Hot Topics in Retina

TRENDING NOW

Mark T. Dunbar, OD, FAAO
Bascom Palmer Eye Institute
University of Miami
Miami, FL 33136
mdunbar@miami.edu

1

Mark Dunbar: Disclosure

- Optometry Consultant/Advisory Board for:
  - Allergan
  - Carl Zeiss Meditec
  - Regeneron
  - Genentech

Mark Dunbar does not own stock in any of the above companies

2

Hot Topics in Retina

- The paradigm shift in the diagnosis and management of diabetes
- Better Treatments for Wet AMD
- The search for a treatment for dry AMD
  - Are we getting closer?
- The emergence of OCT/OCTA Imaging in retinal disease
- Targeted therapy for hereditary retinal disease

3

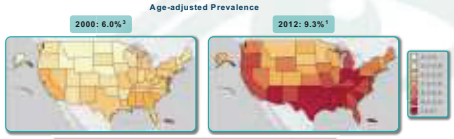
The Optometrist's Role in Diagnosing and Managing Patients with Diabetes

- Optometrists play a critical role as a part of the healthcare team managing patients with diabetes
- It is paramount to recognize the presence of diabetic retinopathy
- Recognizing when it's more than moderate nonproliferative diabetic retinopathy
- Accurate DR staging is critical for timely referral and treatment
  - Clinical exam vs. wide-field imaging

4

Fact 1:
Diabetes is Occurring in Epidemic Proportions

- Affects 9.3% of the US population (29.1 million people)[1]
- By 2050 between 1 in 5 and 1 in 3 US adults (estimated) will be diabetic



	2000	2012
Diabetes Incidence (cases/1000)	6.0[4]	7.8[1]
Obesity Prevalence (%)	20.1[5]	27.6[6]

5

6

ETDRS vs. International Classification of DR

Diabetic Retinopathy	ETDRS	International Scale
Mild NPDR	At least one Ma	Ma only
Moderate NPDR	H/Ma ≥ Standard phone 2A or soft exudates, VA, IRMA	More than just Ma, but less than Severe NPDR
Severe NPDR	One of the following: • H/Ma ≥ standard photo 2A in all 4 quadrants • VB present in at least 2 quadrants • IRMA > standard photo 8A in at least 1 quadrant	No signs of PDR with any of the following: • > 20 intraretinal hemorrhages in each of 4 quadrants; • Definite VB in ≥2 quadrants; • Prominent IRMA in ≥1 quadrant
PDR/High Risk PDR		Severe NPDR and one or both of the following: • Neovascularization; • Vitreous/preretinal hemorrhage

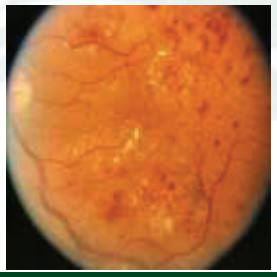
Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. Ophthalmology 1991;98:742.

7

Severe Nonproliferative Diabetic Retinopathy (NPDR)

4-2-1 Rule

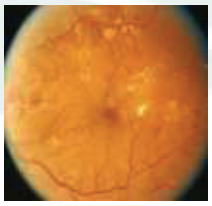
- 20 Hemorrhages & Ma in each 4 quadrants
- Significant venous beading in 2 quadrants
- Prominent IRMA in 1 quadrant



8

Risk for Progression to PDR

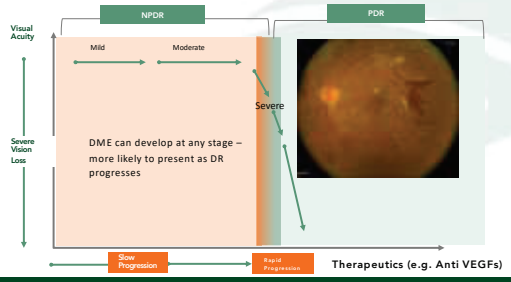
	1 year	5 year High-Risk PDR
Mild NPDR	5%	15%
Moderate NPDR	12%	33%
Severe NPDR	52%	60-75%
Very Severe NPDR	72%	75%



https://aoa.uberflip.com/i/1183026-evidence-based-clinical-practice-guideline-eye-care-of-the-patient-with-diabetes-mellitus-second-edition/59?m4=

9

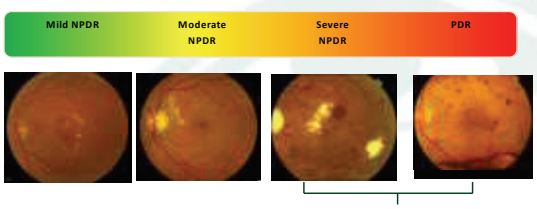
Vision Loss in Diabetic Retinopathy



10

Diabetic Retinopathy Severity Scale

International Scale

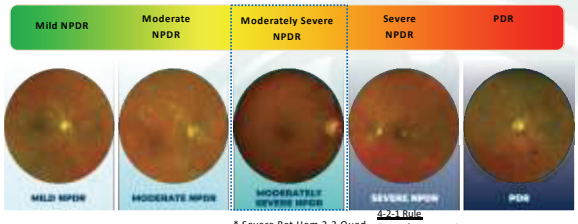


Wilkinson CP, Ferris FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales Ophthalmology 2003;110:1677-1682

11

Diabetic Retinopathy Severity Scale

International Scale



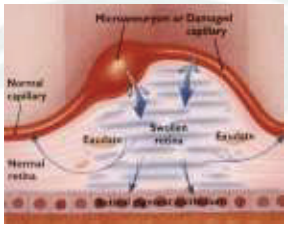
* Severe Ret Hem 2-3 Quad
* VB in 1 Quad

4-2-1 Rule
* Hem/MA 4 Quad
* VB in 2 Quad
* IRMA 1 Quad

12

Macular Edema

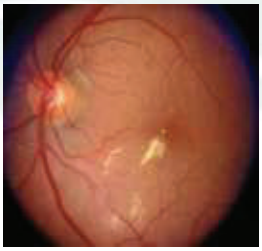
- Thickening of the retina
- Secondary to leaky microaneurysms
- **90% of visual loss in diabetes**



13

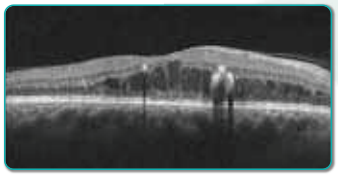
CSME

- Retinal thickening within 500 microns from the center of the FAZ
- Hard exudates associated with retinal thickening 500 microns from center of FAZ
- Zones of retinal thickening > 1 DD in area, any part of which is 1 DD from the center of the fovea

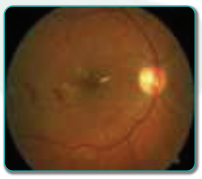


14

Diabetic Macular Edema (DME)



SD-OCT of a retina with DME



Color Fundus photo with DME

15

How we diagnose diabetic macular edema is changing

ETDRS definition has been modified in the era of OCT and anti-VEGF therapy

16

Diabetic Macular Edema (DME)

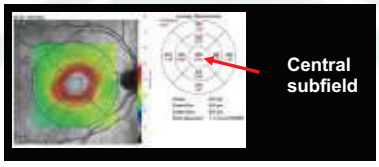
- CSME
- Center involved vs. Not center involved

17

2017 DME Classification:

Center Involved of Not?

- ETDRS definition of "clinically significant macular edema" modified in era of OCT
- Randomized clinical trials of anti-VEGF agents used presence of DME in **OCT central subfield**



Nguyen, Quan Dong, et al. "Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE." Ophthalmology 119.4 (2012): 789-801.

Boyer, David M., et al. "Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies." Ophthalmology 122.10 (2015): 2044-2052.

