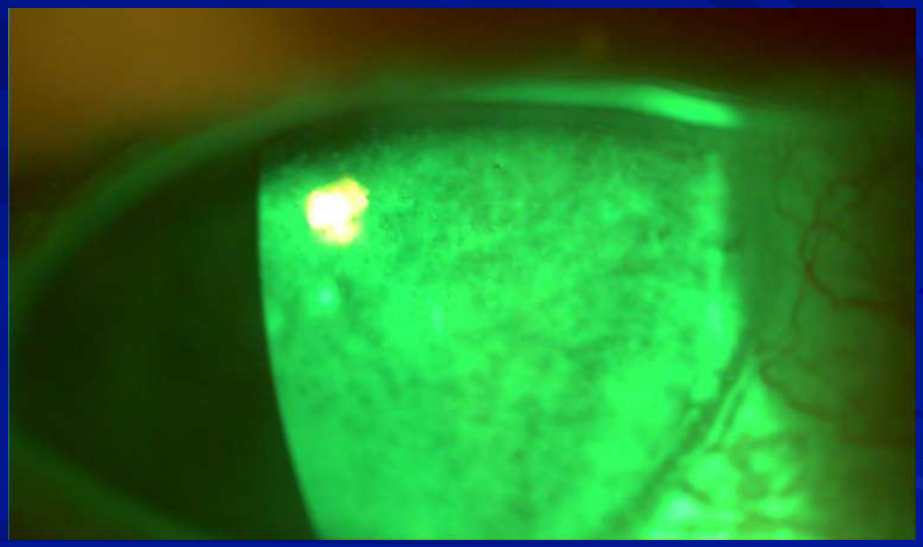


Mackie Classification

Moderate - Stage 2



Moderate - Stage 2



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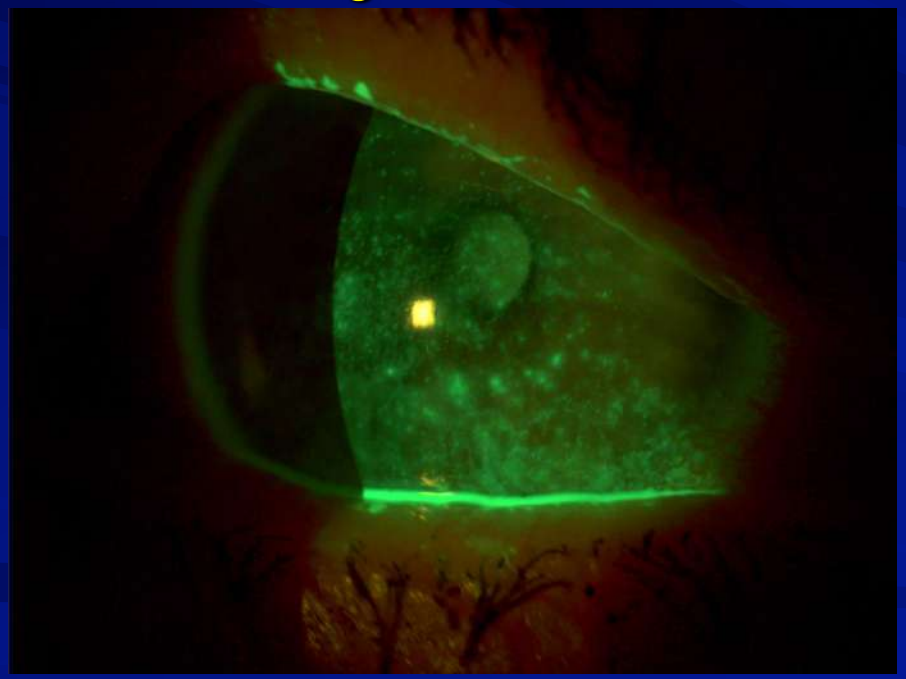

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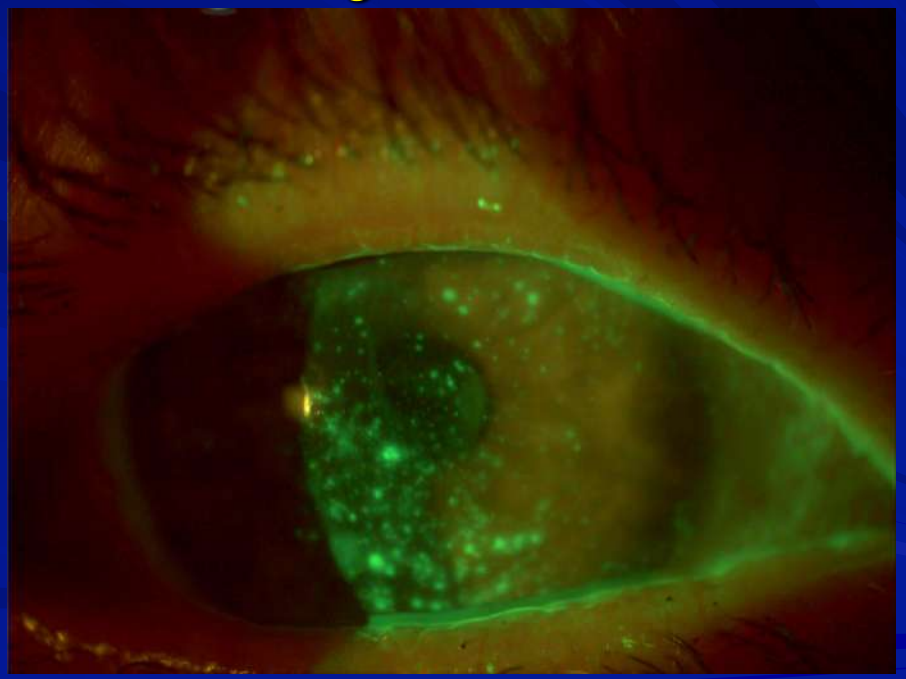
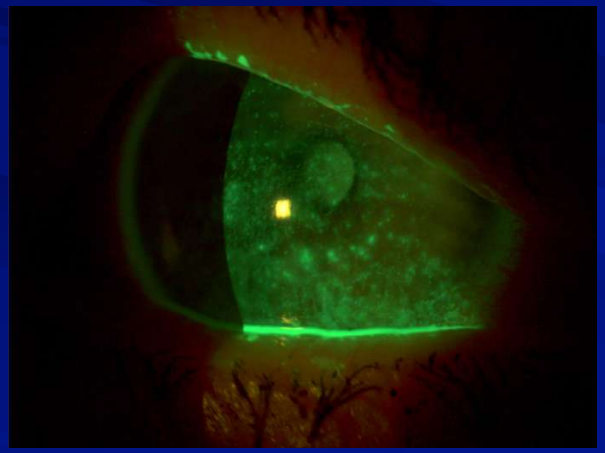


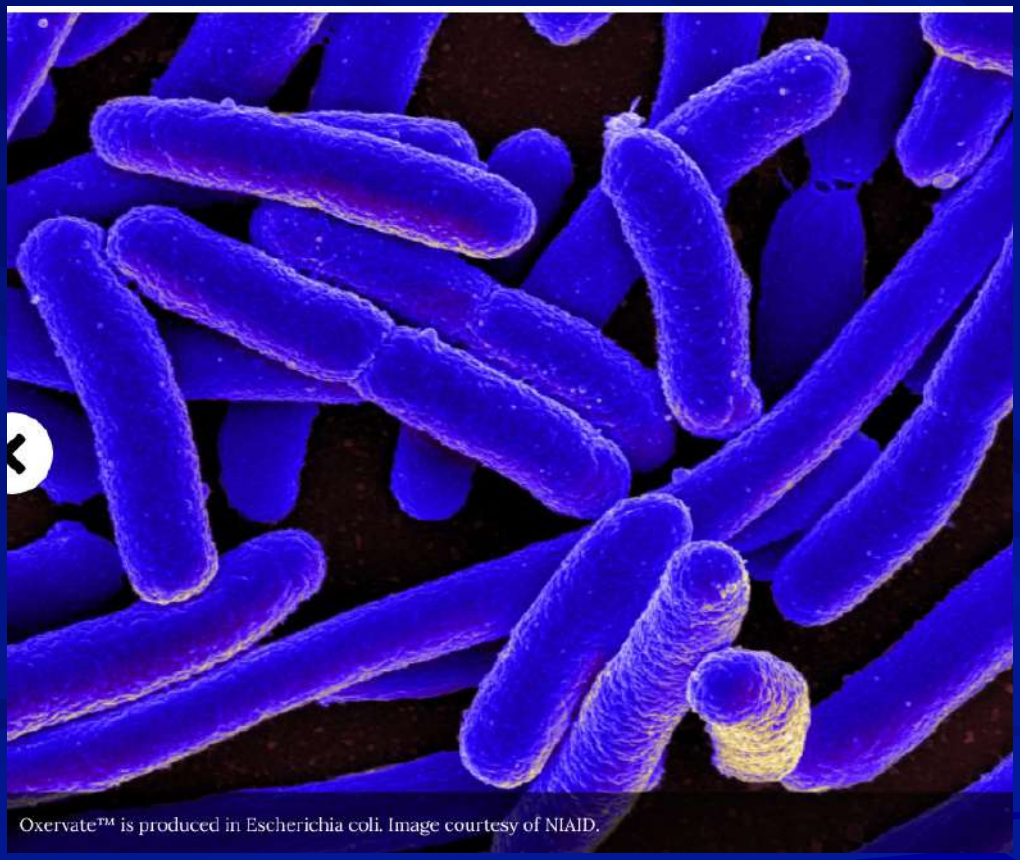
Resolved



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



Oxervate™ is produced in Escherichia coli. Image courtesy of NIAID.

