Vision Quest: Modernizing the Approach to Retinal Diseases With New and Emerging Therapies

Rishi P. Singh, MD
Staff Physician and President, Cleveland Clinic Martin Health, Cleveland Clinic Florida
Professor of Ophthalmology, Case Western Reserve University
Cleveland Clinic Lerner College of Medicine
Stuart, FL

1

Financial Disclosures

- **Dr Rishi Singh** discloses the following
  - Personal fees from Apellis Pharmaceuticals, Iveric Bio, EyePoint Pharmaceuticals, REGENXBIO, Genentech, Bausch + Lomb, Zeiss, Alcon, and Regeneron Pharmaceuticals; research grants from Janssen

All relevant financial relationships have been mitigated.

- During the course of this lecture, Dr Singh may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

2

Learning Objectives

- Apply knowledge of the pathophysiology of AMD, DR/DME, ROP, and RVO to diagnostic and therapeutic strategies
- Identify patients with AMD, DR, ROP, and RVO who could benefit from anti-VEGF agents using guideline-recommended care
- Analyze clinical trial data on the efficacy and safety of anti-VEGF agents for the management of patients with AMD, DR, ROP, and RVO
- Develop treatment plans for patients with AMD, DR, ROP, and RVO based on disease characteristics and up-to-date clinical trial data

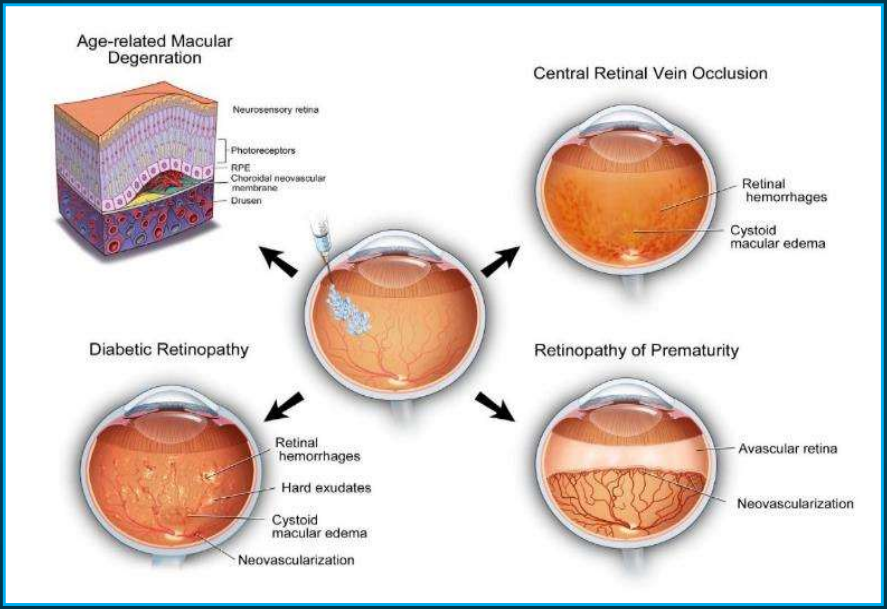
AMD = age-related macular degeneration; DR = diabetic retinopathy; ROP = retinopathy of prematurity; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.

3

Overview of VEGF-Related Retinal Diseases

4

VEGF Implicated in Multiple Retinal Diseases



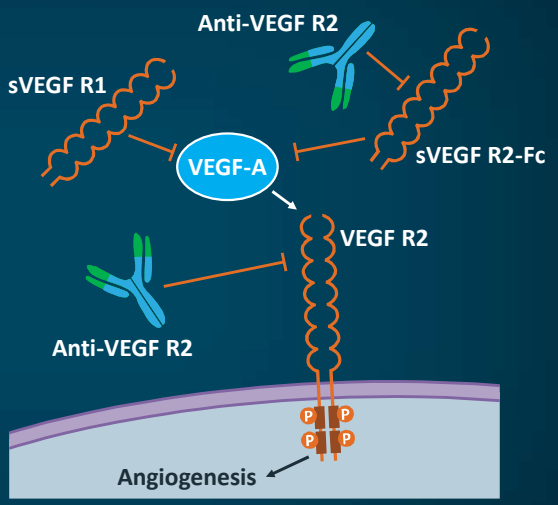
RPE = retinal pigment epithelium.

Stewart MW. *Mayo Clin Proc.* 2012;87(1):77-88.

5

The Role of VEGF

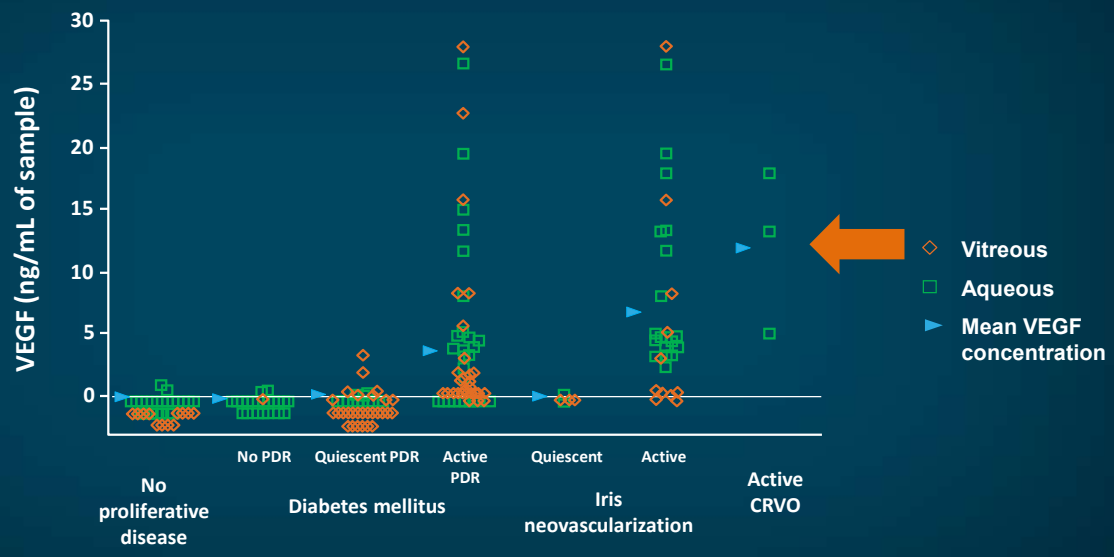
- VEGF is a glycoprotein normally secreted in various parts of the body as part of a normal healing response
- Can also be pathologically upregulated by retinal injury
- Excess VEGF can weaken retinal vessel walls, increasing permeability
  - Making the vessel "leaky"
- Excess VEGF can also promote neovascularization