18

The ABC's of DME

- DRCR.net
  - Protocol I
  - Protocol T
- RISE
- RIDE
- READ

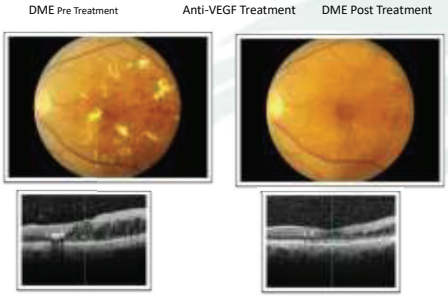
Genentech

- VISTA
- VIVID
- Bolt

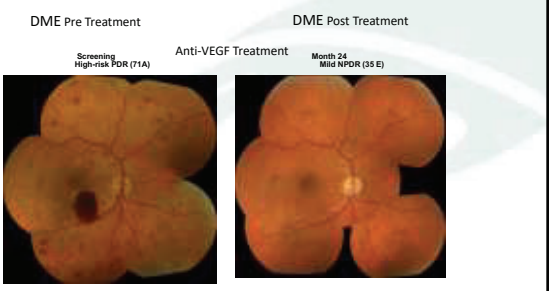
Regeneron

Essentially establishing the effectiveness of all the anti-VEGF drugs for the treatment of DME

19



20



21

"The Fate of 47…"

22

The Debate…

- Is it better to treating early – before they develop PDR?
  - Would earlier treatment result in better visual outcomes?
  - Would it result in less # of injections?
  - Does the cost/burden of treatment warrant early treatment?

23

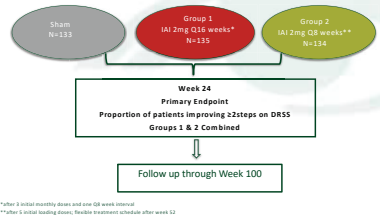
PANORAMA

- Phase 3 double-masked, randomized **Prospective Study**
- Efficacy and safety of intravitreal **aflibercep**t (IAI) in patients with **moderately severe to severe NPDR**
  - DRSS 47 & 53
- Primary Endpoint:
  - Week 24
  - Proportion of patients improving ≥2 steps on DRSS
  - IAI groups combined
- Follow up through week 100

Wykoff, CC. Keypoints from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

24

Phase 3 Double-masked, Randomized Prospective Study
Efficacy and Safety of Intravitreal Aflibercept (IAI) in Patients with Moderately Severe to Severe NPDR (DRSS Level 47 and 53) N=402

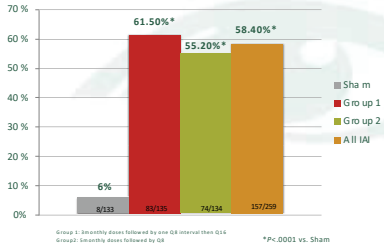


*after 3 initial monthly doses and one Q8 week interval
**after 5 initial loading doses; flexible treatment schedule after week 12

Wykoff, CC. Key points from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

25

Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS 24 weeks



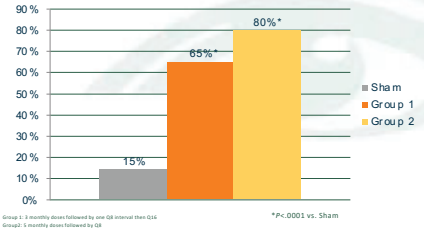
Group 1: 3 monthly doses followed by one Q8 interval then Q16
Group2: 5 monthly doses followed by Q8

*P<.0001 vs. Sham

Wykoff, CC. Key points from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

26

Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS: 52 Weeks



Group 1: 3 monthly doses followed by one Q8 interval then Q16
Group2: 5 monthly doses followed by Q8

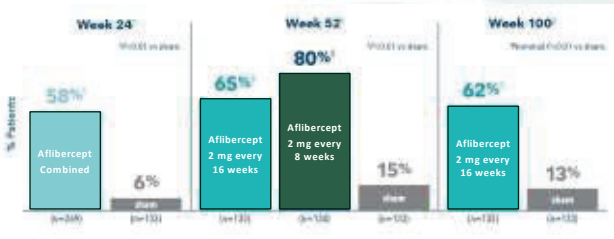
*P<.0001 vs. Sham

Aflibercept Improves Diabetic Retinopathy and Reduces Vision Threatening Complications in Phase 3 Trial; October 25, 2018. www.prnewswire.com

Wykoff, CC. Key points from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

27

Patients achieving a > 2 step improvement in ETDRS-DRSS Score at 52 and 100 Week

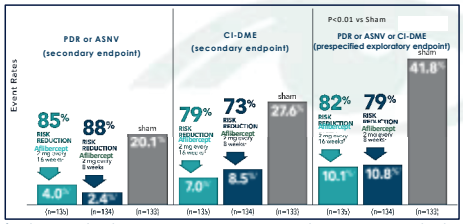


Wykoff CC. Intravitreal Aflibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR): 2-Year Outcomes of the Phase 3 PANORAMA Study. Data presented at: Angiogenesis, Exudation and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

28

Prevent the Development of PDR, ASNV, or CI-DME

Progression to PDR or ASNV or Development of CI-DME Through Week 52

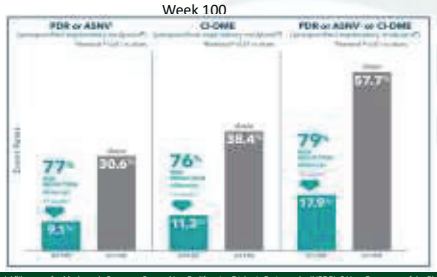


Significantly Fewer Moderately Severe to Severe NPDR Patients Progressed to PDR or ASNV, or Developed CI-DME vs Sham Through Week 52 in the PANORAMA Study

29

Prevent the Development of PDR, ASNV, or CI-DME

Week 100

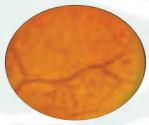


Wykoff CC. Intravitreal Aflibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR): 2-Year Outcomes of the Phase 3 PANORAMA Study. Data presented at: Angiogenesis, Exudation and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

30

Diabetic Retinopathy Severity Score (DRSS)

Level*	ETDRS DRSS Severity	Description
1	10 and 12	DR absent
2	14, 15, 20	DR questionable, microaneurysms only
3	35	Mild NPDR
4	43	Moderate NPDR
5	47	Moderately severe NPDR
6	53	Severe NPDR
7	60, 61	Mild PDR
8	65	Moderate PDR
9	71	High-risk PDR
10	75	High-risk PDR



2-step improvement in DRSS
From DRSS level 53, Severe NPDR (level6)
To DRSS level 43, Moderate NPDR (level 4)

The Diabetes Control and Complications Trial. *Arch Ophthalmol*. 1995;113:36-51; Aiello LM. *Am J Ophthalmol*. 2003;136:122-135

31

PANORAMA
Week 52 Results

- Vision threatening complications were reduced by 82% to 85% compared with sham injection
- Development of CI-DME was reduced by 68% to 74% compared with sham

32

Ophthalmology Retina October 2018

Ranibizumab Induces Regression of Diabetic Retinopathy in Most Patients at High Risk of Progression to Proliferative Diabetic Retinopathy

Charles C. Wykoff, MD, PhD,[1] David A. Eichenbaum, MD,[1] David R. Brill, MD,[1] Lauren PM, MS,[1] Anne R. Fung, MD,[1] Zdenka Hudson, MD, FRCP[1]

- The main objective of this exploratory post hoc analysis of the RIDE and RISE clinical trials was to examine DR outcomes in patients who were at highest risk for progressing to PDR (baseline DRSS levels 47/53).