Corneal Homeostasis

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

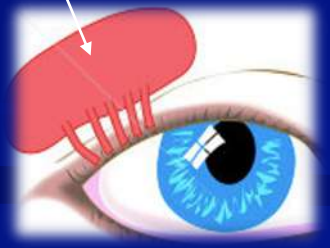
Corneal nerves stimulate blinking and tear production

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

- Stimulates wound healing
- Maintains anatomic integrity

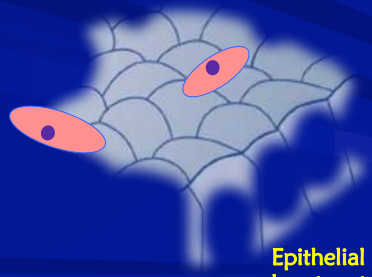
Neurotrophins, neuropeptides and growth factors (e.g., NGF) from epithelial cells and keratocytes mediate nerve fibre survival, differentiation and maturation

Tear gland



Tear secretion

Tears contain growth factors and nutrients that stimulate epithelial cells

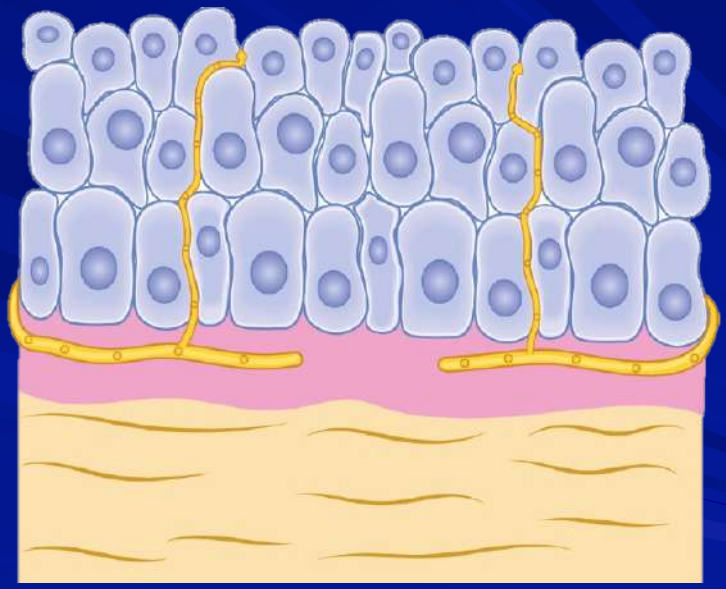


Epithelial cells and keratocytes

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

Pathophysiology of NK[1]

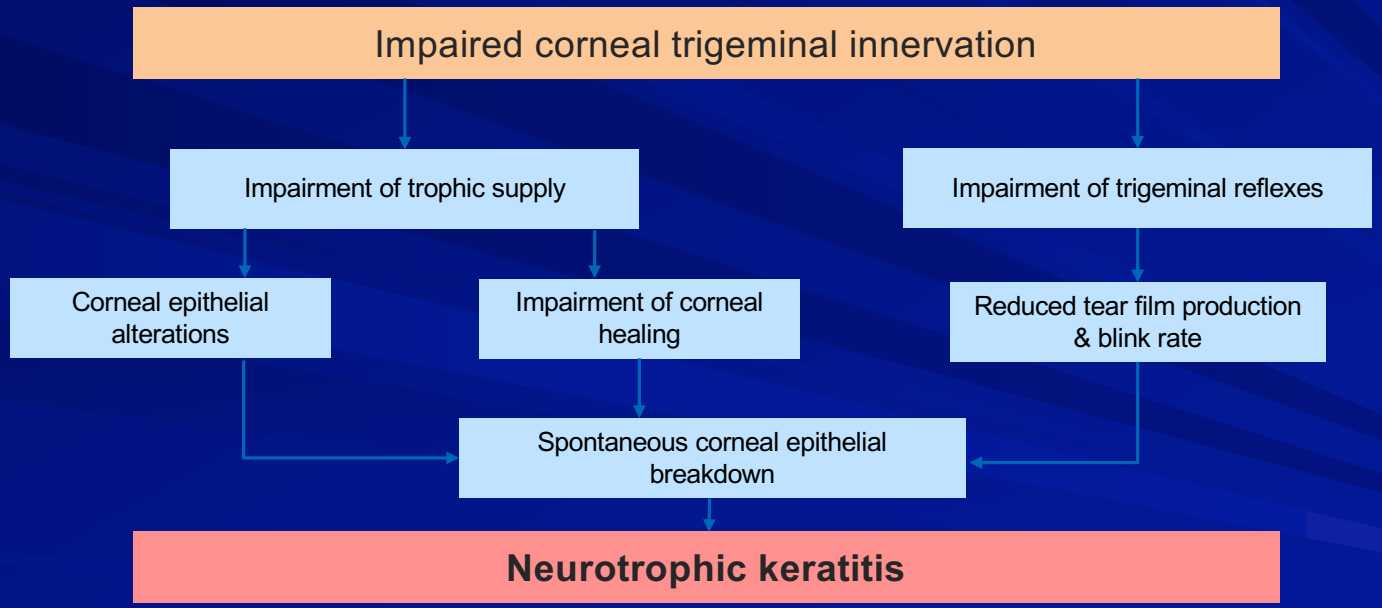
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production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

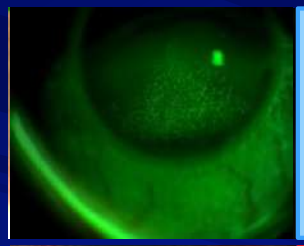
Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

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

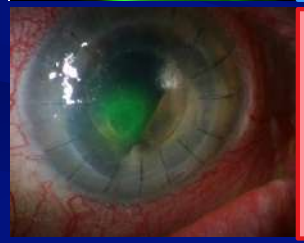
1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