Science of CRVO. An informational guide to central retinal vein occlusion (http://www.angio.org/downloads/Informational_Guide-Science_of_CRVO.pdf). Lazarus R. How do anti-VEGF injections work? 2020 (https://www.optometrists.org/eye-conditions/management-of-ocular-diseases/diabetic-retinopathy/how-do-anti-vegf-injections-work/). Turbert D. Anti-VEGF treatments. 2019 (https://www.aao.org/eye-health/drugs/anti-vegf-treatments). R & D Systems. Soluble VEGF R2: controlling lymphangiogenesis (https://www.rndsystems.com/resources/articles/soluble-vegf-r2-controlling-lymphangiogenesis). URLs accessed 4/23/2024.

6

VEGF Levels Are Elevated in Patients' Vitreous

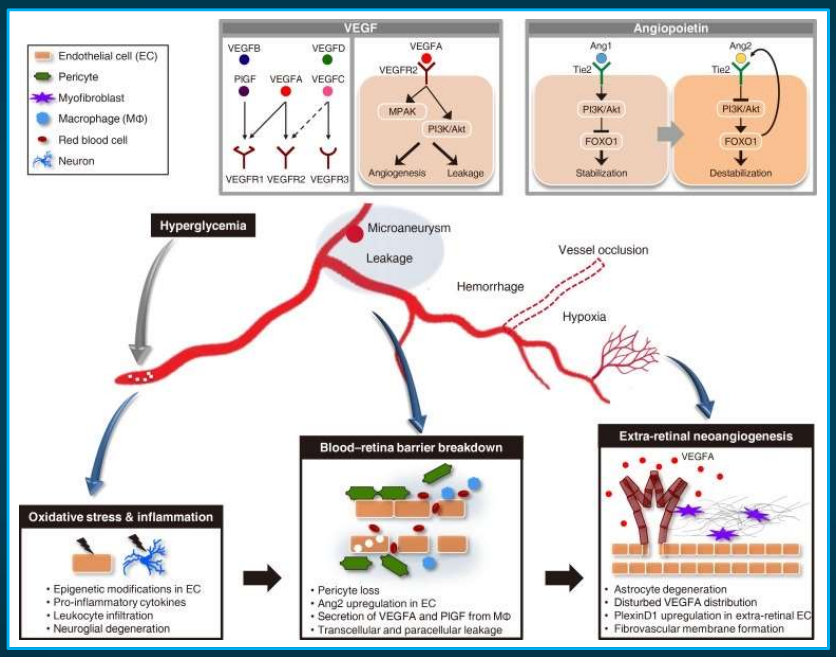


CRVO = central retinal vein occlusion; PDR = proliferative diabetic retinopathy.

Aiello LP, et al. *N Engl J Med*. 1994;331(22):1480-1487.

7

Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME)

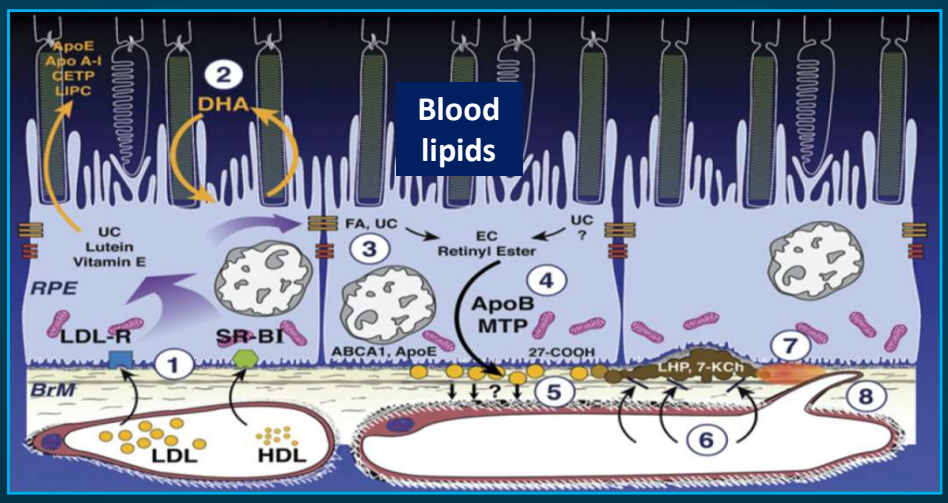


Kusuhara S, et al. *Diabetes Metab J*. 2018;42(5):364-376.

