THERAPEUTIC INNOVATIONS: THE GAME CHANGERS

JESSICA STEEN OD, FAAO, DIPL ABO

1

FINANCIAL DISCLOSURES

- Speaker-Carl Zeiss Meditec
- Advisory Board-Bausch + Lomb, Santen.
- *All relevant relationships have been mitigated*

2

Making an Impact

Filling an unmet need

Common conditions

Rare disease

Providing additional options

Novel products

Repurposed molecules

3

Framework for Development

Orphan drug designation (1983)

<200,000/year
Federal grants and contracts to support clinical trials
Tax credits-25% of clinical testing costs (reduced from 50% in 2018)
Exclusive right to market the drug for 7 years from date of marketing approval
Maximum flexibility to the design of pivotal trials
More likely to be single arm trials, un-blinded and use surrogate endpoints

Fast Track Designation (1988)

Drugs which fill an unmet clinical need
More frequent communication with FDA
Rolling review
Eligible for accelerated approval and priority review
Surrogate measures
2 tiered system-standard (10 months) vs. priority (6 months)

4

Framework for Development

PDUFA (1992)

Authorized the FDA to collect fees from drug companies-important role in expediting drug approval process
Is there industry influence when 45% of the FDA's budget is funded through user fees?

Application fee: $3,117,218 (2022) + program fee ($369,413)
Either 10 months; or 6 months if granted priority review

When the FDA takes too long or too little time to review a drug→criticism
Balance between regulation and efficiency

Remember, the FDA doesn't guarantee safety of a product
It ensures that the data presented is credible and ensures benefit with acceptable risks

Balance of safety and efficacy

5

How do you stay up to date?

6

HOW DO YOU STAY UP TO DATE?

Medscape OPHTHALMOLOGY | MedPulse

Eyewire News

AMD and Retinal Disease

Gene Therapy Shows Potential for RPE65-Related Retinal Dystrophy
Medscape Medical News

With Approval Pending, Pegcetacoplan Phase 3 Results Mixed
Medscape Medical News

Glaucoma

Normal-Tension Glaucoma Linked to Alzheimer's Risk
Medscape Medical News

Pediatric Ophthalmology

Pediatricians Urged to Check for Vision Problems After Concussion
Medscape Medical News

Drops Help Pink Eye in Kids, No Antibiotic Necessary?
Medscape Medical News

10.11.2022
Tarsus Announces Transition Plans for Board of Directors
Eyewire News

10.10.2022
PatientPoint Acquires Rendia to Accelerate Expansion into Ophthalmology Specialty
Eyewire News

10.10.2022
TearClear Announces Positive Topline Results from CLEAR Phase 3 Study for the Treatment of Glaucoma with TC-002 (latanoprost ophthalmic solution 0.005%)
Eyewire News

7

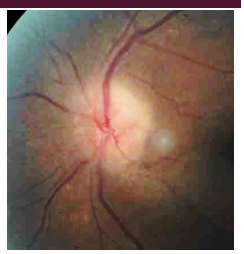
BREAK DOWN

- IOP raising agents
- IOP lowering agents
- Anterior segment
- Posterior segment

8

CASE

- 72 year old female
- Woke up with vision loss in the left eye yesterday morning
  - No ocular medications, no systemic medications
  - No headache, scalp tenderness, nausea, malaise, change to appetite
- BCVA: 20/25 OD; CF @ 2 ft OS
  - 3+ APD OS
- PCIOL OU, IOP 12mmHg OD and OS



9

NOW WHAT?

- Unilateral disc edema
  - DDx? ***First, think "where?"…then "what?"***
    - Optic neuritis
    - GCA
    - Medications (i.e. sildenafil, amiodarone)
    - Compressive, infiltrative optic neuropathy
    - Neuroretinitis
    - Impending CRVO
    - NAION

10

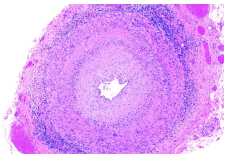
NOW WHAT?