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

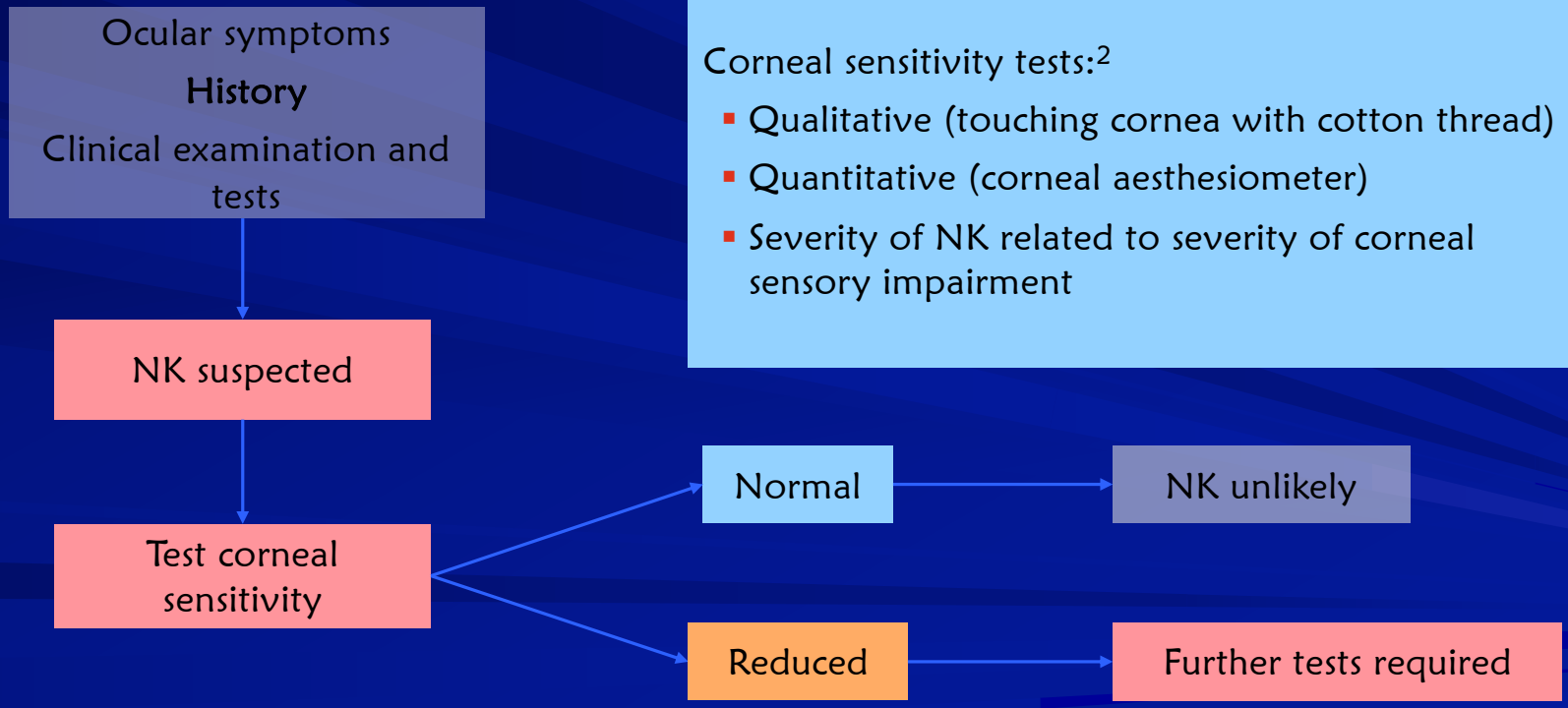
Stage 3: Severe

(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]



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.

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]

TEAR SECRETION

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

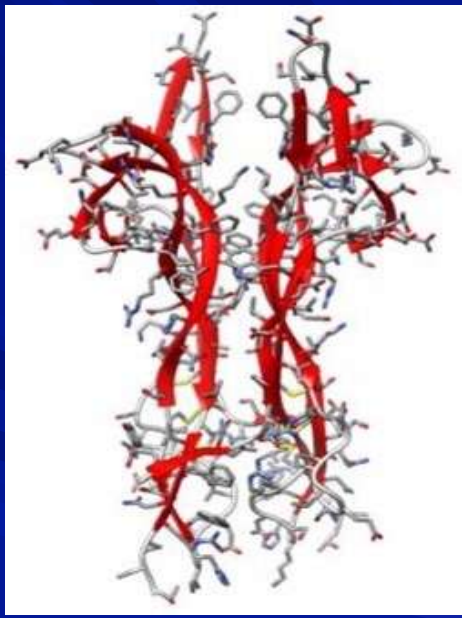
CELL PROLIFERATION AND DIFFERENTIATION

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

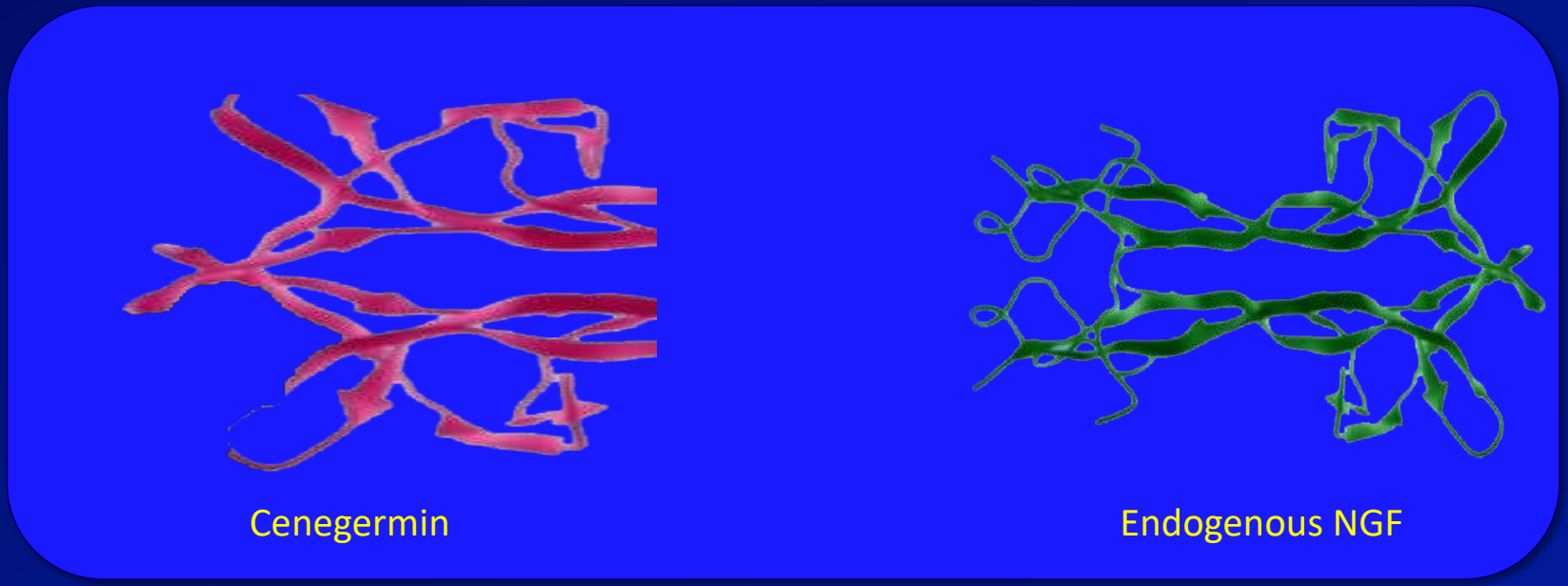
The Delivery System Kit Contains:

- 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-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

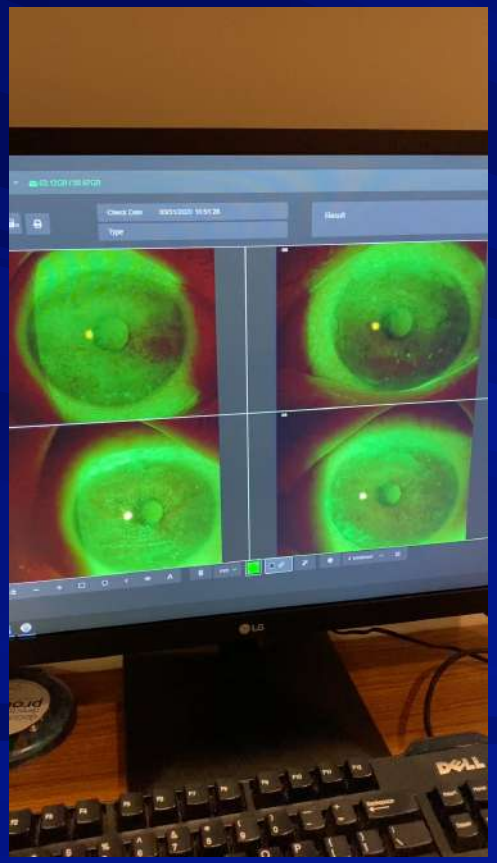
Apply 6 times daily

Continue for 8 weeks

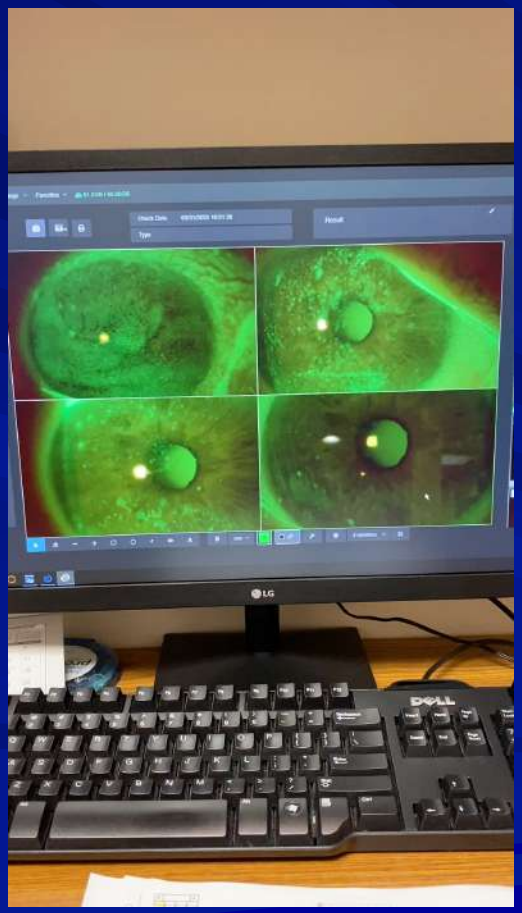
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