8

Age-Related Macular Degeneration (AMD): The "Oil Spill" in Bruch's Membrane

Blood lipids Photoreceptors → *Bruch's membrane* → **Drusen** → *Proinflammatory / Angiogenic factors* → **Choroidal neovascularization**

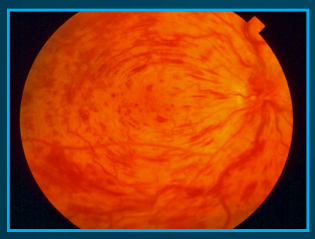


Curcio CA, et al. *Br J Ophthalmol.* 2011;95:1638-1645.

9

Retinal Vein Occlusion (RVO): Pathophysiology

BRVO



CRVO

Retinal vein compression and narrowing

↓

Turbulent blood flow

↓

Thrombus formation

↓

Ischemia and hypoxia

↓

Increased VEGF production

↓

Increased capillary permeability

↓

Leakage and edema

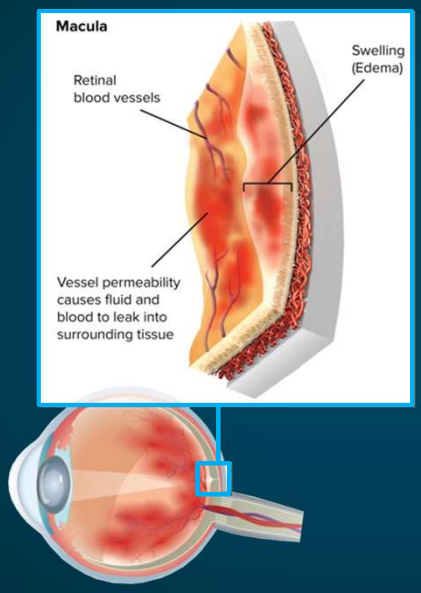
VEGF= vascular endothelial growth factor.

Christoffersen NL, Larsen M. *Ophthalmology.* 1999;106(11):2054-2062. Fegan CD. *Eye (Lond).* 2002;16(1):98-106. Noma H, et al. *Graefes Arch Clin Exp Ophthalmol.* 2006;244(3):309-315.

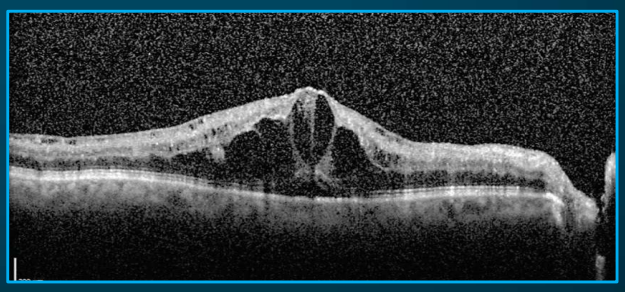
Images courtesy Dr David Eichenbaum.

10

Macular Edema as a Consequence of RVO



- Macular edema may be a **common complication** and cause of vision loss in CRVO and BRVO
- Anti-VEGF treatment is considered first-line treatment for RVO-associated macular edema



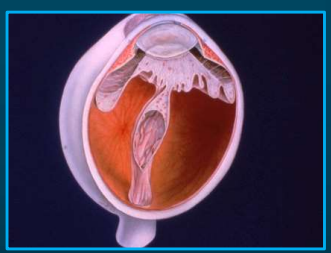
BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion

Science of CRVO. An informational guide to central retinal vein occlusion (http://www.angio.org/downloads/Informational_Guide-Science_of_CRVO.pdf). Schaab T, et al. *Ophthalmol Manage*. 2018 (https://www.ophthalmologymanagement.com/issues/2018/ july-2018/navigating-retinal-imaging). URLs accessed 4/23/2024. Flaxel CJ, et al. *Ophthalmology*. 2020;127:P288-P320.

11

Retinopathy of Prematurity (ROP)

- Initially described as *retrolental fibroplasia* (1942)
- Incomplete vascularization along with mismatch between normal vascularization and oxygen need of the developing retina
- Key risk factors include
  - **Premature birth** (≤30 weeks GA), **low birthweight** (≤1500 grams), high/unregulated supplemental oxygen at birth or fluctuations in oxygenation, and poor postnatal growth



GA = gestational age.

Heidar K. Retinopathy of prematurity. (https://eyewiki.aao.org/Retinopathy_of_Prematurity). Accessed 4/23/2024. Fierson WM, et al. *Pediatrics*. 2018;142:e20183061. *Images courtesy of Dr Audina Berrocal.*

12

What Do We Know About VEGF in ROP?

- VEGF promotes retinal vascularization
- Baby is born prematurely
  - Hyperoxic → ↓ VEGF → delays maturation
- Tissue hypoxia/avascular retina → ↑ VEGF → **ROP**

VEGF signaling dysregulation and VEGF receptor activation are believed to be *integral mechanisms* in the conversion from physiologic to pathologic angiogenesis in ROP.

Eldweik L, Mantagos IS. *Semin Ophthalmol.* 2016;31:163-168. Hellström A, et al. *Lancet.* 2013;382:1445-1457.

13

Screening and Diagnostic Strategies for AMD, DR, ROP, and RVO

14

Screening Mechanisms for DR

- Dilated eye exam is only one part of the clinical diagnosis of DR and DME
- Various ways to monitor

Ultra-widefield fundus photography

Optical coherence tomography (OCT)

Image of normal retina

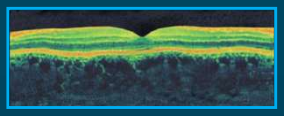
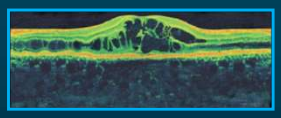


Image of retina with DME



Fluorescein and OCT angiography

University of Iowa. Carver College of Medicine. Color fundus photography (http://www.medicine.uiowa.edu/eye/Ocular-Fundus-Photography/). Accessed 4/23/2024.