33

RISE AND RIDE POST HOC ANALYSIS
PATIENTS WHO HAD NPDR AND PDR WITH DME

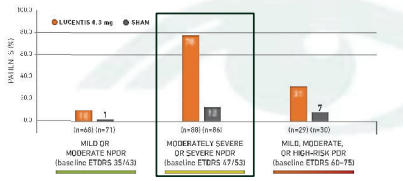
Post hoc analysis:

- Included 746 patients (LUCENTIS 0.3 mg, n=245; LUCENTIS 0.5 mg, n=247; sham, n=254) who had DR with DME and were randomized for treatment in RISE & RIDE
- DR outcomes with LUCENTIS were evaluated in patients along the spectrum of the severity scale (baseline ETDRS levels 10–75)
- Patients with prior panretinal photocoagulation (PRP) were not included in this analysis

Wykoff et al. *Ophthalmology Retina*. 2018.

34

RISE AND RIDE POST HOC ANALYSIS
≥2-STEP REGRESSION IN DR AT 2 YEARS



Limitations of this analysis include that it is post hoc (ie, not prespecified in protocols). The statistical significance of these results cannot be determined, and the clinical significance of these results is unknown. Results between groups should not be compared.

Wykoff et al. *Ophthalmology Retina*. 2018.

35

Ranibizumab induces Regression of Diabetic Retinopathy

Wycoff et al, Ophthalmology Retina October 2018

- At month 24, DR levels 47/53 **80% of eyes had a 2-step** improvement in ranibizumab treated eyes vs 12% in the sham treated eyes
- The regression of DR was not seen in earlier in less severe DR or in more severe DR
- **Study Conclusion**: In patients with baseline DR levels 47/53, ranibizumab treatment reduced the probability of patients experiencing a new proliferative event at month 36 by **3 times vs. sham treatment**

36

JAMA Ophthalmology | Original Investigation

Effect of Intravitreous Anti-Vascular Endothelial Growth Factor vs Sham Treatment for Prevention of Vision-Threatening Complications of Diabetic Retinopathy
The Protocol W Randomized Clinical Trial

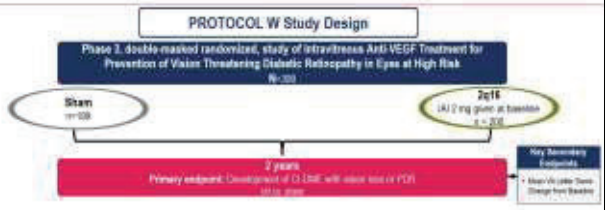
Raj K. Maturi, MD; Adam R. Glassman, MS; Jennifer Liu-Graf, PhD; Andrew N. Antoszyk, MD; Barbara A. Blodi, MD; Lee M. Jampol, MD; Daniela M. Marcus, MD; Daniel F. Martin, MD; Michele Melia, ScM; Joan Sala-Puigdollers, MD; Cynthia R. Stockdale, MSPH; Oscar S. Pusateri, MD; Jennifer K. Sun, MD, MPH; for the DRCR Retina Network

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, among eyes with moderate to severe NPDR, the proportion of eyes that developed PDR or vision-reducing CI-DME was lower with periodic aflibercept compared with sham treatment. However, through 2 years, preventive treatment did not confer visual acuity benefit compared with observation plus treatment with aflibercept only after development of PDR or vision-reducing CI-DME. The 4-year results will be important to assess longer-term visual acuity outcomes.

Jama Ophthalmology, March 30, 2021

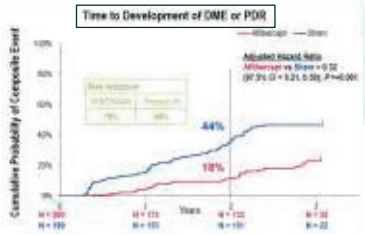
37

PROTOCOL W: EYLEA VS. SHAM IN MODERATE TO SEVERE NPDR (DRSS OF 43 – 53)



38

Protocol W: 2 Year Conclusions



- The 2-year data did not confer visual acuity benefit compared to sham group
  - Note: sham group received aflibercept once they developed DME or PDR

Jama Ophthalmology, March 30, 2021

39

Is there a benefit from early Tx of Severe NPDR?

- So, what is the benefit of early treatment if it doesn't result in any visual acuity improvement?
- Does it matter that there is a regression in DR if when all and said and done the patient ends up with the same visual outcome?

40

Artificial Intelligence

41

npj | Digital Medicine Nov 2019

ARTICLE

Deep learning algorithm predicts diabetic retinopathy progression in individual patients

In-person expert examinations are impractical and unsustainable given the pandemic size of the diabetic population. As such, AI may offer a solution to this conundrum. DL, and specifically, deep convolutional neural networks (DCNNs), can be used for an end-to-end assessment of raw medical images to produce a target outcome prediction, the authors wrote.

42

AI device for detecting diabetic retinopathy earns swift FDA approval

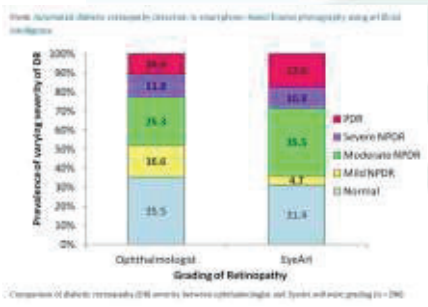
- Images captured by Topcon NW400 non-mydriatic retinal camera
- Images sent to a cloud-based server that utilizes the IDx-DR software and a 'deep learning' algorithm
- The technology was **87% sensitive and 90% specific** for detecting **more than mild** diabetic retinopathy
- The algorithm correctly identified **100% of with ETDRS level 43 or higher (moderate NPDR)**

43

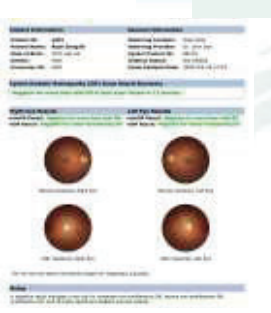
August 6, 2020 FDA Clears EyeArt: AI System for Diabetic Retinopathy Detection

EyeArt is the first FDA cleared AI technology for autonomous detection of both more than mild and vision-threatening diabetic retinopathy. It is the most extensively validated autonomous AI technology, tested in the real-world on more than half million patients and nearly two million retinal images globally.

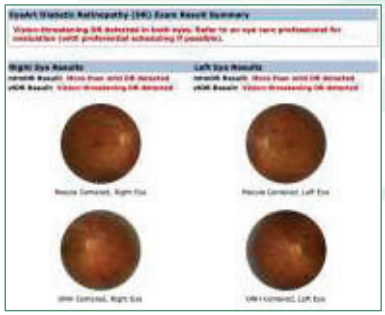
44



45



46



47

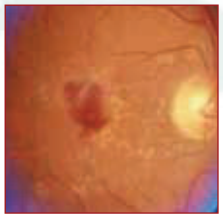
Eye

Automated diabetic retinopathy detection in smartphone-based fundus photography using artificial intelligence

48

Age-related Macular Degeneration (AMD)

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2 to CNV



49

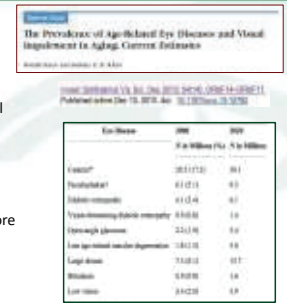
ARMD

- Patients Affected
  - 90% dry or nonexudative
  - 10 % wet or exudative
- VA < 20/200
  - 80-90% exudative
  - 10-20% dry

50

AMD "Factoids"

- 1 in 3 people older then 75 will be affected by AMD
  - The number of people > 75 is steadily increasing
  - 10,000 people turn 65 in the US every day
- By 2025, there will be **44%** more people in the US in this "high-risk" age group than there are today



51

Neovascular AMD: Risk Factors

- Emerging risk factors
  - Age[1]
  - Race[1]
  - Smoking[2]
  - Family history[3]
  - Variation in the complement factor H gene[4-6] and other genes[7]

1. Friedman et al. *Arch Ophthalmol*. 2004;122:564; 2. Kahn et al. *Br J Ophthalmol*. 2006;90:75; 3. Buch et al. *Acta Ophthalmol Scand*. 2005;83:409; 4. Klein et al. *Science*. 2005;308:385; 5. Haines et al. *Science*. 2005;208:419; 6. Sepp et al. *Invest Ophthalmol Vis Sci*. 2006;47:536; 7. Haines et al. *Invest Ophthalmol Vis Sci*. 2006;47:329.