- Does this patient need:
  - 1) Emergent laboratory evaluation
    - *Tests?*
      - *CBC with differential, CRP, Sed Rate (ESR)*
  - 2) Emergent neuroimaging

11

GIANT CELL ARTERITIS

- Idiopathic, **multisystem** inflammation
  - Affects medium and large vessels (internal elastic lamina)
- Upregulation of **IL-6** pathway
  - Infiltration by T cells, macrophages, histiocytes, plasma cells, multinucleate giant cells
  - Leads to occlusion and collapse of the vessel lumen = **ischemia**



12

GCA TREATMENT

- **Steroids**
  - Typical initial pulse (methylprednisone 1-2g/day IV)-**inpatient**
  - Then 60-100mg prednisone daily by mouth—may be for 2+ years!
  - *Need to keep ESR down*

13

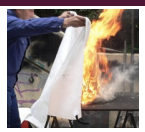
WHAT'S THE TROUBLE WITH LONG-TERM STEROIDS?

- **Significant ocular and systemic side effects**
  - Cataract
  - Elevated blood pressure
  - Blood glucose dysfunction
  - Gastrointestinal ulceration
  - Fluid retention
  - Weight gain
  - Osteoporosis
  - Neuropsychiatric effects including changes in mood

14

IN MEDICINE, IN GENERAL

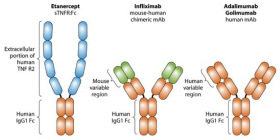
- The trend is towards providing 'precision-based medicine'
- Steroids act to suppress the entire immune system
- Biologic agents have a specific therapeutic target in the inflammatory cascade



15

BIOLOGIC AGENTS

- Bioengineered complexes that alter the expression of components of the immune system
- Include monoclonal antibodies
  - Attach to a specific antigen on the surface of an affected cell



16

ACTEMRA

- Tocilizumab 162mg/0.9mL
  - Subcutaneous injection (or intravenous infusion)
  - Weekly injection + steroid taper
- Reduces steroid load in GCA treatment
  - Also approved for RA, JIA, cytokine release syndrome

18

A LITTLE LESS NEW: HUMIRA

- Adalimumab
- Subcutaneous injection
  - 80mg loading dose
  - 40mg subcutaneous injection every 2 weeks
- Approximately $5000/carton (2 pens)
- FDA approved June 2016 for the treatment of non-infectious intermediate, posterior, and panuveitis
  - Patent expires in USA in 2023-*get ready*
    - Already 5 FDA approved biosimilars

19

BIOSIMILARS

- Analogous to biologics as generic medications are to branded small molecule drugs
- Biologic agents are large molecules (i.e. 150,000 Daltons vs. netarsudil 453 Da)
  - 3D structure is complex!
  - Produced from living molecules
- Goal is to be a lower-cost alternative (usually 15-30% of originator biologic)
  - But—manufacturing process is more complicated than for generic medications
  - Drugs need to be prescribed (cannot be substituted)—requires marketing to physicians

21

ADVERSE EFFECTS OF TNF ALPHA INHIBITORS

- Unmasking or induction of multiple sclerosis
  - Intermediate uveitis is associated with development of MS
- Reactivation of viral hepatitis, tuberculosis
- "Lupus-like syndrome"
  - Autoantibody formation
- Possible increased risk of lymphoma
  - Medical vs. systemic disease?

22

PRIOR TO INITIATION OF THERAPY

- Patients will undergo complete physical examination
  - Complete blood count with differentiation, complete metabolic panel
  - Purified protein derivative testing (or **Quantiferon gold**) and chest radiograph
  - MRI of brain to rule out demyelinating disease in some cases (intermediate uveitis)

23

WHILE UNDERGOING THERAPY

- CBC with differential and metabolic panel
  - Monthly for the first three months
  - Then typically, every 2-4 months

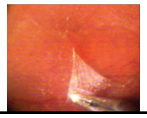
24

NEW OCULAR STEROIDS

25

NOT-NEW: INJECTABLE STEROIDS

- Triamcinolone acetonide
  - Kenalog (periocular—sub-Tenon's or subconjunctival)
    - Off-label for intraocular injection
  - Triesence-preservative-free Kenalog
    - Used for intravitreal injection