15

Screening for DR/DME

When to screen

- T1DM 5 years after diagnosis
- T2DM At diagnosis

When to follow up

- At least annually
  - More frequently as needed
- Be careful in pregnancy!

International classification of DR* and DME for high-resource settings

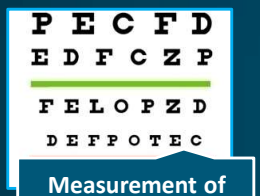
Classification	Reexamination or next screening schedule
DR	
No apparent DR, mild nonproliferative DR, and no DME	Reexamination in 1 to 2 years
Mild nonproliferative DR	6 to 12 months
Moderate nonproliferative DR	3 to 6 months
Severe nonproliferative DR	<3 months
Proliferative DR	<1 month
DME	
Non-center-involving DME	3 months
Center-involving DME (CI-DME)	1 month

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy.
*In cases where diabetes is controlled.
Adapted from International Council of Ophthalmology (ICO). ICO guidelines for diabetic eye care, 2017 (http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf). Ziemer DC, et al. American Diabetes Association (ADA) 2016 Congress; Poster 617-P. Flaxel CJ, et al. *Ophthalmology*. 2020;127:P66-P145.

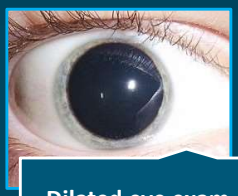
16

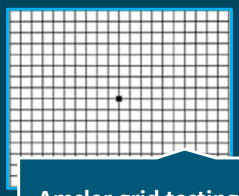
Screening Mechanisms for AMD

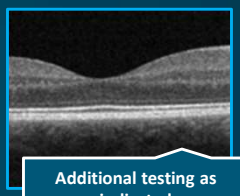
- Patients with early AMD may be asymptomatic or unaware of their diagnosis[1]
- Patients aged >60 years and those at risk for AMD should have an annual eye exam[1,2]



Measurement of visual acuity


Dilated eye exam


Amsler grid testing


Additional testing as indicated (OCT, FA, photos)

- Studies show that *many patients with AMD go undetected*, and **will initially present with vision loss**
  - 25% eyes with macular characteristics undiagnosed in 1 study[3]
  - 79% of patients in another study presented with neovascular AMD and VA of 20/50 or worse[4,5]

FA = fluorescein angiography; OCT = optical coherence tomography; VA = visual acuity.

1. American Academy of Ophthalmology (AAO). AMD Preferred Practice Pattern®, 2019 (www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp). 2. American Optometric Association (AOA). Optometric clinical practice guideline: AMD, 2004 (www.sdeyes.org/docs/CPG-6.pdf). 3. Neely DC, et al. *JAMA Ophthalmol.* 2017;135:570-575. 4. Cervantes-Castañeda, et al. *Eye (Lond).* 2008;22:777-781. 5. Olsen TW, et al. *Ophthalmology.* 2004;111:250-255. URLs accessed 4/23/2024.

17

Simple OCT-Based Scoring System Modeled After AREDS Simple Scale

Intermediate AMD in both eyes		
Risk factors	Scores (OD) Study eye	Scores (OS) Fellow eye
Hyporeflective foci within drusenoid lesion	Yes 1 No 0	Yes 1 No 0
Intraretinal hyperreflective foci	Yes 1 No 0	Yes 1 No 0
Subretinal drusenoid deposits	Yes 1 No 0	Yes 1 No 0
Drusen volume ≥0.03 mm^3	Yes 1 No 0	Yes 1 No 0

Fellow eye already with advanced AMD		
Risk factors	Scores Intermediate AMD	Scores Fellow eye*
Hyporeflective foci within drusenoid lesion	Yes 1 No 0	4
Intraretinal hyperreflective foci	Yes 1 No 0	4
Subretinal drusenoid deposits	Yes 1 No 0	4
Drusen volume ≥0.03 mm^3	Yes 1 No 0	4

*Fellow eye with evident choroidal neovascularization or atrophy automatically receives 4 points.

Maximum score = 8

AREDS = Age-Related Eye Disease Study; OCT = optical coherence tomography; OD = right eye; OS = left eye.

Lei J, et al. *Graefes Arch Clin Opthalmol.* 2017;255:1551-1558. Ferris FL, et al. *Arch Ophthalmol.* 2005;123:1570-1574.

18

Simple OCT-Based Scoring System Modeled After AREDS Simple Scale

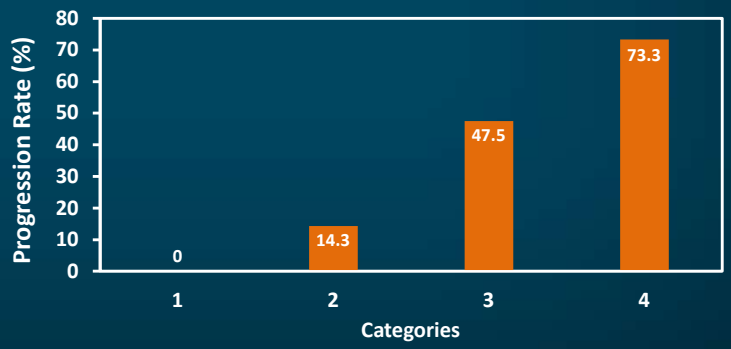
Combined Risk Categories for Comparative Analysis: Progression Rate

Risk categories	I	II	III	IV
Cumulative score	0, 1, or 2	3 or 4	5 or 6	7 or 8
Progression rate to late AMD, % (n/N)	0% (0/14)	14.3% (5/35)	47.5% (28/59)	73.3% (22/30)

Logistic regression model

Category 4 vs category 3:
3.0 times likelihood of progression (95%CI, 1.2-7.9)

Category 4 vs category 2:
16.4 times likelihood of progression (95%CI, 4.7-58.8)



Lei J, et al. *Graefes Arch Clin Opthalmol*. 2017;255:1551-1558.