Let's Hear From a Patient

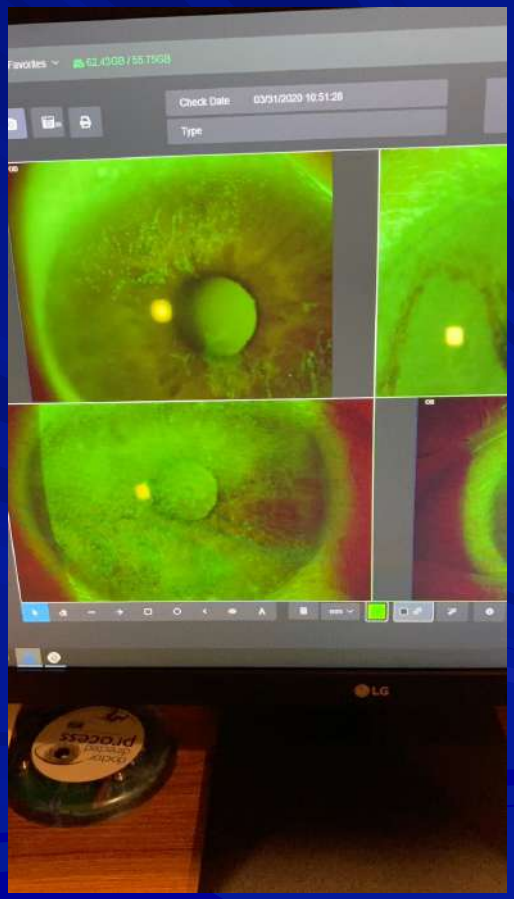
April 7, 2020 - After 1 week



April 21, 2020 - After 3 weeks



May 12, 2020 - After 6 weeks



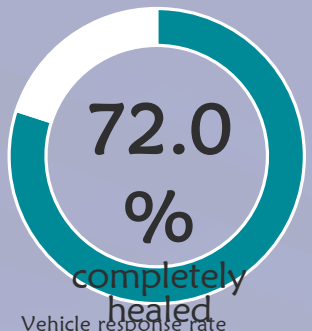
Study Conclusions

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

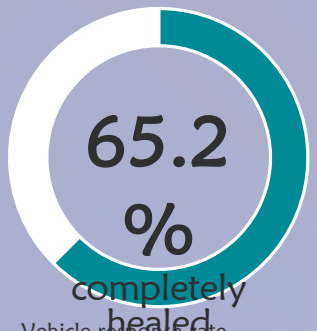


Vehicle response rate 33.3%

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]

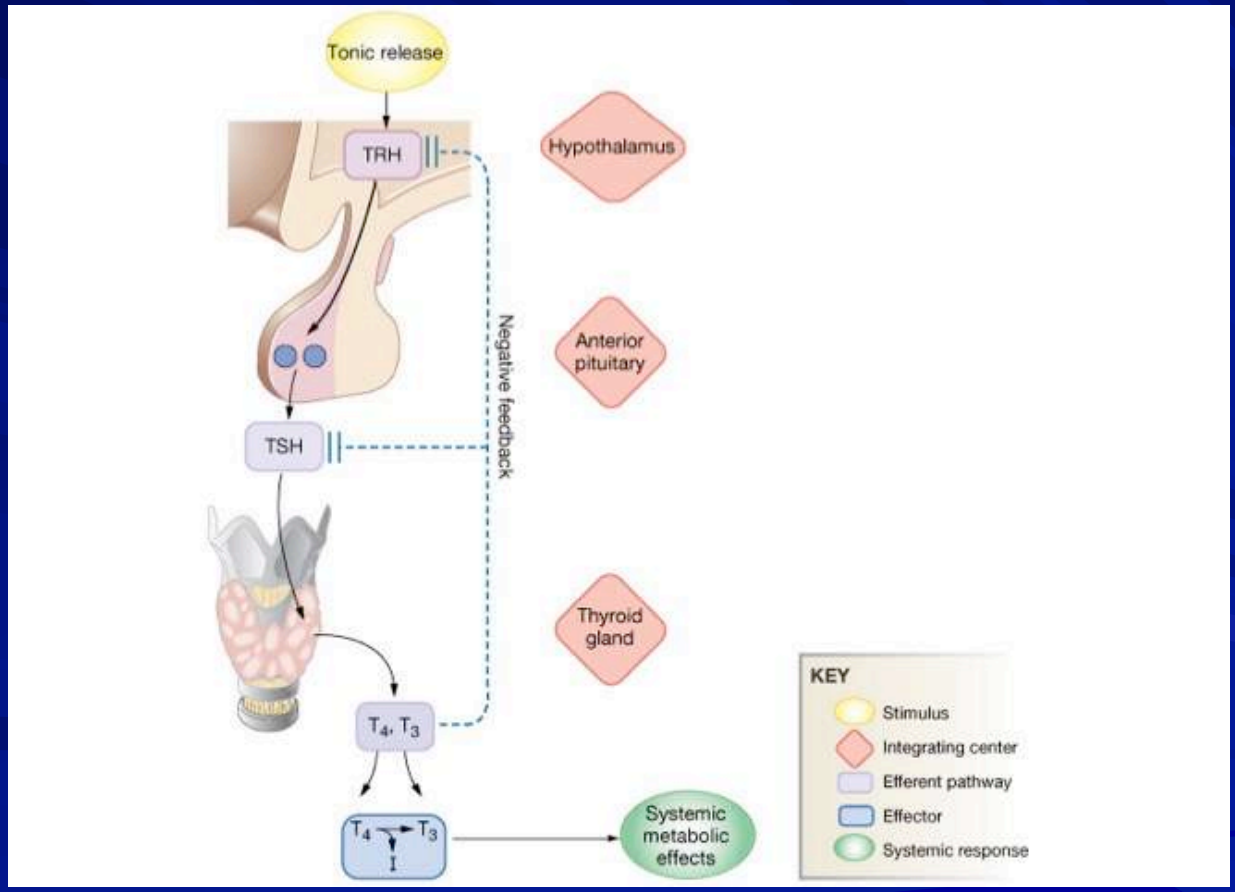
1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. Chao W, J. ROC, R. D. et al. Data on file. Healing of persistent epithelial defects or corneal 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

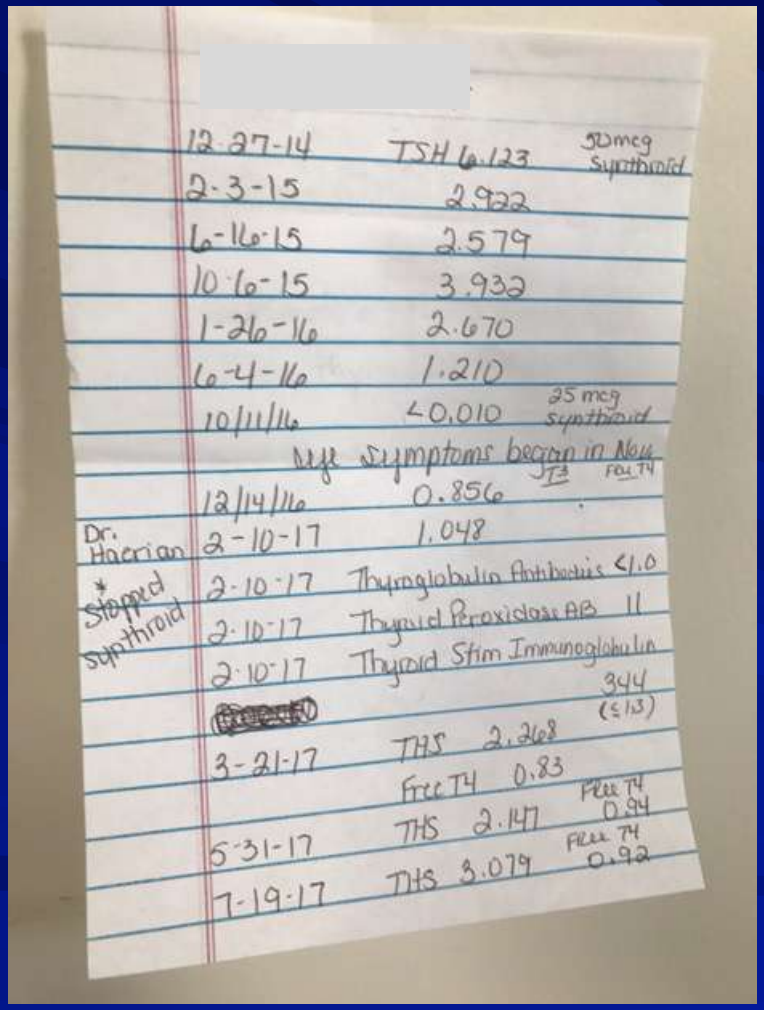
Secondary/Tertiary

- 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

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



You're in the Know

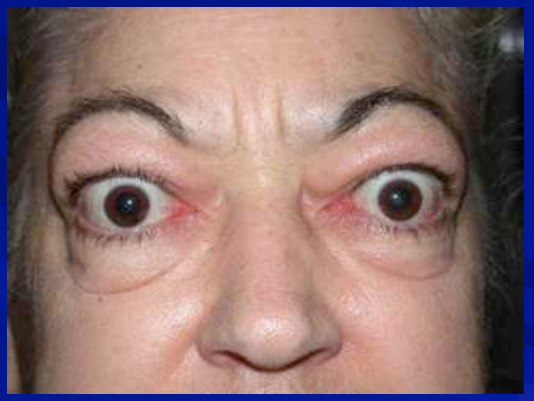
Normal Values
Thyroglobulin 20 IU/ml
Peroidase <35 IU/ml
TSI 1.75 IU/ml

It does work!