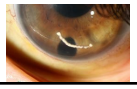


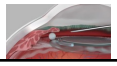
26

28

INJECTABLE STEROIDS

- Intravitreal implants-provide sustained release of steroid
  - Ozurdex (dexamethasone 0.7mg) 3-6 months
  - Retisert (fluocinolone acetonide 0.59mg)
  - Iluvien (fluocinolone 0.19mg)—off-label for posterior uveitis-up to 3 years!
  - Yutiq (fluocinolone 0.18mg)—indicated for treatment of non-infectious posterior uveitis-3 years
- Dexamethasone **intraocular** suspension 9% (Dexycu)
  - 5uL dose at the conclusion of cataract surgery



Dexycu


29

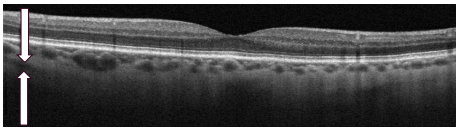
Retinal Disease

Alternative routes of drug delivery

Suprachoroidal space

J code received June 21, 2022

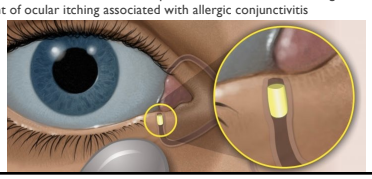
Triamcinolone acetonide injectable suspension 40mg/ml (Xipere)



30

STEROID INSERT

- Dextenza (dexamethasone insert 0.4mg)
  - Intracanalicular insert approved November, 2018
  - Indicated for the treatment of ocular pain and inflammation following ocular surgery and treatment of ocular itching associated with allergic conjunctivitis



31

OTHER "NEW" STEROIDS

- Lotepredrnol etabonate suspension 1% (**Inveltys**)
  - Proprietary mucus penetrating particle technology to increase drug delivery
  - BID for post surgical dosing
- Lotepredrnol etabonate suspension 0.25% (**Eysuvis**)
  - Approved October 27, 2020
  - Short-term (up to two weeks) for the signs and symptoms of dry eye disease. QID
    - Ocular discomfort severity scale 0-100 (improvement from about 70-58 after 2 weeks). Improved about 9 points with vehicle
    - Improvement in conjunctival hyperemia (CCLRU scale)


33

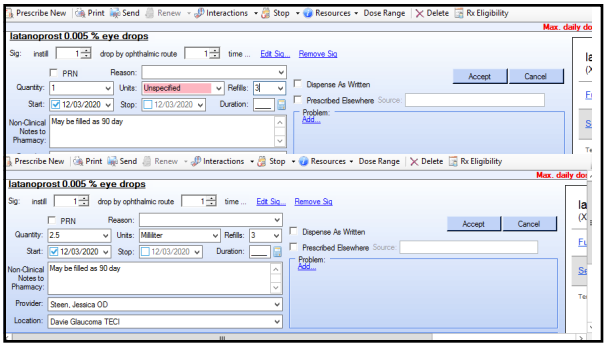
LOTEMAX SM

- Lotepredrnol etabonate ophthalmic gel 0.38%
- SubMicron Technology
  - Greater anterior chamber penetration
  - Faster drug dissolution

34

AS WE GET INTO TOPICAL OCULAR FORMULATIONS…

35



36

Bottle Design and Drop Size

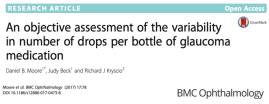
Plant-derived eye drop bottle

Sugarcane-derived material

Many droppers release upwards of 30µL per drop-also depends how you hold the drop!

Manufacturers tend to overfill bottles

Significant variation



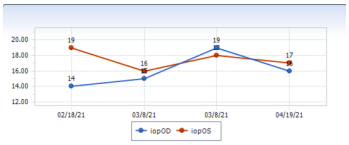
41

IOP LOWERING AGENTS

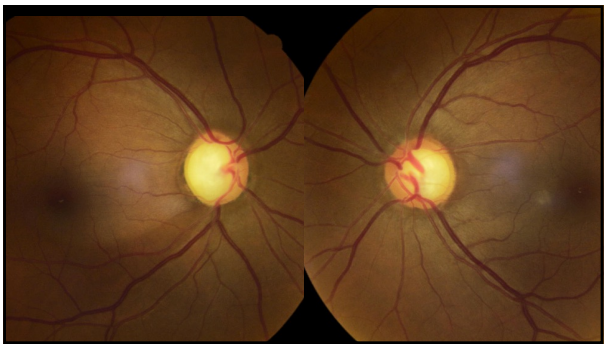
42

56 YEAR OLD AFRICAN AMERICAN FEMALE

- 56 year old African American female referred for evaluation due to suspicion of glaucoma secondary to optic disc appearance
  - No family history of glaucoma
  - No systemic diagnoses; no systemic medications