19

AMD Monitoring

"Dry" AMD

- Should be seen every 3 to 12 months, depending on severity of disease
- Tailor exam to detect conversion from "dry" to "wet" AMD
- Home Amsler grid, Foresee Home device, or similar tool to help monitor between visits
  - Amsler grid—low compliance, low beneficial effect

"Wet" AMD

- Any change in vision or metamorphopsia
  - **Assume "wet" AMD until proven otherwise**
- Unless able to determine no fluid/CNV, should be referred to retinal specialist
- Any patient with "wet" AMD should undergo evaluation and consideration of treatment
  - Studies show patients exhibiting CNV **do better with early detection and prompt treatment**

CNV = choroidal neovascularization

Flaxel CJ, et al. *Ophthalmology*. 2020;127:P1-P65. Fine AM, et al. *Arch Ophthalmol*. 1986;104:513-514. Keane PA, et al. *Clin Ophthalmol*. 2015;9:353-366.

20

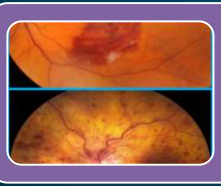
Recognizing RVO

Typical patient

- History of hypertension, high cholesterol, DM, heart disease
- Often high blood pressure on vital signs assessment
- Smokers

Typical symptoms

- Sudden painless unilateral distortion or loss of central vision
- Can be asymptomatic in mild cases



Potential findings

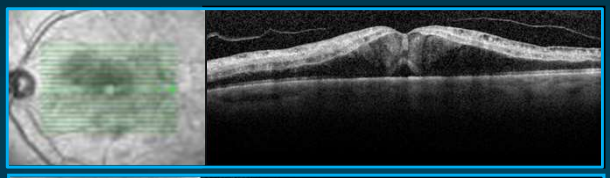
- Superficial retinal hemorrhage
- Cotton wool spots
- Retinal edema
- Dilated and/or tortuous venules
- Optic disc edema
- Lipid deposition

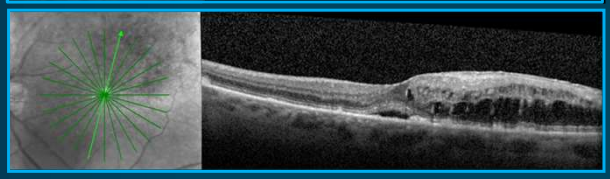
Song P, et al. *J Glob Health*. 2019;9(1):010427. Flaxel CJ, et al. *Ophthalmology*. 2020;127:P288-P320. In Sight Full Life (https://www.insightfulllife.com/what-does-myopic-macular-degeneration-look-like/).
RVO fundus images courtesy of Dr Judy Kim.

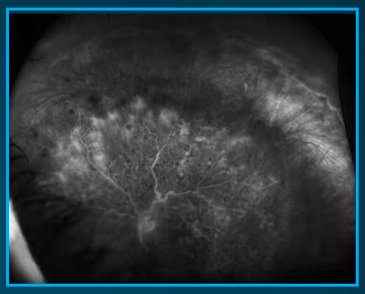
21

Screening Mechanisms for RVO

OCT

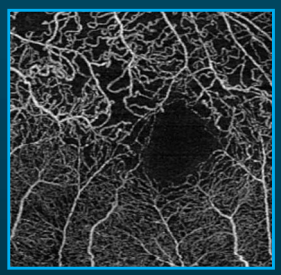






Ultrawidefield fluorescein angiogram

OCT angiography



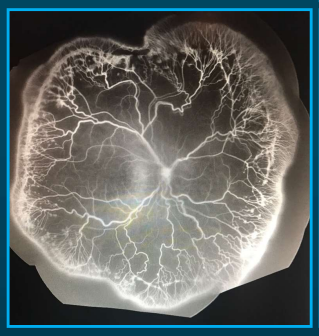
Images courtesy of Dr Judy Kim.

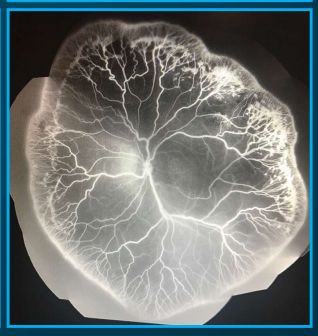
22

Screening Mechanisms for ROP

Indirect ophthalmoscopy (dilated eye for optimal peripheral retina assessment)

Fluorescein angiography





Heidar K. Retinopathy of prematurity (https://eyewiki.aao.org/Retinopathy_of_Prematurity). Foundation American Society of Retina Specialists (ASRS). Retinopathy of prematurity (https://www.asrs.org/patients/retinal-diseases/17/retinopathy-of-prematurity). URLs accessed 4/23/2024.

Images courtesy of Dr Audina Berrocal.