52

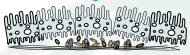
What We Now Know

- Genetic background
- Environmental/lifestyle risk factors
- The interaction between these variables, predispose to AMD
- Treatments for wet AMD target VEGF
  - Hugely successful
- The future of AMD will target dry AMD

53

Current Hypothesis for AMD Pathophysiology

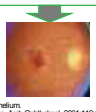
Oxidative stress **Genetic predisposition** **Environment**



Complement deposition between retinal pigment epithelium (RPE) and Bruch's membrane[1]
Loss of complement regulation[2]
Blood-retina barrier breakdown[2]

Dry AMD

Wet AMD

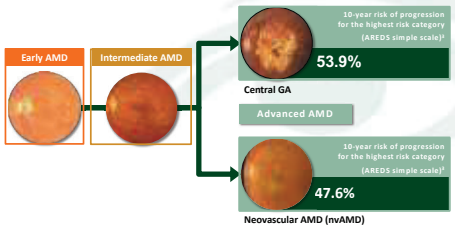


Geographic atrophy

GA, geographic atrophy; RPE, retinal pigment epithelium.
1. Age-Related Eye Disease Study Research Group. Arch Ophthalmol. 2001;119:1417-1436. 2. Ambati J, et al. Nat Rev Immunol. 2013;13(6):438-51.

54

AMD Is the Leading Cause of Blindness for Caucasians in the US[1]



AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; GA, geographic atrophy; nvAMD, neovascular AMD.
1. Eye Diseases Prevalence Research Group. Arch Ophthalmol. 2004;122(4):477-485. 2. Ferris FL, et al. Ophthalmology. 2013;120(4):844-851. 3. Chew EY, et al. JAMA Ophthalmol. 2014;132(3):272-277. 4. Age-Related Study Disease Study Research Group. Arch Ophthalmol. 2005;123(11):1570-1574.

55

Anti-VEGF Standard of Care for Wet AMD

- Require frequent injections
- 1/3 of eyes develop atrophy
- Significant vision loss after 5–7 years of therapy

56

39 Clinical Trials on Wet AMD

57

58

59

New Treatment for Wet AMD

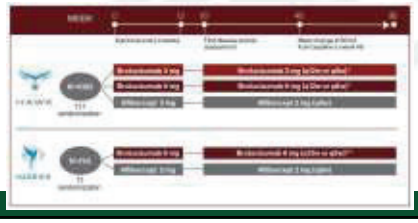
- Beovu (Brolucizumab - Novartis)
  - Small size of the molecule allows higher dosing per volume results in a longer-lasting effect
- Abicipar (Allergan)
- Port Delivery System (Genentech)
  - Surgically implanted, refillable reservoir
  - Median time to first refill was 18 months
    - But large range: 7-8 months - 2 years

60

(Brolucizumab)

HAWK and HARRIER:

- 2 year randomized, double-masked, multicenter studies comparing the efficacy and safety of brolucizumab versus aflibercept in nAMD

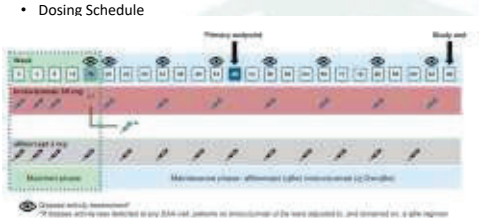


61

Beovu (Brolucizumab)

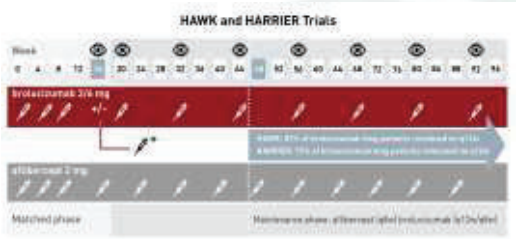
HAWK and HARRIER:

- Dosing Schedule



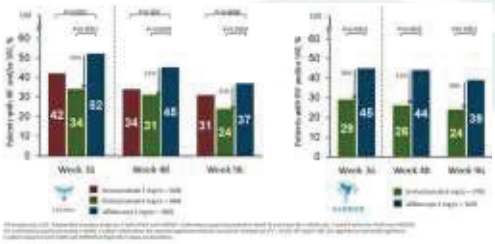
62

Majority of Patients who Completed Week 48 on a q 12 Interval Remained on a q 12 Week Interval Until week 96 Completed



63

HAWK and HARRIER: Fewer patients on brolucizumab had IRF and/or SRF fluid at Weeks 16, 48, and 96.



64

Tx with Broluizumab

- 50% of patients were maintained on q12 week dosing without requiring rescue treatments.
  - Eyes that could not be maintained on a regimen of q12 weeks tended to show a need for early re-treatment
- ~ 1/3 fewer patients (vs Lucentis) had fluid (IRF and/or SRF)
- At week 48, 31% fewer patients had IRF and/or SRF in HAWK, and 41% fewer in HARRIER ($P < .0001$ for both).
- Patients receiving brolucizumab 6 mg demonstrated superior reductions in central subfield thickness.

65

Beovu (Brolucizumab)

- Received FDA approval October 7, 2019 for treatment of neovascular AMD
- Shortly after approval the American Society of Retina Specialists (ASRS) began receiving reports of inflammation following intravitreal brolucizumab administration for NVAMD
- Several reported cases included **retinal vasculitis** that frequently resulted in vascular occlusion and **significant vision loss**

66

Abicipar (Allergan)

Accepted by FDA Sept 2019

- Abicipar pegol is a DARPin directed to bind all VEGF-A isoforms, similar to ranibizumab
- It has a higher affinity and a longer half-life than ranibizumab (>13 days vs. 7.2 days) with longer duration and need for less frequent injections
- *CEDAR and SEQUOIA*
  - *90% had stability of vision*
  - *6-8 injections vs.* 13 ranibizumab injections at 52 week

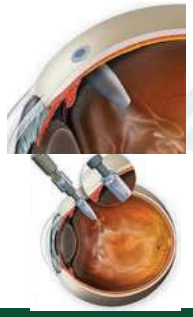
67

68

Port Delivery System (Genentech)

- Surgically implanted, refillable reservoir
- Median time to first refill was 18 months
  - But large range: 7-8 months - 2 years

69



70

Port Delivery System (PDS)

- A permanent refillable eye implant that continuously delivers ranibizumab over a period of months
- Refilled every six months, PDS demonstrated non-inferior and equivalent efficacy compared to the standard of care – monthly ranibizumab eye injections
- Archway Study: Phase 3 results presented July 2020
  - Port delivery equivalent to monthly Ranibizumab injections
  - 248 pts PDS vs. 167 monthly injections
  - **98% did not need supplement injection**

71

Wet AMD Patients Prefer PDS Implant Over Injections

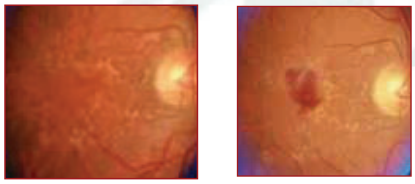
Patients underwent only 2 procedures in 40 weeks.