Lid Retraction

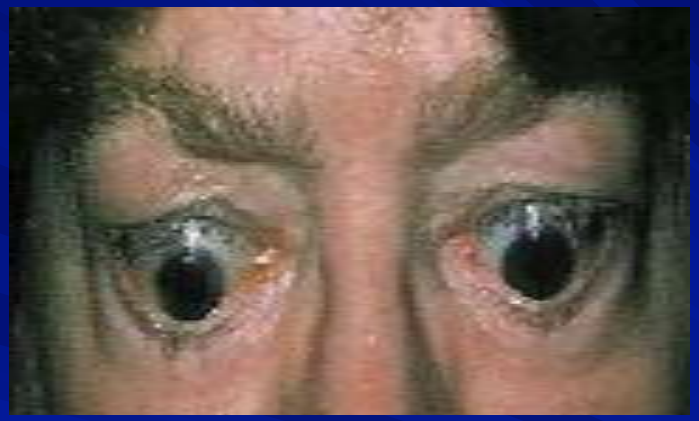
- Scleral show in primary gaze
- Occurs in ~90% of Grave's patients
  - Excess stimulation of Muller's muscle
  - Fibrotic inferior rectus
  - Mechanical restriction or infiltration of levator
  - Increased orbital volume causes exophthalmos

- 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



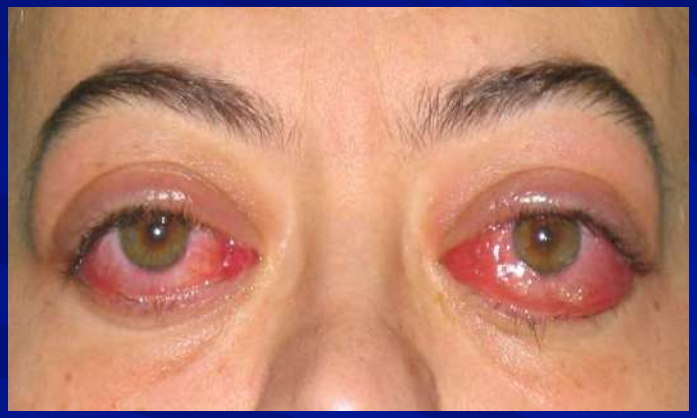
Eyelid Lag: von Graefe's Sign

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



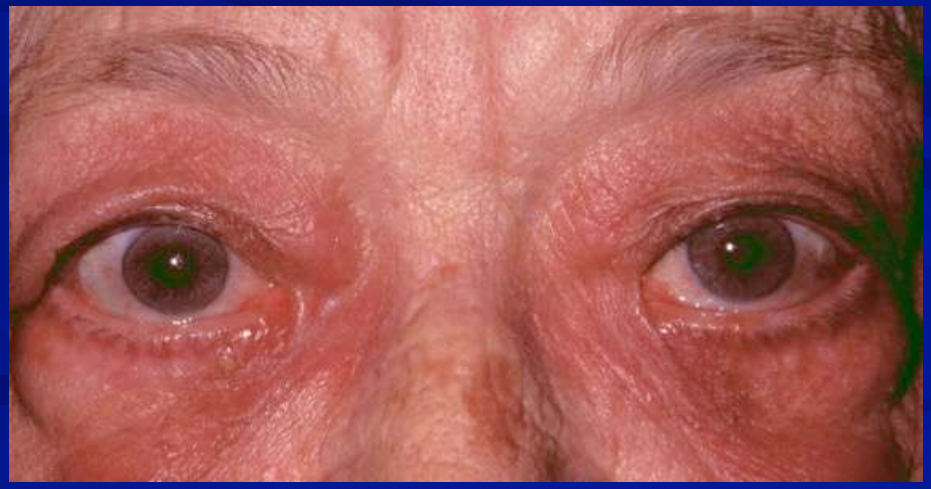
Conjunctiva

- 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

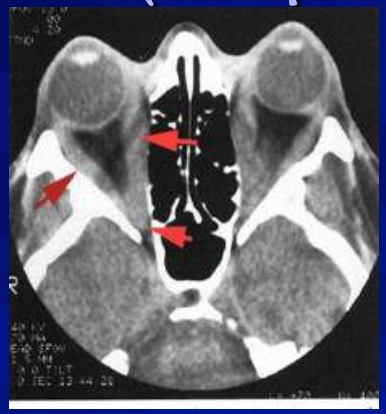


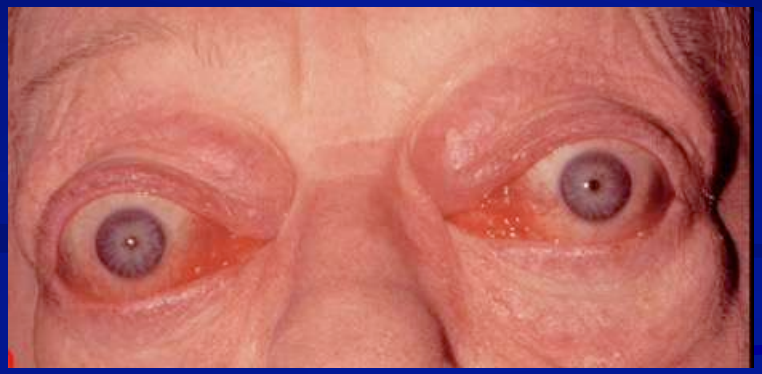
Periorbital Edema

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

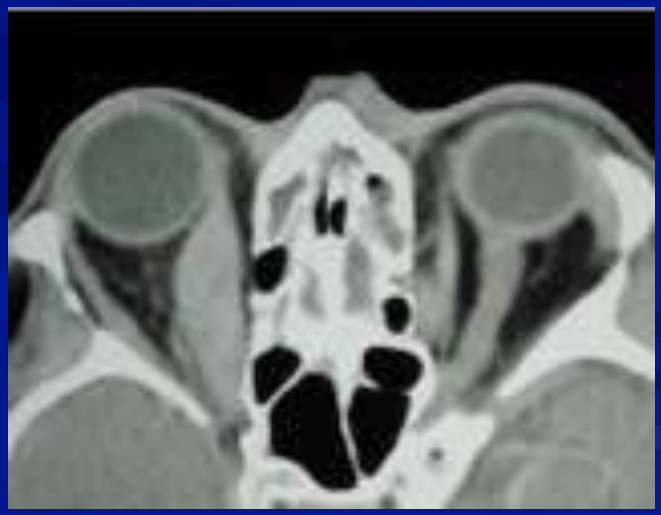


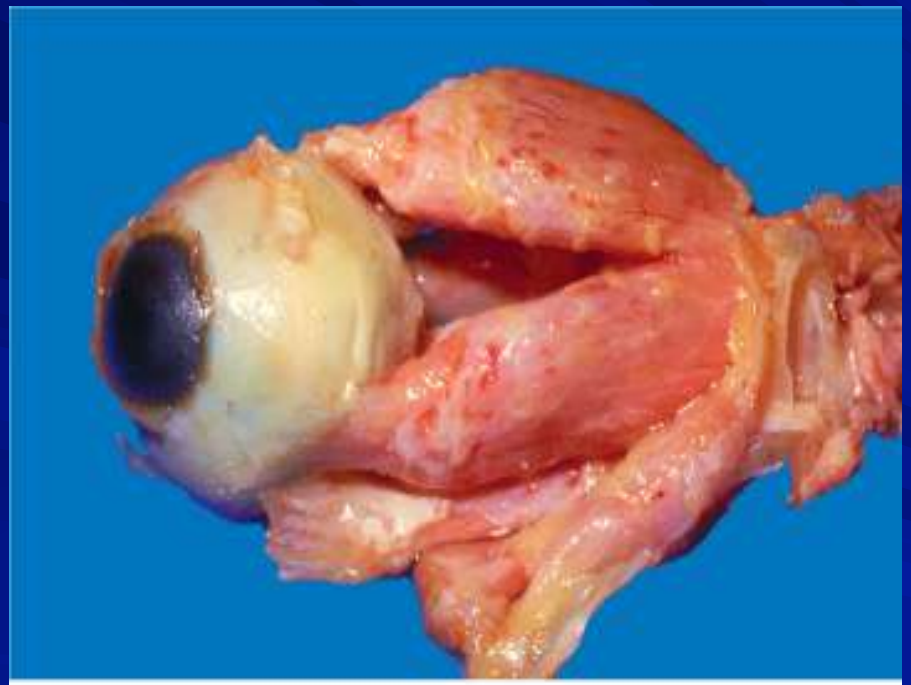
Infiltrative Orbitopathy
(Exophthalmos/Proptosis)