23

Screening for ROP

- Acute ROP either progresses to a point requiring timely treatment (within 48–72 hours) or spontaneously regresses
- Screenings should be carefully timed to identify eyes in need of treatment

Recommended timing of first exam based on GA in the United States

Gestational age at birth	Postmenstrual age (PMA) [weeks]	Chronologic [weeks]
22 weeks	31	9 - Consider earlier screening per clinical judgment
23 weeks	31	8 - Consider earlier screening per clinical judgment
24 weeks	31	7
25 weeks	31	6
26 weeks	31	5
27 weeks	31	4
28 weeks	32	4
29 weeks	33	4
30 weeks	34	4
>30 weeks with high risk factors	—	4

Foundation ASRS. Retinopathy of prematurity (https://www.asrs.org/patients/retinal-diseases/17/retinopathy-of-prematurity). Heidar K. Retinopathy of prematurity (https://eyewiki.aao.org/Retinopathy_of_Prematurity). URLs accessed 4/23/2024.

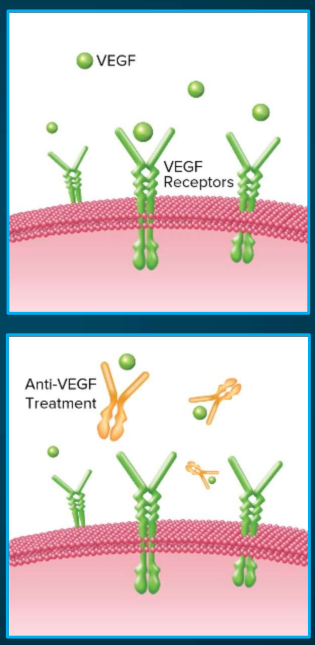
24

Use of Anti-VEGF Agents in the Treatment of nAMD, DR, RVO, and ROP

25

Anti-VEGF Agents

- Anti-VEGF agents bind to and neutralize VEGF
  - Results in decreased intraretinal and subretinal fluid
  - May also decrease risk of scar tissue formation
- Serious adverse effects (endophthalmitis) are rare
- Less serious events (subconjunctival hemorrhage, vitreous hemorrhage, floaters) are also uncommon



Pongsachareonnont P, et al. *Clin Ophthalmol*. 2018;12:1877-1885. Yeo NJY, et al. *Front Pharmacol*. 2019;10:1363. Holz FG, et al. *Br J Ophthalmol.* 2016;100: 1623-1628. The Foundation ASRS. Intravitreal injections (www.asrs.org/content/documents/fact-sheet-30-intravitreal-injections.pdf). Sukgen EA, et al. *Int Ophthalmol.* 2017;37:215-219. Prevent Blindness. Betadine and eye pain. (https://lowvision.preventblindness. org/2013/06/25/betadine-and-eye-pain/). The Angiogenesis Foundation (http://www.scienceofdme.org/treat/). URLs accessed 4/23/2024.

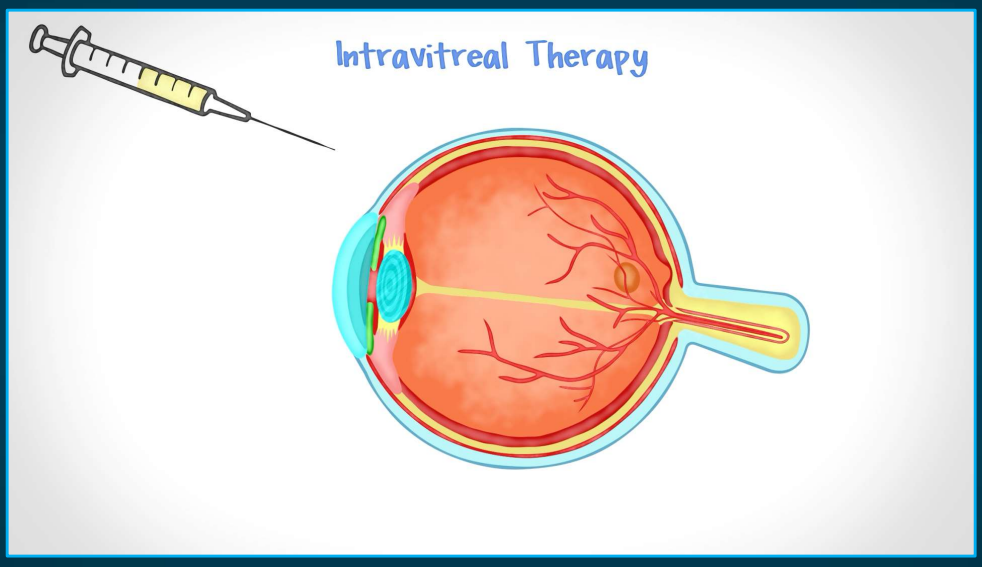
26

Animation Presentation

We will now watch a brief animation examining the best practices in anti-VEGF injection therapy techniques.

27

Best Practices in Anti-VEGF Injection Therapy Techniques



28

Anti-VEGF Approaches

		nAMD	DR	DME	ROP	RVO
First generation	Aflibercept (2 mg)	✓	✓	✓	✓	✓
	Aflibercept-yszy†	✓	✓	✓		✓
	Aflibercept-jbvf†	✓	✓	✓		✓
	Bevacizumab	*		*		*
	Brolucizumab	✓		✓		
	Ranibizumab	✓		✓		✓
	Ranibizumab-nuna	✓			✓	✓
	Ranibizumab-eqrn	✓	✓	✓		✓
Next generation	Aflibercept (8 mg)	✓	✓	✓		
	Faricimab	✓		✓		✓
	Ranibizumab port delivery system (PDS)	✓**				

†= Newly approved aflibercept biosimilar indications added after recording
✓ = FDA approved
* = off-label use
** = who have previously responded to at least 2 intravitreal injections of anti-VEGF therapy

nAMD = neovascular age-related macular degeneration.
Source: Product information.

29

Anti-VEGF Treatments for AMD

- **Anti-VEGF agents** can also slow or stop vessel leakiness and decrease thickening of retinal tissues may improve vision
- Generally well tolerated; risk of endophthalmitis from injection is rare

Anti-VEGF agents are generally considered first-line therapy in neovascular macular AMD.