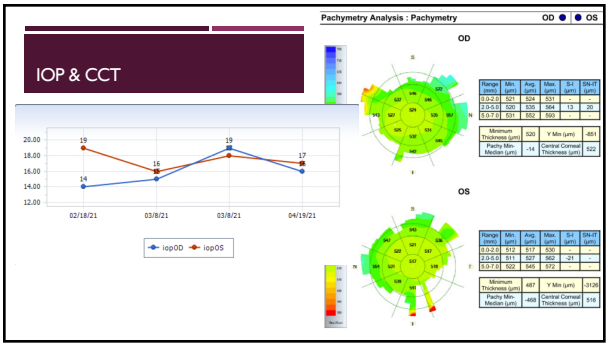


43



44

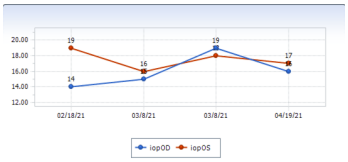
IOP & CCT



48

MANAGEMENT

- 1) Medication(s)?
  - Topical & oral
- 2) Laser?
- 3) Surgical options?



49

IOP LOWERING MEDICATION OPTIONS

- First line treatment:
  - Prostaglandin analog
    - Best adherence at FDA approved dosing
- What does 'maximum medical therapy' mean?
  - ***Classically***:
    - 1) Prostaglandin analog
    - 2-4) CAI
      - Alpha-2 agonist
      - Beta blocker
    - Rho kinase inhibitor
    - ?Pilocarpine

50

"NEW" PROSTAGLANDINS

- Latanoprostene bunod 0.024% (Vyzulta)
  - Latanoprost acid + butanediol mononitrate
    - Butanediol monohydrate releases NO which increases outflow through the trabecular meshwork and Schlemm's canal
      - Relaxes trabecular beams
- Latanoprost ophthalmic emulsion 0.005% (Xelpros)
  - BAK-free—uses a different preservative: potassium sorbate 0.47%
    - BAK can decrease goblet cell density
  - *Not available from pharmacies*
  - *Uses a "direct pay" method*

51

DIRECT PAY EXAMPLE

53

Latanoprost Drops

MD: **JESSICA STEEN OD**
3200 S UNIVERSITY DR

DAVIE, FL 33328

Express Scripts manages the prescription drug benefit for your patient at the request of their plan sponsor. Your patient's prescription benefit requires that we review certain requests for coverage with the prescriber. You have prescribed a medication for your patient that requires Prior Authorization before benefit coverage or coverage of additional quantities can be provided. Please complete the following questions then fax this form to the toll free number listed below. Upon receipt of the completed form, prescription benefit coverage will be determined based on the plan's rules.

SECTION A — Please answer the following questions *(Please fill in the entire circle ● which corresponds to your answer for each question)*

1. What is the indication or diagnosis?
   - ϴ Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Note: Open-angle glaucoma includes normal-tension glaucoma, which is also referred to as low-tension glaucoma or normal-pressure glaucoma.
   - ϴ Cosmetic conditions (for example, eyelash growth)
   - ϴ All other indications or diagnoses

54

PATIENT:
Name:

DOB:

Address:

Phone:

PRESCRIPTION INFORMATION:
Rx #:

Drug:
ROCKLATAN 0.02%-0.005% EYE DRP
Sig:
INSTILL 1 DROP INTO BOTH EYES EVERY DAY IN THE EVENING

Quantity: 2.5
Date Written: 06-21-2022

REASON FOR REQUEST:
ALTERNATIVE REQUESTED

PHARMACY COMMENTS:
ALTERNATIVE REQUESTED NOT COVERED

Thank you in advance for taking the time to review this information.
Sincerely,
Your local Pharmacist