Infiltrative Orbitopathy
(Exophthalmos/Proptosis)





Treatment of Thyroid Eye Disease

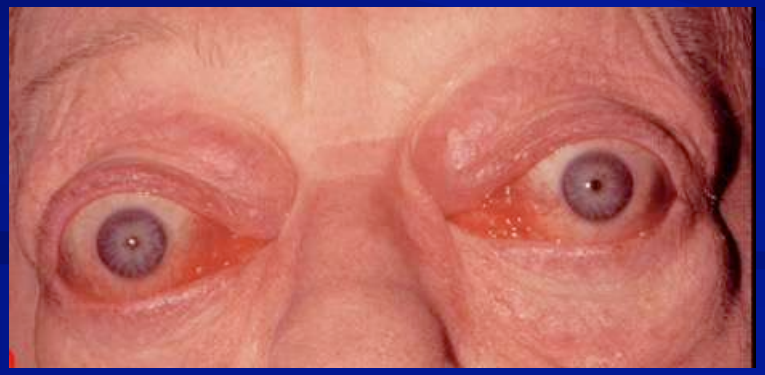
- Palliative (hormone imbalance, active, passive)
  - Lubricants
  - Topical anti- inflammatory (Lotemax/Restasis)
  - Prisms
- Steroids (active phase)
  - Orals
  - Peri-ocular injections
  - IV with oral steroid taper
- Orbital radiotherapy (active phase)
- Orbital Decompression (passive phase)
  -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

Infiltrative Orbitopathy
(Exophthalmos/Proptosis)

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



NOSPECS: Grading System

- 1969 by S.C. Werner
  - Class 0: No signs or symptoms
  - Class 1: Only signs, upper lid retraction
  - Class 2: Soft Tissue involvement with symptoms
  - Class 3: Proptosis
  - Class 4: EOM involvement
  - Class 5: Corneal Involvement
  - Class 6: Sight Loss

- Class 2-6 document severity
  - 0: absent
  - A: minimal
  - B: moderate
  - C: marked

- Within classes 2 to 6 the investigator has to differentiate the severity grades 0, A, B, C
- NOSPECS, classifies severity but not the activity or stage (active/inflammatory or passive/congestive)

LEMO Classification

- 1991-Boergen and Pickardt
- Complements NOSPECS
- 4 finding-categories
  - Lid
  - Exophthalmos
  - Muscular
  - Optic nerve
- Grade between 0 and 4 depending on severity
- LEMO, classifies severity but not the activity or stage (active/inflammatory or passive/congestive)

Clinical Activity Score (CAS)

- Thyroid disease characterized by:
  - Severity
  - Activity – want 3 or above
    - CAS (1-7)
- Studies for Tepezza
- Payers using CAS for approval
  - Due to wide open label
  - Those infusing are charting the CAS

Table 2 | Clinical Activity Score

	Clinical Activity Score
1	Painful feeling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
6	Inflammatory eyelid swelling
7	Inflammation of caruncle or plica
8	Increase of ≥2 mm in proptosis in last 1–3 months
9	Decrease in visual acuity in last 1–3 months
10	Decrease in eye movements of ≥8° in last 1–3 months

For initial CAS, items 1–7 are tallied at one point each for a final CAS based on a 7-point scale. On follow-up visits, the final three items are added for a CAS out of 10 points

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 25, 2019

March 25, 2019

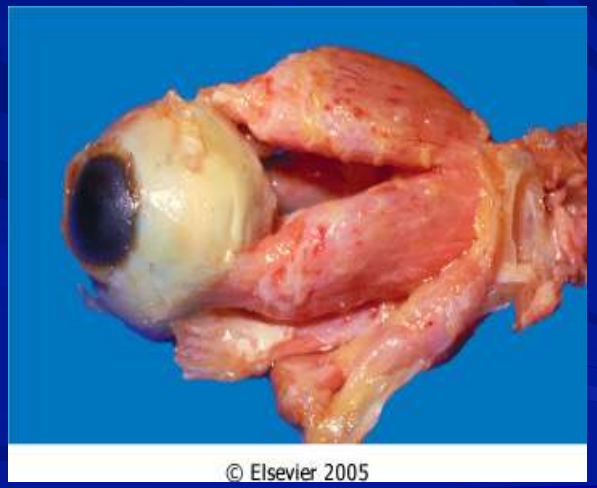
April 22, 2019

Immunosuppression?

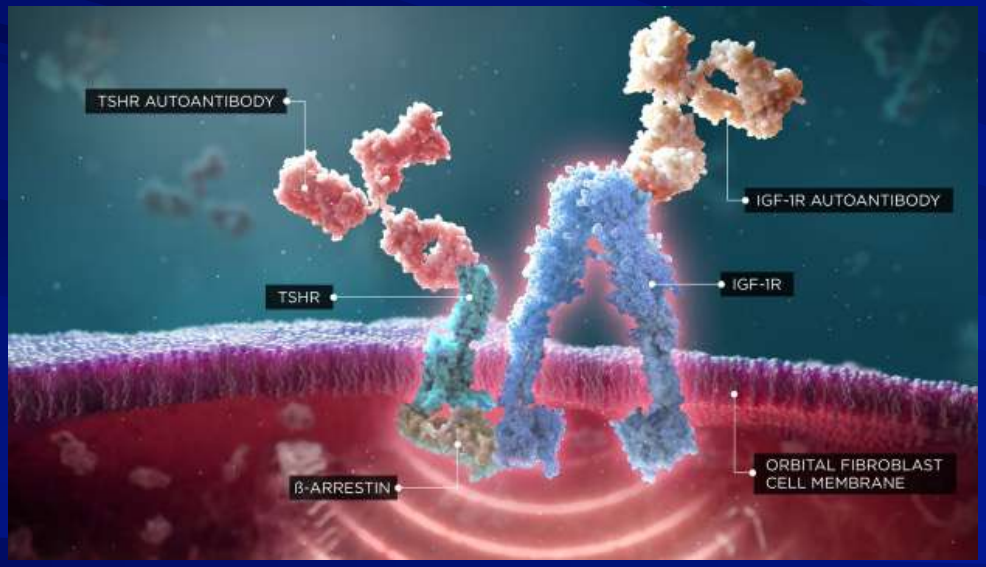
- Biologics
  - ★ Immunosuppression biologics – suppress the immune system to get the effe3ct
    - Remicade – "1st generation"
      - Chimeric molecule – mouse and human protein, a lot of sensitivity
    - Humira
      - Anti-TNF (RA and Crohn's Disease
      - Fully human protein, less sensitivity
    - Rituxan
      - CD 20 suppressor (B cell suppression)
    - Actively suppress the immune system
  - ★ Immunomodulary
    - Tepezza
      - IGF-1R inhibitor
      - Full humanized monoclonal antibody
        - All the proteins are human – less to no sensitivity – more focused effect
      - Obital fibroblasts to myofibroblast or adipocytes
      - Hyaluronic acid, glycosaminoglycan

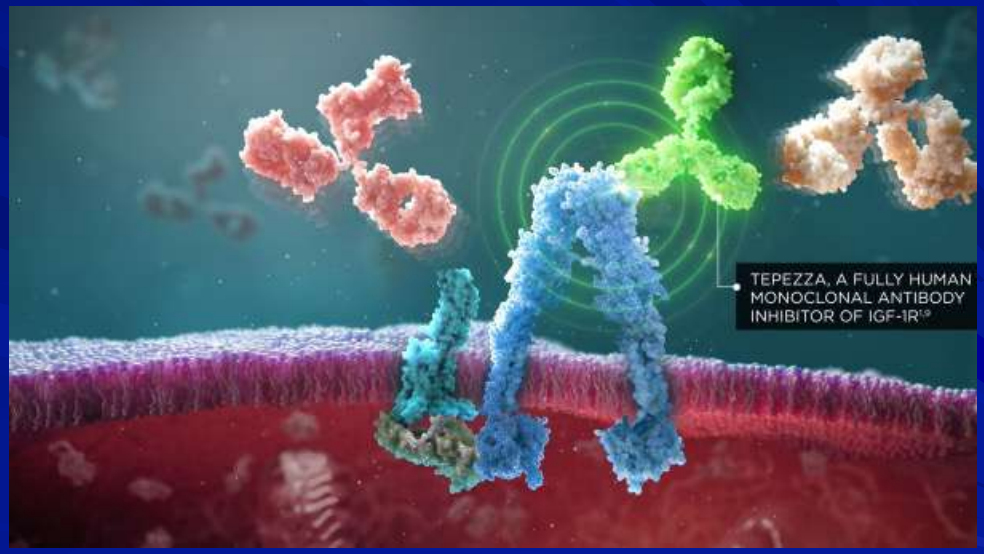
Teprotumumab-trbw (Tepezza)

- 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 - will occur within 1.5 hours of an infusion
  - For those who have had a previous reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate.