- Patients with wet AMD who participated in Genentech's phase 3 ARCHWAY trial strongly preferred the PDS sustained-release implant over regular injections of ranibizumab. More than 93% of the 228 patients who received the implant cited such reasons as fewer injections, reduced discomfort, and less nervousness and apprehension. All of the patients in the trial had been previously treated with anti-VEGF injections.
- Patients in the trial who did not receive the PDS had an average of 10 injections over 40 weeks, while those with the implant had only the initial implantation in the operating room and a mandated in-office refill at 24 weeks. Only 4 of 228 patients required a PDS refill prior to 24 weeks.
- At AAO Virtual 2020, Nancy Holekamp, MD, reported that the PDS with a custom formulation of ranibizumab provided essentially the same efficacy as monthly injections of regular ranibizumab. Vision and retinal thickness were both maintained with the PDS at basically the same level as with regular ranibizumab, although there was a wider variety of mild adverse events associated with the surgical procedure. The PDS is also currently in the phase 3 PAVILION trial for diabetic retinopathy and the phase 3 PAGODA trial for diabetic macular edema.

72

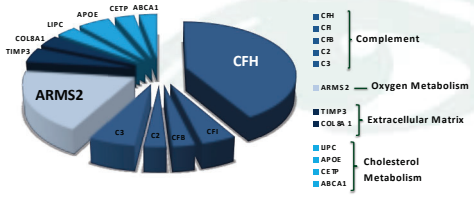
Holy Grail

- Treating Dry AMD and GA
  - Preventing it from progressing to Wed AMD



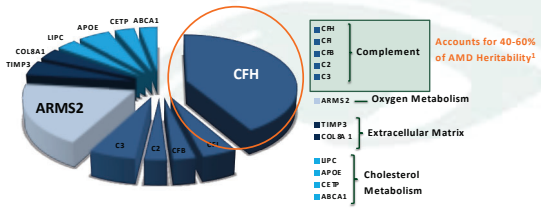
73

Key Genes Involved in the Development of AMD



74

Key Genes Involved in the Development of AMD

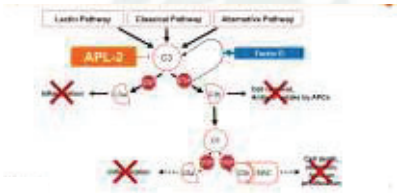


1. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: Genetics and biology coming together. Annu Rev Genomics Hum Genet. 2014;15:151-171.

75

Potential Treatments for Geographic Atrophy

- APL-2: C3 inhibitor by Apellis
- Blocks all the pathways of complement activation

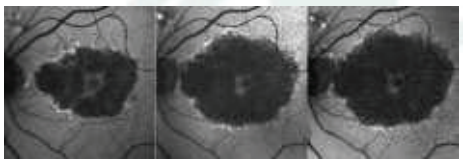


MAC = membrane attack complex

76

Filly 2 Trial

- Phase 2 FILLY trial: showed a 29% reduction in the growth of geographic atrophy lesions after 12 months in the monthly treatment group, and a 20% reduction in the **every-other-month** treatment group



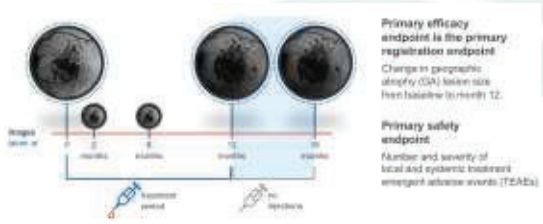
77

Filly Key Takeaways

- APL-2 reduced the progression of GA in the largest Phase 2 GA trial (n=246)
- Results correlated treatment frequency with increasing effect size over time
- Upon discontinuation of APL-2 treatment effect declines

78

Filly Time Line and Endpoints

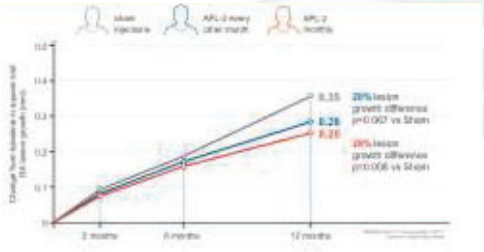


79

Lesion growth by 6 month periods (square root) – 18 months

80

APL-2 Shows GA growth at 12 months (square root)



81

18 Month Data

February 2018

- "The 18-month results of the FILLY trial support the positive effect seen at 12 months. In the FILLY trial, APL-2 significantly reduced the growth of GA, and may for the first time offer these patients hope of preserving their vision. We eagerly anticipate the start of the Phase 3 trials."

82

Phase 3 Study: DERBY/OAKS

Dec 2018

- Company voluntarily implemented a temporary pause in dosing in the DERBY and OAKS Phase 3 trials due to observed cases of **non-infectious inflammation in patients** treated from a single manufacturing lot of APL-2 intravitreal drug product.

83

July 2020

84

Risuteganib for Dry AMD

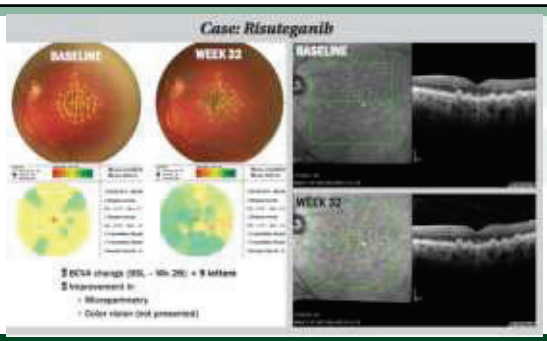
- Risuteganib is a small synthetic peptide that regulates integrin function
- Downregulates oxidative stress response and restores retinal hemeostasis

85

Luminate (Risuteganib) Phase 2 Study

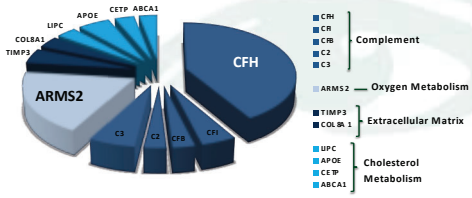
- 40 patients with **intermediate dry AMD** randomized to receive either intravitreal 1.0mg risuteganib or sham injection
- **48% of patients in Tx group** vs. 7% in sham group had a **≥ 8 letter improvement** from baseline at 28 weeks
- The clinical trial met its primary endpoint

86



87

Key Genes Involved in the Development of AMD



88

Genetic Testing for AMD

- Artic Dx is the only commercially available genetic test for identifying high-risk AMD patients
- For those high risk patients – can genetic testing be used to determine which patients benefit the most from nutritional supplements?
- No **prospective** clinical trials showing the value
  - There are retrospective studies but the data analysis varies

89

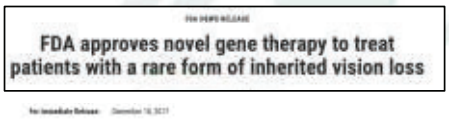
The Compliment System

- Complement Factor H is a gene that gives instructions for making Factor H
  - Factor H is an important *inhibitory regulator* of this system
- **Complement Pathway** is one of the body's primitive defense immune systems
  - Made up of a group of proteins that:
    - Mounts inflammation
    - Destroys foreign invaders
    - Removes debris resulting from that destruction
- Drusen contain most all of the proteins that make up the complement system

90

Gene Therapy for Hereditary Retinal Disease

- Hereditary retinal dystrophies are a broad group of genetic retinal disorders associated with progressive visual dysfunction
- Caused by mutations in any one of over 220 different genes



91

Leber's Congenital Amaurosis (LCA)

- **Monogenetic inherited retinal disease** (IRDs) that develops as a result of a Biallelic RPE65 mutation
- Approximately 1,000 to 2,000 patients in the U.S.
- Biallelic mutation carriers have a mutation (not necessarily the same mutation) in both copies of a particular gene (a paternal and a maternal mutation)
- The RPE65 gene provides instructions for making an enzyme that is essential for normal vision
- Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 activity, blocking the visual cycle and resulting in impaired vision
- Individuals with LCA will experience progressive deterioration of vision over time beginning in childhood or adolescence, ultimately progresses to complete blindness

92

Genome Editing and Gene Therapy to Treat Angiogenesis
New developments have the potential to change the way retina specialists treat disease.