SUGGESTED ALTERNATIVES:

55

RHO KINASE

- Rho kinase family includes proteins which regulate cell shape, motility, proliferation, and apoptosis
  - **Regulate smooth muscle contraction in the trabecular meshwork and ciliary body**
- *May also affect ocular blood blow and retinal ganglion cell survival*
  - *Role in cardiovascular procedures, corneal procedures*
  - *Role in development of fibrosis*

56

RHO KINASE INHIBITOR/NOREPINEPHRINE TRANSPORT INHIBITOR

- **Increase trabecular outflow**
- **Lower episcleral venous pressure**
- Netarsudil 0.02% (Rhopressa)
  - QHS
- Netarsudil/latanoprost 0.02%/0.005% (Rocklatan)
  - QHS
- Hyperemia-most common effect
  - Typically improves over time
  - *When do you see your patients back after altering medical therapy?*
- Subconjunctival hemorrhage
- Less common-corneal verticillata
  - Level of the epithelium

58

WHERE DO RHOPRESSA & ROCKLATAN FIT IN?

- Efficacy is similar to timolol 0.5% (BID)
  - **In clinical trials
- Ideally a second line treatment
  - Seems to work better with low/moderate IOP (<25mmHg)
- Advantage of once daily dosing vs. other typical second line medication
- Cost?

59

OMIDENEPAG ISOPROPYL 0.002% (OMLONTI)

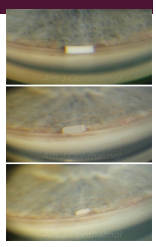
- Prostanoid EP2 receptor agonist
- Increased uveoscleral and trabecular outflow
- Dosed once daily in the evening
- Does not inhibit adipose tissue formation, does not promote eyelash growth; but can cause pigmentation increase

- *Hyperemia, macular edema (possible in pseudophakic and aphakic eyes)*
- *As of November 18, 2021: Complete response letter from the FDA identified deficiencies at contracted manufacturing sites*
  - *June 10, 2022 FDA accepted the resubmitted NDA-PDUFA date November 6, 2022-**approved September 23, 2022***

60

SUSTAINED RELEASE AGENTS

- Durysta (bimatoprost implant 10mcg)
  - Sustained release bimatoprost
    - Equivalent to about 2-3 drops of Lumigan
    - Drug release complete in 3-4 months
  - Effect lasts about 6 months (may be longer)…Extension of the ARTEMIS trial
    - ARTEMIS 1 and 2-Implant on day 1, week 16, week 32
      - Endpoint studied at end of week 12
  - No eyelash growth, no redness
  - Iris change? Probably not

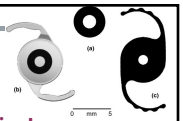


61

ANTERIOR SEGMENT MEDICATIONS

63

Presbyopia



Small aperture = reduced spherical aberration, increased depth of focus

Pilocarpine 1.25% ophthalmic solution (Vuity)

FDA approved October 30, 2021

Currently under investigation:

Phenotolamine 0.75%**alpha adrenergic antagonist (reversal of pharmacological dilation)

Phentolamine 0.75% + pilocarpine 0.4%

Brimonidine + carbachol

Pilocarpine

Pilocarpine 0.302% + phenylephrine 0.624% + pheniramine 0.0772%

64

PILOCARPINE 1.25% (VUITY)

- Presbyopia is a "prevalent and degenerative eye illness"
- Cholinergic muscarinic agonist indicated for the treatment of presbyopia in adults
  - Constricts the pupil-but maintains some response to light
- Preserved with BAK
- Pilocarpine initially FDA approved in 1974
- pHast technology
  - Adjusts to physiological pH of tear film—improves comfort and solubility