- **Preexisting Inflammatory Bowel Disease:** may cause an exacerbation of preexisting inflammatory bowel disease ("IBD")
  - Monitor patients for flare; may require discontinuation of Teprotumumab (Tepezza)

- **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

Biologics Used Off Label for TED

Table 1 | Biologic therapies for TED

Small Molecule Therapies	Target	Dosing	Findings	Side Effects
Rituximab	CD20	2 infusions of 1000 mg each 2 weeks apart	Mixed results in improvement of CAS, proptosis, and motility	Exacerbation of inflammatory bowel disease, arthralgias, hypotension
Adalimumab	TNF-α	Subcutaneous injections of initial 80 mg dose, then biweekly 40 mg doses for a total of 10 weeks	6/10 showed decrease in inflammation, no changes in proptosis or extraocular motility	Sepsis (1/10)
Infliximab	TNF-α	Infusions at 5 mg/kg each dose over 2 hours	Case reports showed improvement in visual acuity and CAS after 1 dose and complete resolution in 3 cases after 3 doses	Infections, malignancies (especially lymphoma), drug-induced lupus
Tocilizumab	IL-6	3 infusions at 8 mg/kg given every 4 weeks	93% with ≥2-point improvement in CAS, mean proptosis reduction of 1.5 mm, no change in diplopia	High recurrence rate, transaminitis, pyelonephritis
Teprotumumab	IGF-1R	Initial infusion at 10 mg/kg, followed by 7 infusions at 20 mg/kg given every 3 weeks	Reduced proptosis in 79–83% of patients, improved CAS in 69%, reduced diplopia in 68%	Most common: muscle spasms fatigue, nausea, diarrhea, hyperglycemia, hearing impairment, and alopecia. Between 5% and 12% with serious adverse events requiring early withdrawal

CAS, Clinical Activity Score; **CD**, cluster of differentiation; **FcRn**, neonatal Fc receptor for immunoglobulin G; **IL**, interleukin; **TNF**, tumor necrosis factor.

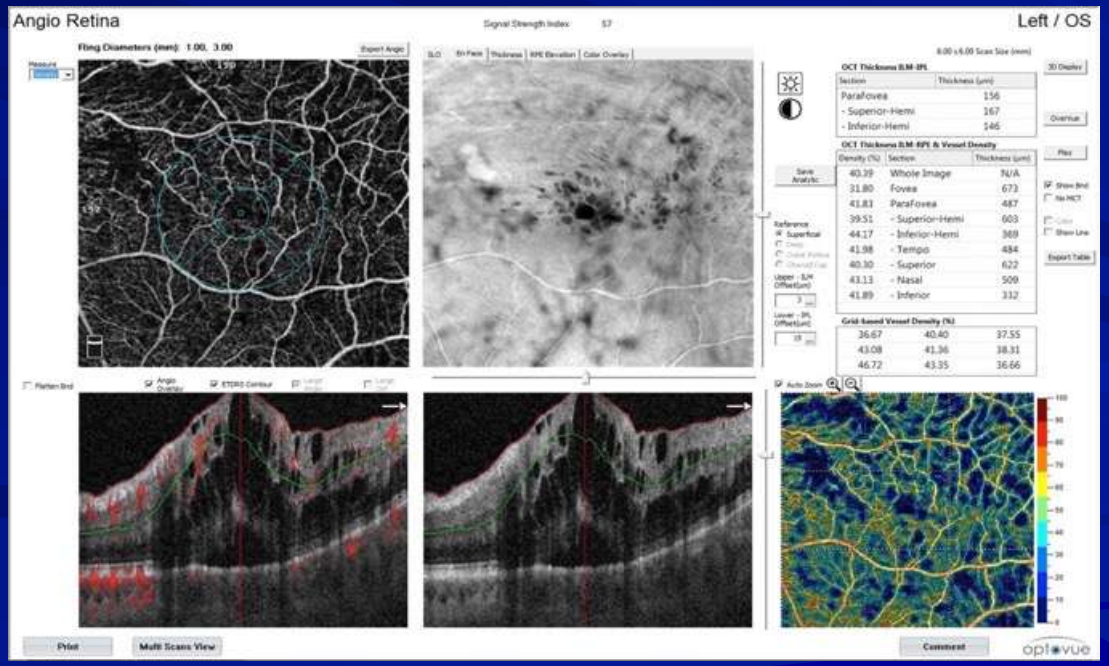
Additionally, multiple case reports published since

Humira™ (adalimumab)

- Company: Abbvie
  - Approved July 2016
  - Indication: uveitis
    - Specifically indicated for the treatment of non-infectious intermediate, posterior and panuveitis
  - Mechanism of action: binds to TNF and blocks its action in the body
  - 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)

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).

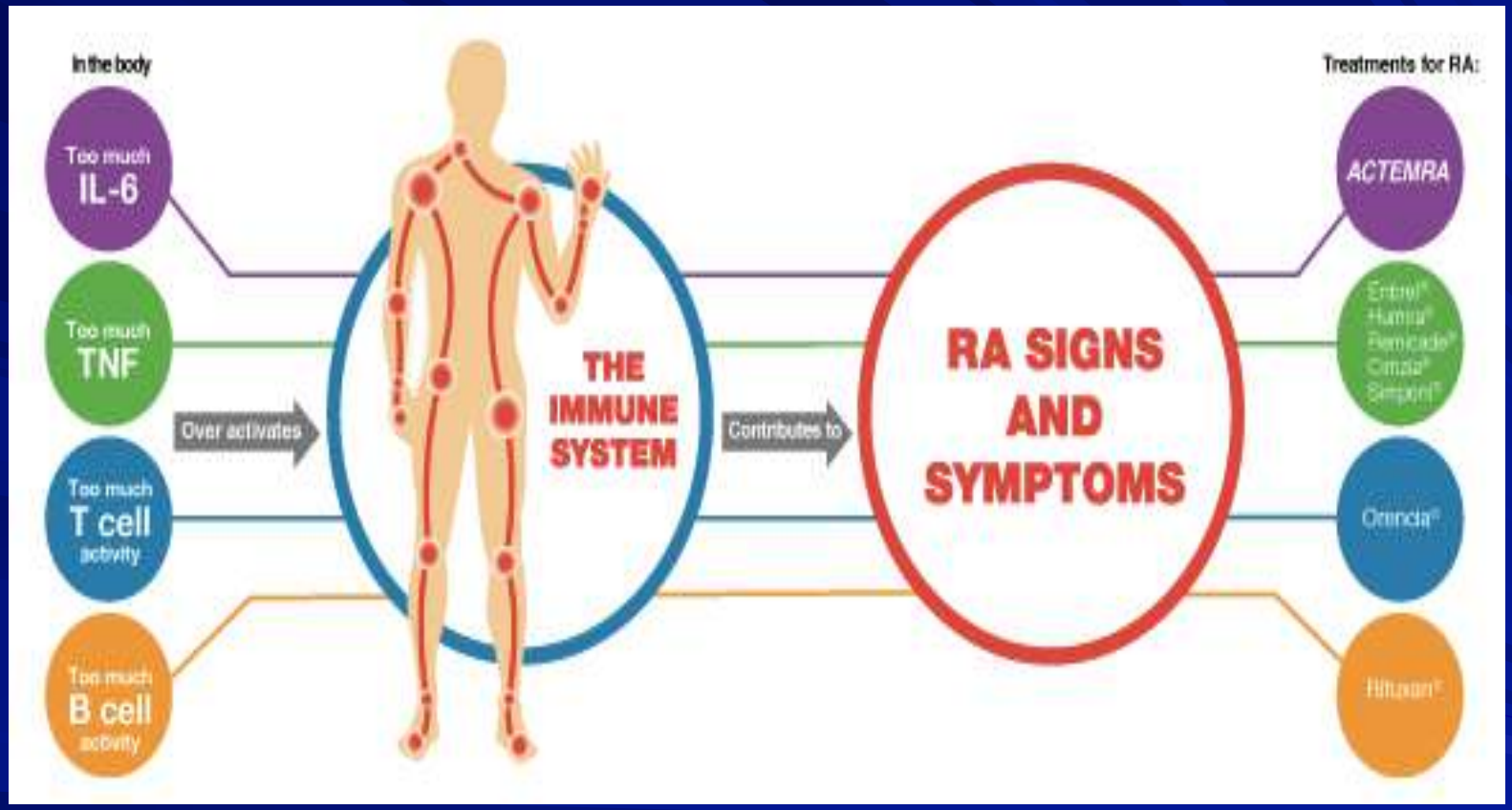
ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