- **L**uxturna (voretigene neparvorec-rzyl; Spark Therapeutics) became the 1st in vivo gene therapy approved by the US Food and Drug Administration, in 2017
- This historic landmark demonstrated that gene therapy is not only safe and effective, but also that it is potentially the answer to a number of medical conditions
- This new frontier of precision medicine aims to target disease more directly. These therapies are exciting in that they may be a one-time treatment delivering genes that express therapeutic factors for months or years..

93

Biallelic RPE 65 Mutation

- 41 patients between the ages of 4 and 44 years enrolled
- All participants had confirmed biallelic RPE65 mutations
- The primary endpoint: Ability to navigate an obstacle course at various light levels
  - The group of patients that received Luxturna demonstrated significant improvements in their ability to complete the obstacle course at low light levels as compared to the control group.

94

Gene Therapy for LCA

- Luxturna works by delivering a normal copy of the RPE65 gene directly to retinal cells
- These retinal cells then produce the normal protein that converts light to an electrical signal in the retina to restore patient's vision loss
- Luxturna uses a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as the vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision

95

2 Main Delivery Approaches for Gene Therapy

- Adenoviral vectors
  - Examples of viral vectors include adenoviruses, adeno-associated viruses (AAVs), and lentiviral vectors
  - AAV viruses have shown significant promise due to safety profile and proven efficacy
- (CRISPR) and CRISPR-associated (Cas) proteins,
  - "**Clustered regularly interspaced short palindromic repeats**"
  - The CRISPR-Cas9 system can be used to edit the genome of any organism
- Mechanism of delivery can vary:
  - Intravitreally, subretinally, or suprachoroidally

96

Gene Therapy in Eye Care

- 2 companies are using adenoviral vectors (AAV) to deliver genes that makes cells produce either a ranibizumab-like protein or an aflibercept-like protein
  - Reduce/Stop the need to anti-VEGF injections
- Numerous companies are using this same technique to target monogenetic inherited retinal degenerations
- Allergan is using viral vectors to deliver CRISPR-Cas9 to genetically treat Leber congenital amaurosis.
  - The is a very precise gene editing technique

97

Gene Editing for AMD: RGX-314: (Regenxbio)

- RGX-314: (Regenxbio) is a gene therapy that is delivered by subretinal injection and induces the eye to produce an anti-VEGF A fab
  - This product is a monoclonal antibody fragment, which is similar to ranibizumab, that binds to and neutralizes VEGF
- Currently in phase 1/2a, multicenter, dose-escalation study
- Given by a one-time subretinal delivery of the AAV8 viral vector that delivers the encoded gene
- A single treatment that has the potential to produce constitutive anti-VEGF A and eliminate or drastically decrease the need for additional intravitreal injections.
- Early results have demonstrated that the effects appear to be dose dependent with high viral loads leading to more efficacious treatment
- The higher-dose cohorts, 4 and 5, have shown the most significant results
  - At 1 year, there was a 61% and 85% reduction of anti-VEGF injections in cohorts 4 and 5, respectively, while 73% of patients (8 of 11) in cohort 5 remained anti-VEGF injection free.
  - The phase 2 trial (AAVIATE; NCT04514653) will consist of a new suprachoroidal delivery system that will bypass the need for intravitreal surgery and delivery..

98

Clustered regularly interspaced short palindromic repeats" (CRISPR) and CRISPR-associated (Cas) proteins

- CRISPR-Cas9 is an antiviral defense mechanism that has been modified as a genetic engineering technique where particular genetic sequences can be cut at a desired location, allowing removal of existing genes or addition of new ones
- The CRISPR-Cas9 system can be used to edit the genome of any organism

99

Gene Editing for AMD: ADVM-022

- ADVM-022 (Adverum Biotechnologies) is a gene therapy that was designed to produce anti-VEGF A fusion aflibercept protein via the AAV.7m8 viral vector
- Delivered by intravitreal injection,
- Currently in phase 1 clinical trial (OPTIC; NCT03748784) assessing 30 participants and 2 different dose groups with a single intravitreal injection.
- The multicenter, dose-ranging trial was designed to assess the safety and tolerability of a single intravitreal ADVM-022 in patients with nAMD who are responsive to anti-VEGF treatment
- Recent updates revealed that patients in this highest dose cohort did not require rescue injections as far as 15 months out from initial treatment
  - All 6 patients in the high-dose group and 10 of 15 in the low-dose group were rescue-injection-free at the 18-month time point.

100

Gene Therapy for AMD: AAVCAGsCD59

- AAVCAGsCD59 (Hemera Biosciences) is an AAV2 gene therapy delivered as an intravitreal injection that directly blocks membrane attack complex (MAC) for the treatment of nAMD
- Currently Phase 1 multicenter, open-label study to assess the efficacy and safety of 2 doses of the AAV serotype 2 (AAVCAGsCD59) expressing sCD59 administered via intravitreal injection 7 days after a single intravitreal injection of anti-VEGF (NCT03585556)
- 25 total participants enrolled
  - Interim results have shown that of 22 patients with at least 6 months of therapy, 4 of 22 (18%) have not required retreatment
  - Of 11 subjects with at least 12 months of therapy, 2 (18%) have not required retreatment

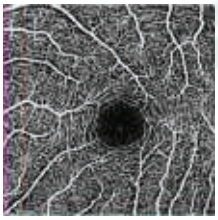
101

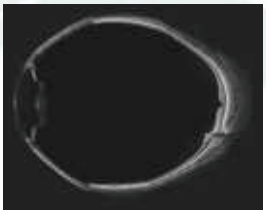
CRISPR and Cas protein gene editing

- This technology is able to directly target angiogenesis at a genetic level and permanently disrupt or reduce the production of pathologic factors
- CRISPR-Cas treatment can potentially be delivered by directly manipulating the genetic code
- BRILLIANCE study (Allergan; Editas Medicine) Phase 1/2, a CRISPR-Cas-based genome editing treatment for the treatment of Leber congenital amaurosis type 10 (NCT03872479).
- 18 participants will be enrolled in up to 5 cohorts to evaluate up to 3 dose levels of AGN-151587 in this study
  - While this work is looking at an inherited retinal disease, the early results look promising in clinical trials and could one day be applicable to a number of diseases, including those with abnormal vasculature.
  - This is the first time this technology has been used for gene therapy in the eye.
  - The medication is administered via a subretinal injection

102

The Emerging Role of OCT/OCTA in Retinal Disease





103

The Evolution of OCT Imaging

- OCT has changed how clinicians look at the retina
- The assessment of retinal abnormalities based on OCT imaging has advanced eye care
- OCT in Optometry practices
- As the technology has evolved -> prices continue to come down

104

Latest Advancement in OCT Technology

OCT Angiograpy (OCTA)

- Zeiss
  - On the Cirrus 5000, Cirrus 6000
- OptoVue
  - Avantis
- Heidelberg Spectralis
- Canon