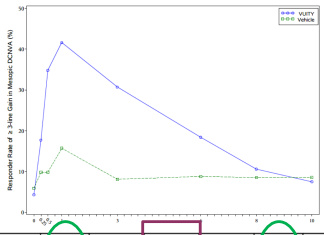
65

GEMINI 1 AND GEMINI 2

- 750 individuals (40-55 years of age)
  - Once daily dosing
- Met endpoints vs. vehicle on day 30 at **hour 3** at day 30
- Statistical significant improvement in near vision in mesopic conditions
  - 3 lines at near or more in mesopic, high contrast, binocular distance corrected near visual acuity without losing more than 1 line of corrected distance visual acuity
- Intermediate vision improvement up to 10 hours after instillation
- Most common adverse effects:
  - Headache (15%), hyperemia (5%), blurred vision (5%)

66

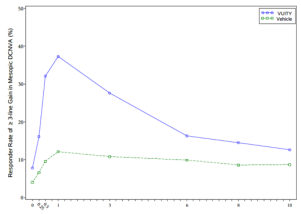
Figure 1: Proportion of Participants Achieving 3-Lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 1 (Intent-to-Treat Population)



Timepoint	Hour 0	Hour 0.25	Hour 0.5	Hour 1	Hour 3	Hour 6	Hour 8	Hour 10
VUITY (%)	4.3	17.7	34.8	41.6	30.7	18.4	10.6	7.5
Vehicle (%)	5.9	9.8	9.8	15.7	8.1	8.8	8.5	8.6
Difference (95% CI)	-1.5 (-6.4, 3.3)	7.9 (0.3, 15.5)	25.0 (16.2, 33.8)	25.9 (16.4, 35.5)	22.5 (14.3, 30.8)	9.7 (2.3, 17.0)	2.1 (-4.4, 8.5)	-1.1 (-7.1, 5.0)

67

Figure 2: Proportion of Participants Achieving 3-lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 2 (Intent-to-Treat population)



Timepoint	Hour 0	Hour 0.25	Hour 0.5	Hour 1	Hour 3	Hour 6	Hour 8	Hour 10
VUITY (%)	7.8	16.1	32.1	37.3	27.6	16.3	14.5	12.6
Vehicle (%)	4.0	6.6	9.6	12.1	10.8	9.9	8.6	8.7
Difference (95% CI)	3.8 (-0.9, 8.4)	9.4 (3.2, 15.7)	22.5 (14.7, 30.3)	25.2 (17.0, 33.4)	16.7 (9.1, 24.3)	6.5 (-0.1, 13.1)	5.9 (-0.5, 12.2)	3.8 (-2.3, 10.0)

68

Presbyopia

Soften the lens

Lipoic acid choline ester 1.5% (UNR844)
Currently under investigation

Reduces disulfide bonds between lens proteins and restore natural ability to accommodate

69

Anterior Segment

FDA approved October 18, 2021

Dry Eye Disease

Varenicline solution nasal spray 0.03mg

Activates the trigeminal parasympathetic pathway = increased production of basal tear film

70

TYRVAYA (VARENICLINE SOLUTION NASAL SPRAY 0.03MG)

- One spray in each nostril twice daily
- Most common adverse reaction:
  - **Sneezing** (82%) of patients
  - *Cough, throat irritation, nose irritation*

72

Anterior Segment

Demodex blepharitis

Lotilaner ophthalmic solution 0.25% (TP-03)
Currently in phase 3 clinical trials

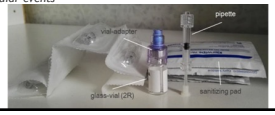
Demodex is more common than we think

Antiparasitic agent

73

OXERVATE

- Cenegermin 0.002% (20mcg/mL)
  - Recombinant human nerve growth factor
- FDA approved August, 2019 for the treatment of neurotrophic keratitis
- 6x daily for 8 weeks
- *What do you think the most common adverse effect was in the pivotal trial?*
  - *39.1% reported ocular events*



74

THYROID EYE DISEASE

- What types of thyroid disease are most likely to cause Graves disease?
- **Autoimmune thyroid disease**
- Autoantibody and autoantigen formation in the orbit leads to production of cytokines (proinflammatory) → activate T lymphocytes → activate orbital **fibroblasts** → proliferate hyaluronan which leads to soft tissue expansion = thyroid eye disease

75

TEPROTUMUMAB (TEPEZZA)