Clinical trials for anti-VEGF therapy in AMD

Anti-VEGF therapy	Mechanism of action	Trial
Aflibercept	Anti-VEGF	PULSAR, VIEW 1, VIEW 2
Bevacizumab*	Anti-VEGF	CATT
Brolucizumab	Anti-VEGF	HAWK, HARRIER, SWIFT
Faricimab	Anti-VEGF and anti-Ang-2	TENAYA, LUCERNE
Ranibizumab	Anti-VEGF	ANCHOR, HARBOR, MARINA, SUMMIT
RGX-314	Suprachoroidal anti-VEGF gene therapy	AAVIATE
OPT-302	Inhibits VEGF C/D	ShORe, COAST

*Off-label use in AMD.

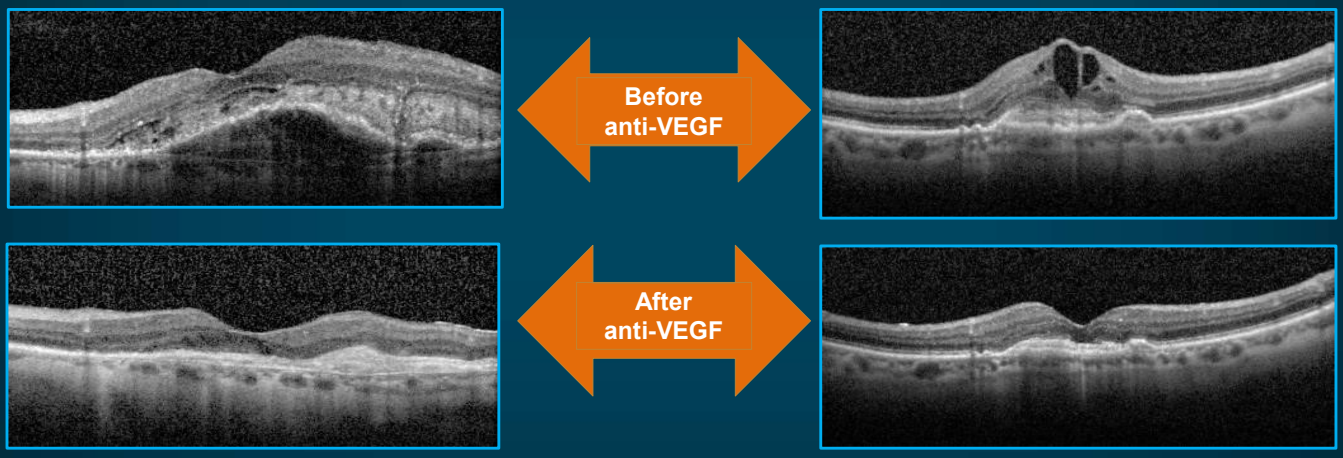
VEGF = vascular endothelial growth factor.

Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65. Turbert D. Anti-VEGF treatments. AAO EyeSmart (https://www.aao.org/eye-health/drugs/anti-vegf-treatments). Moshfeghi AA. Safety of intravitreal anti-VEGF agents (https://www.reviewofophthalmology.com/article/safety-of-intravitreal-antivegf-agents). Opthea. Wet AMD phase 3 pivotal trials (https://opthea.com/clinical-trials/#). Campochiaro PA. AAO 2022. Hinkle J, et al. *Retina Today*, 2020 (https:// retinatoday.com/articles/2020-nov-dec/the-future-looks-bright-the-therapeutics-pipeline-for-diabetic-retinopathy). URLs accessed 10/26/23.

30

Current nAMD Treatment Strategies
Intravitreal Anti-VEGF-A Injections

Bevacizumab*, ranibizumab, aflibercept, brolucizumab



*Not US Food and Drug Administration (FDA)-approved.
Images courtesy of Carl Regillo, MD.

31

Anti-VEGF Agents for DR/DME

Anti-VEGF agents	Ranibizumab	Aflibercept	Brolucizumab	Faricimab	Bevacizumab
FDA approval: DR	2006	2 mg: 2011 8 mg: 2023	Not approved	Not approved	Not approved
Pivotal studies	Protocol S	2 mg: VISTA/VIVID PANORAMA 8 mg: PHOTON			
FDA approval: DME	2012	2 mg: 2014 8 mg: 2023	2022	2022	Not approved
Pivotal studies	Protocol T RISE/RIDE RESTORE Protocol I READ 2	2 mg: Protocol T Protocol V VISTA/VIVID 8 mg: PHOTON	KESTREL KITE	YOSEMITE RHINE	Protocol T

Sun JK, et al. *Ophthalmology*. 2019;126(1):87-95. Jacoba CMP, et al. Diabetic macular edema (https://eyewiki.org/Diabetic_Macular_Edema). Baker CW, et al. *JAMA*. 2019;321:1880-1894. Korobelnick JF, et al. *Ophthalmology*. 2014;121:2247-2254. Bressler SB, et al. *JAMA Ophthalmol*. 2017;135:558-568. Mitchell P, et al. *Ophthalmology*. 2011;118:615-625. Bressler SB, et al. *Retina*. 2015;35:2516-2528. Do DV, et al. *JAMA Ophthalmol*. 2013:131:139-145. Brown DM, et al. *Am J Ophthalmol*. 2022;238:157-172. Wykoff CC, et al. *Lancet*. 2022;399(10326):741-755. Wells JA, et al. *N Engl J Med*. 2015;372:1193-1203. Ranibizumab (Lucentis®) prescribing information (PI) 2024 (https://www.gene.com/download/pdf/lucentis_prescribing.pdf). Aflibercept (Eylea®) PI 2023 (https://www.regeneron.com/downloads/eyleahd_fpi.pdf). Aflibercept HD (Eylea HD®) 2023 (https://www.regeneron.com/downloads/eyleahd_fpi.pdf). Brolucizumab (Beovu®) PI 2023 (https://www.novartis.com/us-en/sites/novartis_us/files/beovu.pdf). Faricimab (Vabysmo®) PI 2023 (https://www.gene.com/download/pdf/vabysmo_prescribing.pdf). URLs accessed 4/23/2024.