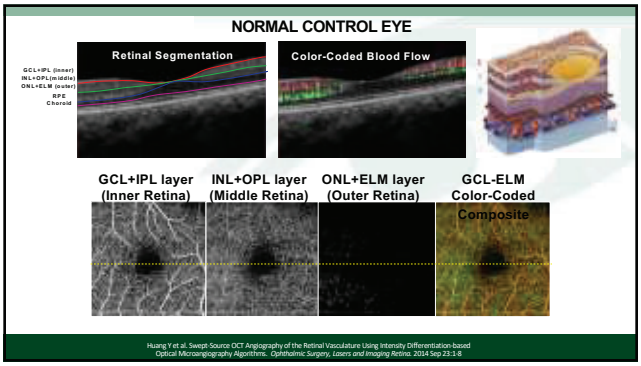
105

OCT Angiography (OCTA)

The Basic Idea of How it Works:

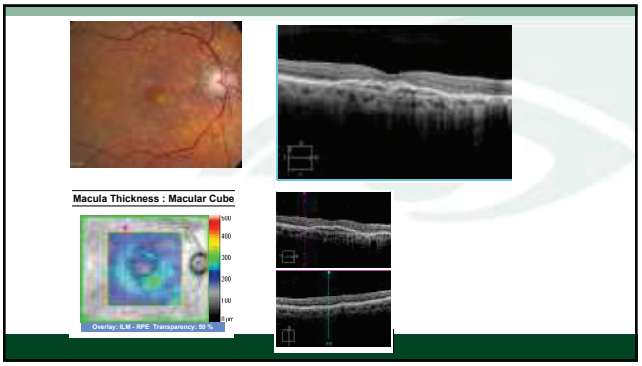
- **Capturing motion** in the retina
- Scans at 68,000 A-scans per second
  - Traditional SD OCT scan at 28,000 to 40,000 A- scans per second
- Compares repeat scans acquired at the same position in the retina to look for changes - motion

106



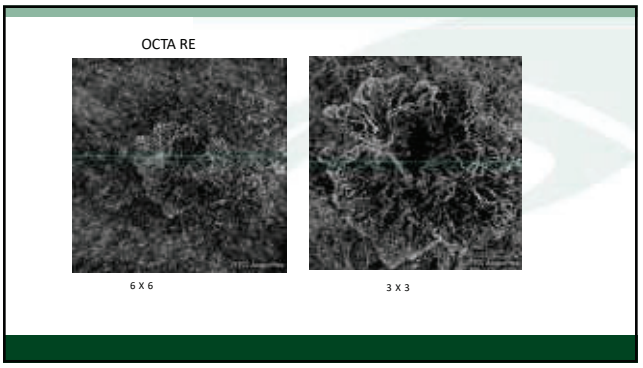
Huang Y et al. Swept-Source OCT Angiography of the Retinal Vasculature Using Intensity Differentiation-based Optical Microangiography Algorithms. *Ophthalmic Surgery, Lasers and Imaging Retina.* 2014 Sep 23:1-8

107



108

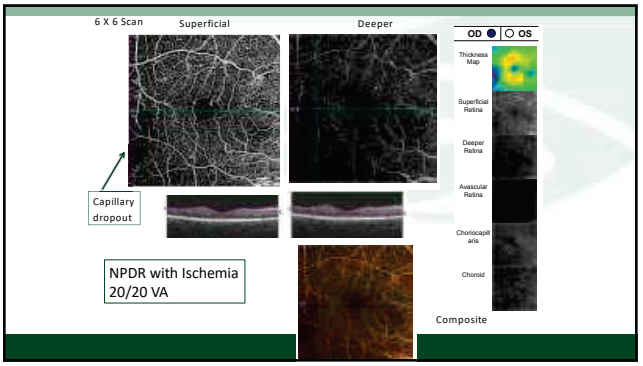
109



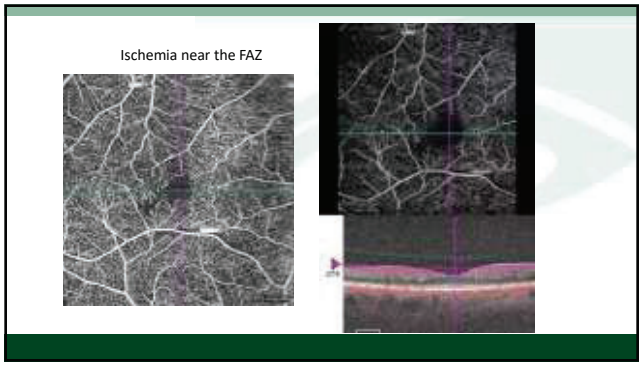
110

Diabetic Retinopathy

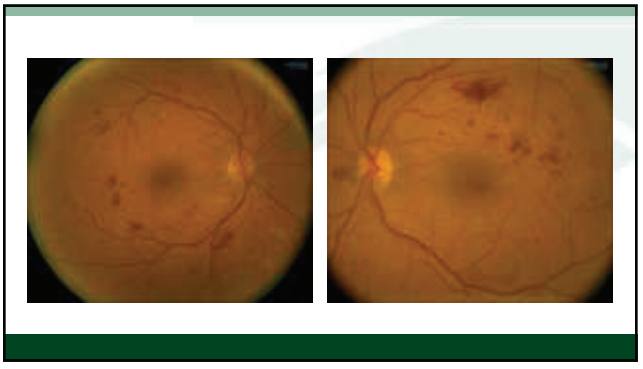
111



112



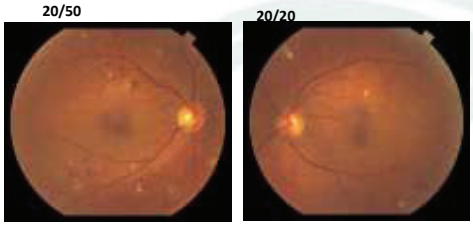
113



114

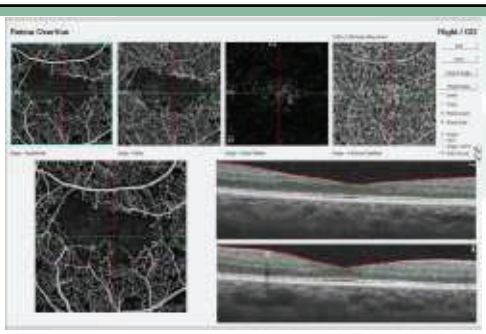
DM OCT-A CASE

20/50 20/20



Case provided by Steve Ferrucci, OD

115



116

Extensive FAZ Measurements Elevate Assessment of Diabetic Eyes

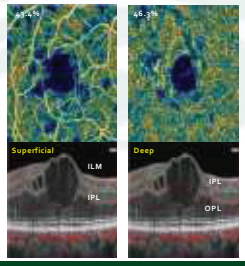
- FAZ measurements based on full retina vasculature (ILM ~ OPL):
  - Area
  - Perimeter
  - Foveal vessel density in a 300µm wide region around FAZ (FD-300)*

*AI and FD-300 measurements are based on the methods described by Dr. Richard Rosen and Dr. Toco Chui in ARVO 2016.