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)

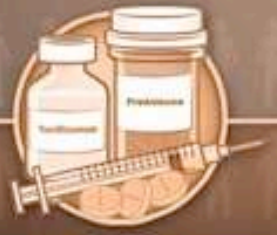
- Actemra™ (tocilizumab)- Genetec
  - First innovative therapy for GCA in more than 50 years
  - Design to speed the development for treatments of serious diseases such as GCA and certain cancers

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

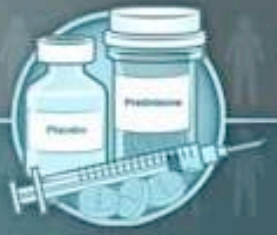
Tocilizumab weekly
+ 26 weeks of
prednisone taper
(N=100)



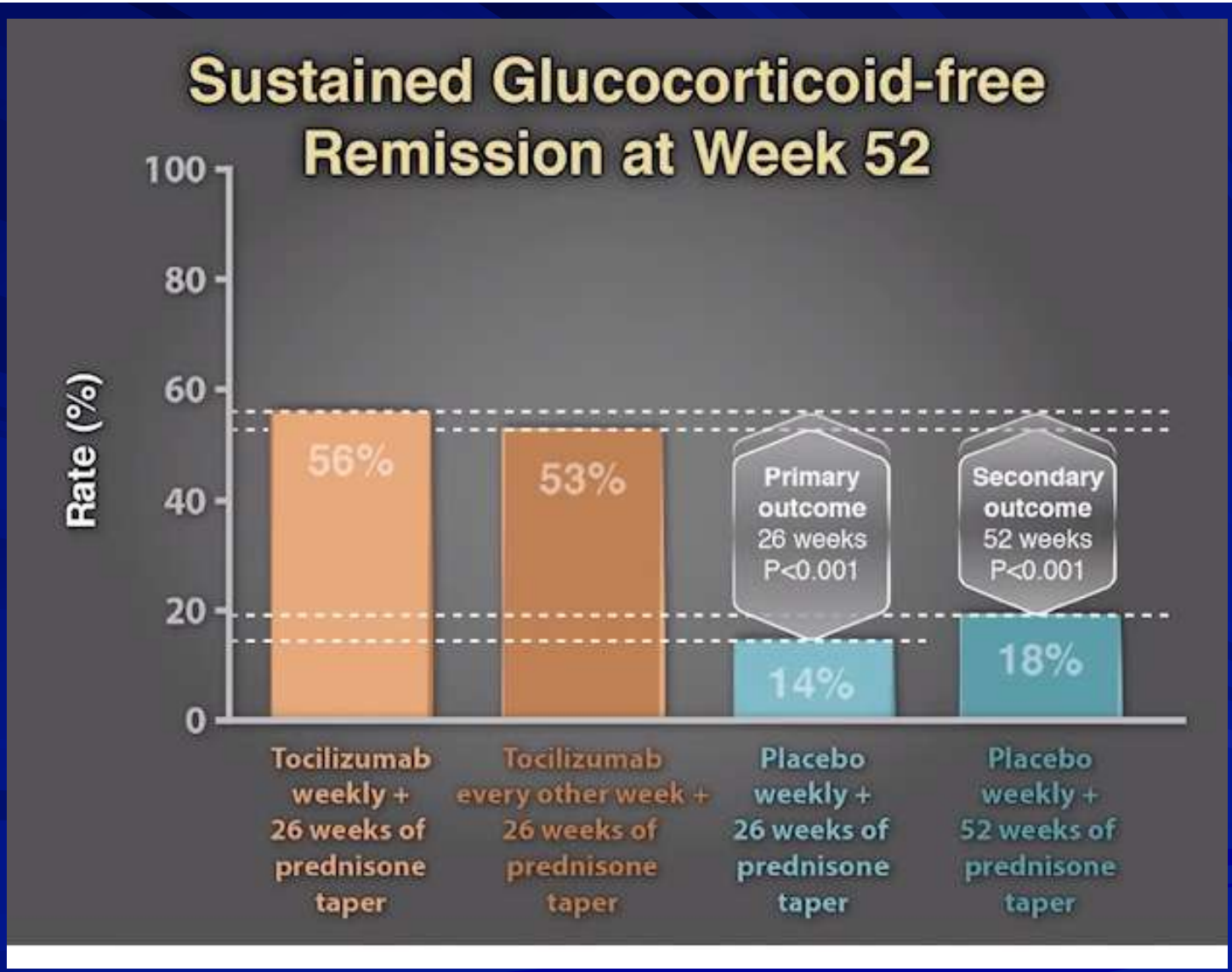
Tocilizumab every other week
+ 26 weeks of prednisone taper
(N=50)

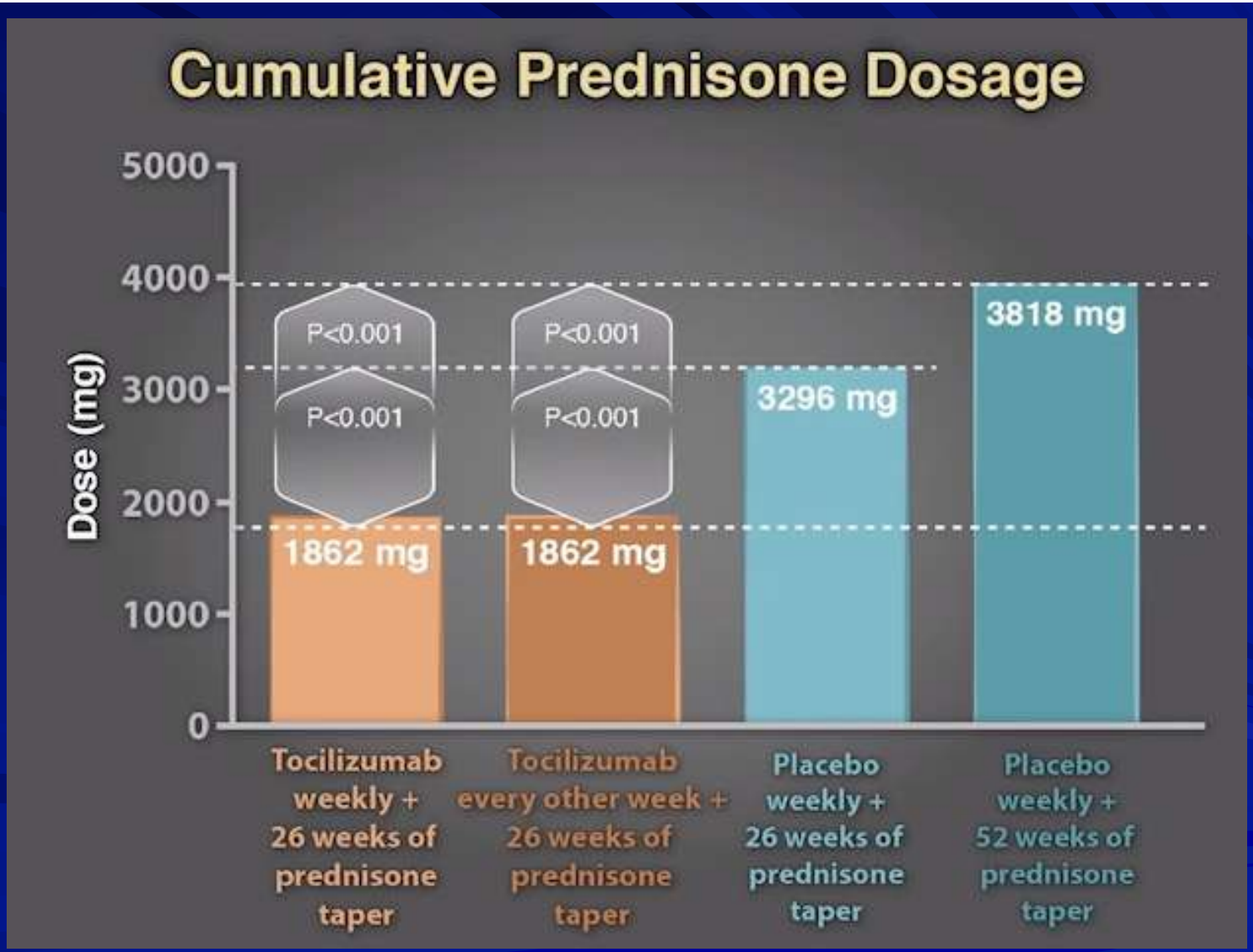
Placebo

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
  - 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.

Optometric Education Consultants

Questions and Thank Ypu!

Ocular Biologics, Biosimilars, and Drugs for the Eye

What's the Difference and What is New

Greg Caldwell, OD, FAAO
Tracy Offerdahl, PharmD, Bpharm, RPh, FAAO

CE Sarasota 2023
Optometric Education Consultants
Saturday, March 4, 2023