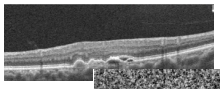
- Monoclonal antibody
  - Targets insulin like growth factor 1-binds to IGF-1R and blocks its activation
  - Fibroblasts often have IGR-1R
    - Autoantibodies have no binding site!
- Intravenous infusion-series of 8 treatments over 24 weeks
  - Every 3 weeks

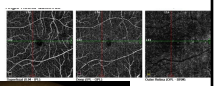
Autoantibody and autoantigen formation in the orbit leads to production of cytokines (proinflammatory) → **activate T lymphocytes** → activate orbital fibroblasts → proliferate hyaluronan which leads to soft tissue expansion = thyroid eye disease

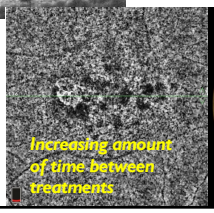
76

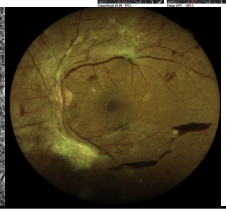
Retinal Disease

Durability









Increasing amount of time between treatments

78

Retinal Disease

Neovascular AMD

(and diabetic eye disease…more generally, retinal vascular disease)

Extracellular VEGF pathways

VEGF-A
VEGF-B
VEGF-C
VEGF-D
PlGF

TKI pathways

TIE2 activation pathways

Integrin pathways

Gene therapy

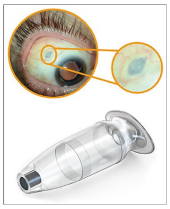
Unmet needs in management of retinal disease?

79

PORT DELIVERY SYSTEM WITH RANIBIZUMAB

As of July 1, 2022-permanent J-code

- Permanent, reusable, surgically-'placed' reservoir
- 3.5mm pars plana incision
- Holds 20 µL of custom formulation of ranibizumab
  - Phase 2: LADDER → PORTAL
  - Phase 3: ARCHWAY
    - Refill every 6 months
    - Met primary endpoints
      - 10.7 injections in ranibizumab arm vs. 2 fills

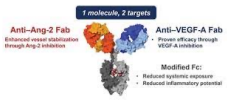


80

FARICIMAB (VABYSMO)

Permanent J-code as of October 1, 2022

- FDA approved January 28, 2022-the newest! **(currently)
- Bispecific antibody
  - Targets angiopoietin-2 (Ang-2) and VEGF-A
    - Ang-2 and VEGF work in concert-increases permeability and inflammation
- TENAYA and LUCERNE (nAMD)
  - Vs. aflibercept
  - Treated every 3-4 months (after 4 monthly doses)
    - 80% of individuals were able to go 3+ months between treatments in the first year
  - YOSEMITE and RHINE (DME)



84

COST EFFECTIVENESS OF ANTI-VEGF

- $2190 faricimab (6mg/0.05mL)-Vabysmo
- $1850 brolucizumab (6mg/0.05mL)-Beovu
- $1850 aflibercept (2.0mg/0.05mL)-Eylea
- $1170 ranibizumab (0.3mg/0.05mL)-Lucentis
- $60 bevacizumab (1.25mg/0.05mL)-Avastin

- **Bevacizumab is a typically the first line anti-VEGF in the USA**

85

WHILE WE'RE SPEAKING ABOUT BEVACIZUMAB

- Bevacizumab-vikg (Lytenava)
  - BLA submitted March 31, 2022
  - Anticipated approval late 2022 or first quarter 2023
- NORSE 2-superiority trial
  - 113 patients received 12 bevacizumab-vikg (monthly)
  - 115 patients received 5 ranibizumab injections

  1, 2, 3, 6, 9)-based on PIER (2008) dosing regiment from the package label
- ***Who did better?***

----------DOSAGE AND ADMINISTRATION----------
For Ophthalmic Intravitreal Injection Only (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the nine months after 3 initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly.

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly.