117

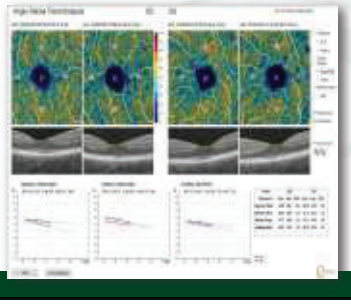
Deep Plexus Vessel Density Map Enhances Analysis

- Vessel density analysis provided for
  - Superficial (SVC)
  - Deep (DVC)
- Vessel density of DVC enabled with 3D PAR



118

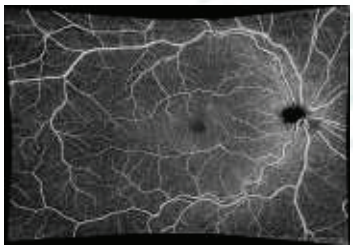
OU Vessel Density Trend Report



119

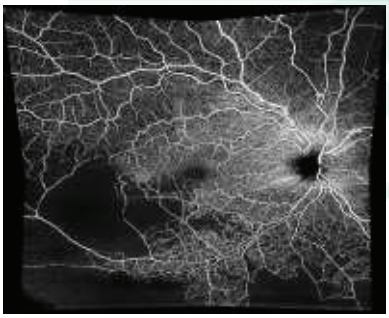
There is a need for Wide-Field Angiography

14x10mm Montage of five 6x6 OCTA scans



Zeiss Angioplex

120



121

Swept Source OCT

- Topcon: Triton
- Zeiss: PLEX Elite

122

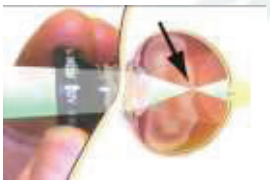
I was told there was nothing to do about my floaters?

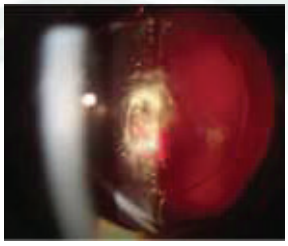
"I am a 45 yo Male and am very bothered by floaters in my vision. They are constantly in my vision and interfere with may daily activities. I was told there was nothing I can do?"

123

Options for Treatment of Floaters

- Yag vitreoloysis
- Pars plana vitrectomy





124

Important Considerations in Patients with Floaters

Are they acute or chronic?

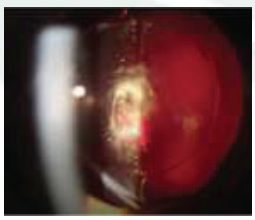
- Acute Floaters – often from PVD
  - Usually resolve
- Chronic floaters that impact daily activities

125

Reasons for Surgery for Floaters

Symptoms that impact the quality of life

- Unable to read continuously
- Unable to safely drive a car
  - The floaters/cloud moves in front of their vision and they nearly have to pull over for fear of having an accident
- Affects ability to perform your job



126

The Ideal Candidate for Treatment of Floaters

- Symptomatic
- Pseudophakic
- PVD

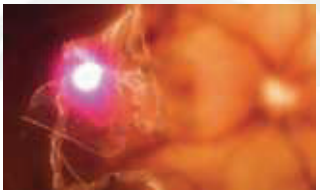
The **NOT** Ideal Candidate for Treatment of Floaters

- Young
- Phakic
- Attached vitreous
- High myope

127

Laser Vitreolysis for Floaters

- Done with a Yag
- Highly variable results
- Complications:
  - Cataract (hitting the lens)
  - Posterior capsule tears
  - Retinal burns
  - Foveal burns
  - Choroidal rupture
  - Choroidal hemorrhages
  - Retinal tear



128

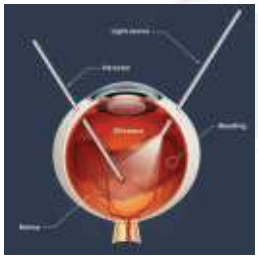
Long-Term Follow-Up of Efficacy and Safety of YAG Vitreolysis for Symptomatic Weiss Ring Floaters

- 35 of 52 patients randomized to Yag vitreolysis or Control followed for 2.3 yrs
- 50% felt their symptoms were significantly or completely better at 6 mo
  - ~60% overall improvement in symptoms
- 3 patients developed retinal tears after 6 mo (not symptomatic)

Ophthalmic Surg Lasers Imaging Retina 2020

129

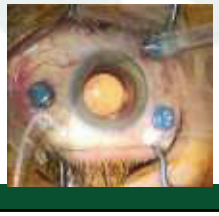
Is Vitrectomy a Better Option?



130

Vitrectomy 2021

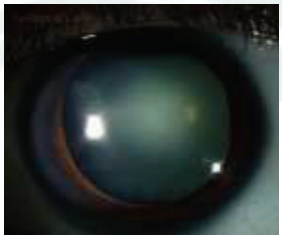
- Smaller-gauge instruments (25 or 27) compared with the 20-gauge needles used less than 15 years ag
- Smaller vitrectomy instruments allow for sutureless procedures
  - Smaller sclerotomy
  - Trocars allow for small, thin-wall cannula
- Less inflammation
- Fewer complications
- Much greater success rate



131

Risk Factors for Vitrectomy

- Cataract
- Retinal tear or detachment
- ERM/Macular pucker
- Macular edema
- Endophthalmitis



132

ARVO Annual Meeting Abstract | June 2013

Long-term Safety of Vitrectomy for Patients with Floaters

- 66 eyes in 52 patients (age = 63 ± 12 years) were included
- 36/66 **(54.5%)** eyes were **phakic**
- Average duration of coping was 30 months
- Etiology of floaters was PVD in 44/66 (67%), myopia in 19/66 (28%), asteroid hyalosis in 8/66 (12%)
- Retinopexy for retinal breaks occurring at the time of PVD was performed in 16 eyes (36% of all eyes with PVD; 24% of all eyes), a minimum of 3 months prior to vitrectomy
- PVD NOT induced and vitreous remained intact peripherally
- Main outcome: incidence of ret tears/detachments and cataract requiring surgery

133

ARVO Annual Meeting Abstract | June 2013

Long-term Safety of Vitrectomy for Patients with Floaters

- Floater symptoms resolved in 65 of 66 eyes (98.5%)
- No patients (0/66; 0%) developed retinal breaks, hemorrhage, infection, or glaucoma (3 mo – 3 yrs)
- No retinal breaks/ detachments in the 22 patients without PVD pre-operatively (0/22 vs 9/30)
- Only 7/36 (19%) phakic eyes developed cataracts requiring surgery, an average of 16.5 months post-vitrectomy (7/36 vs 18/36 (50%)

134

Long-Term Safety and Efficacy of Limited Vitrectomy for Vision Degrading Vitreopathy Resulting from Vitreous Floaters

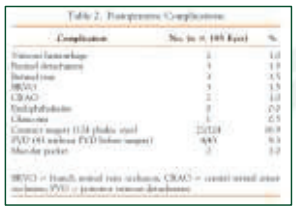
Methods

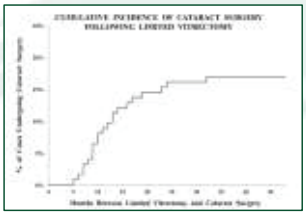
Limited vitrectomy with 25-gauge instruments was performed without surgical PVD induction, preserving 3 to 4 mm of retrolental vitreous in phakic eyes. Follow-up averaged 32.6 ± 23.3 months (range, 3–115 months), with 2 years or more in 144 eyes, 3 years or more in 69 eyes, 4 years or more in 51 eyes, and 5 years or more in 24 eyes.

Conclusions

Limited vitrectomy for Vision Degrading Vitreopathy decreases vitreous echodensity, improves patient well-being, improves VA, and normalizes CSF. The long-term efficacy and safety profiles suggest this may be a safe and effective treatment for clinically significant vitreous floaters, warranting a prospective randomized trial.

135





136

Hot Topics in Retina: Summary

- Exciting time for innovative treatments for retinal disease
- Paradigm shift in the management of diabetic retinopathy
  - Earlier treatments
  - Earlier referrals
- New Treatments for Wet AMD that may reduce the burdon to treatments for patients
  - Emerging treatments in the pipeline for dry AMD
- We are witnessing the dawn of a new age in using genetics to treat eye disease
- Imaging continues to get better and better and important part of clinical practice

137