86

RETINAL BIOSIMILARS

- **The first:**
- Ranibizumab-nuna (Byooviz) FDA approved September 17, 2021
  - nAMD, macular edema following RVO, and myopic choroidal neovascularization
  - Launch July 2022-list price $1130/vial
- **The most recent:**
  - *Interchangeable biosimilar to Lucentis:* ranibizumab-eqrn (Cimerli)
    - *Launched! List price: $1360 for 0.5mg dose*

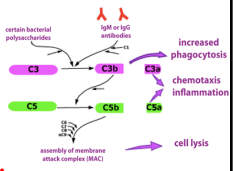
87

Retinal Disease

Dry age-related macular degeneration

CFH polymorphism increases risk of AMD (complement control protein)

Components of drusen and oxidative stress can trigger complement cascade → apoptosis



Complement over-activation is implicated in pathogenesis of AMD

Classical, alternative, lectin pathways converge to activate C3 C5 activation can lead to increased VEGF expression by the RPE

90

COMPLEMENT INHIBITORS IN GA

- ***Geographic atrophy doesn't get better-the goal is to slow progression***
- APL-2 (Pegcetacoplan)-C3 inhibitor
- Met phase 2 endpoints (FILLY) in September 2019-slows GA rate of progression **in a dose-dependent manner**
- Phase 3 trials (DERBY & OAKS)
  - Endpoints met in OAKS, very close in DERBY
  - Pooled data met endpoints
- **Slows the growth rate of geographic atrophy**
- *Fast track designation from FDA (GA)-Unmet clinical need*
  - *Interesting safety signal: increased risk of exudation*
- ***Whatever drives a druse towards GA is the same mechanism that seems to cause GA expansion***

91

COMPLEMENT INHIBITION IN GEOGRAPHIC ATROPHY

- C5 inhibitor
  - Zimura (Avacincaptad pegol)
    - Seems to protect mitochondria from oxidative damage
- Phase 3 (GATHER1)-October 28, 2019-met primary endpoints (reduction in growth rate of GA at month 12)
  - Also being investigated in Stargardt's disease
- Phase 3 (GATHER2) began June 30, 2020,
  - Phase 3 trial for intermediate stage dry AMD to begin late 2022
- *Awarded fast-track designation from FDA; expected submission to the FDA early 2023*

92

GEOGRAPHIC ATROPHY

- Elamipretide-subcutaneous injection (daily..)
  - Reduces oxidative stress at the level of **mitochondria**
    - **Acts as a mitochondrial protector**
      - **Did not meet primary endpoints (May 2, 2022)—but enhanced ellipsoid zone preservation on OCT**
        - **Shows proof of proposed mechanism**
- Risuteganib (Luminate)
  - Also investigated in DR
  - Anti-integrin therapy
- ***All about oxidative stress***

93

GENE THERAPY IN RETINAL DISEASE

- Gene augmentation
  - A specific wild-type allele of a gene of interest is inserted using a viral (adenoviral associated) vector
  - Allows expression of 'normal' gene product
- Luxturna (voretigene neparvovec-ryl) FDA approved 2017
  - RPE-65 biallelic mutation
  - Injected subretinally (performed in an OR)
  - AAV-2 vector
  - *5 year data recently released*

94

OPTIC & LUNA TRIALS (IXOBEROGENE SOROPARVOVEC)

- September 2018-FDA awarded fast track designation to a gene therapy for exudative AMD
- Aflibercept coding sequence + adenoviral associated vector (ADVM-022)
  - 30 patients
- Coding sequence (cDNA) injected intravitreally
  - Replicates in deep retina producing detectable 'aflibercept' protein in vitreous, deep retina, and choroid
- May last up to 2 years
- Durability up to 92 weeks (cohort 1-high dose)
  - High dose vs. low dose; 13 day oral steroid vs. 6 week topical ophthalmic steroid
- ***Phase 2 underway!***

95

BOTTOM LINE

- Therapeutic innovations in eye care are changing the way ocular disease is managed
  - Treatment targets and treatment modalities are rapidly evolving
- Ensuring access to the most effective medications in a particular clinical circumstance begins with understanding available options
- The role of regulatory powers, including the FDA is continuing to adapt to environmental circumstances

97

BOTTOM LINE

- Further developments aim to:
  - Identify new treatment targets
  - Reformulate existing agents
  - Develop alternative routes of administration
  - Increase the amount of time between treatments
  - Reduce cost of treatment
  - Improve patient quality of life

98

THANK YOU!

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99