32

Current Management Strategies in DR/DME

Diabetic Retinopathy Preferred Practice Pattern®

American Academy of Ophthalmology
The Eye M.D. Association

Steven Bailey
Amani Fawzi
Jennifer Lim
Ron Adelman
Gurunadh Vemulakonda
Gui-Shang Ying
Christina Flaxel

Severity of retinopathy	Presence of macular edema	Follow-up (months)	Panretinal photocoagulation (scatter) laser	Focal and/or grid laser*	Intravitreal anti-VEGF therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No NCI-DME CI-DME	12 3–6 1	No No No	No Sometimes Rarely	No No Usually
Moderate NPDR	No NCI-DME CI-DME	6–12 3–6 1	No No No	No Sometimes Rarely	No Rarely Usually
Severe NPDR	No NCI-DME CI-DME	3–4 2–4 1	Sometimes Sometimes Sometimes	No Sometimes Rarely	Sometimes Sometimes Usually
Non-high-risk PDR	No NCI-DME CI-DME	3–4 2–4 1	Sometimes Sometimes Sometimes	No Sometimes Sometimes	Sometimes Sometimes Usually
High-risk PDR	No NCI-DME CI-DME	2–4 2–4 1	Recommended Recommended Recommended	No Sometimes Sometimes	Sometimes Sometimes Usually

NPDR = nonproliferative diabetic retinopathy. ** Adjunctive treatments that may be considered include intravitreal corticosteroids or anti-VEGF agents (off-label use, except aflibercept and ranibizumab).

Flaxel CJ, et al. *Diabetic Retinopathy Preferred Practice Pattern®*. 2019:P65-P145.

33

Anti-VEGF Agents for RVO-Related Macular Edema

Anti-VEGF agents	Ranibizumab	Aflibercept	Brolucizumab	Faricimab	Bevacizumab
FDA approval for indication	2010	2012	Not approved	2023	Not approved
Pivotal studies	CRUISE/ BRAVO	COPERNICUS/ GALILEO		BALATON COMINO	

- Additional approaches
  - 1 FDA-approved **corticosteroid therapy**
  - 2 off-label corticosteroid therapies
  - **Laser** for macular edema (ME) in BRVO, neovascularization in RVO

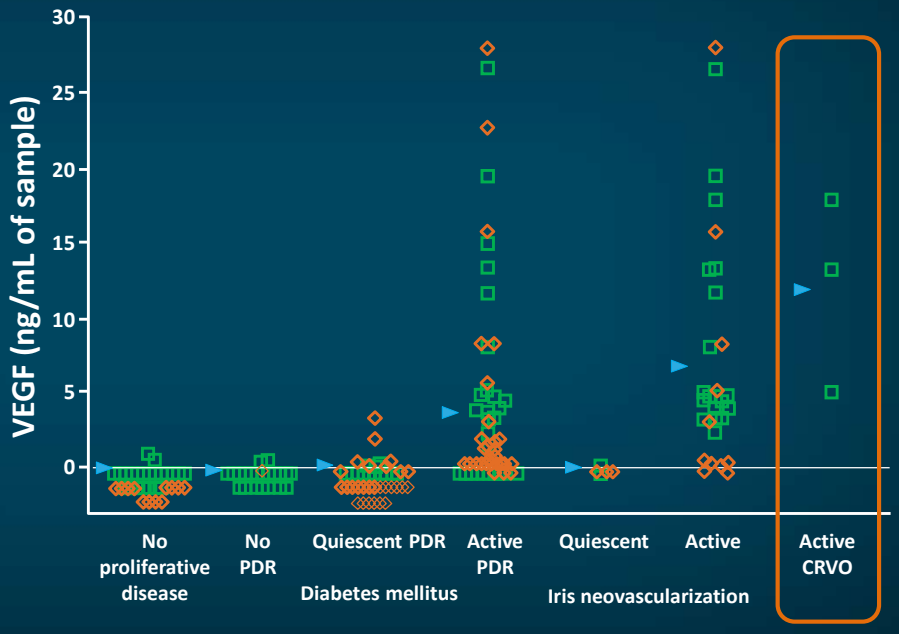
Need to detect macular edema early

Lashay A, et al. *J Ophthalmic Vis Res*. 2019;14(3):336-366. Brolucizumab (Beouvu) PI 2023 (https://www.novartis.com/us-en/sites/novartis_us/files/beovu.pdf). Faricimab (Vabysmo) PI 2023 (https://www.gene.com/download/pdf/vabysmo_prescribing.pdf). URLs accessed 4/23/2024. Flaxel CJ, et al. *Ophthalmology*. 2020;127:P288-P320.

34

Anti-VEGF as First-Line Therapy for ME From RVO

- SCORE2
- BRAVO
- CRUISE
- VIBRANT
- GALILEO
- COPERNICUS
- LEAVO



PDR = proliferative diabetic retinopathy; CRVO = central retinal vein occlusion.

Aiello LP, et al. *N Engl J Med*. 1994;331:1480-1487.

35

Anti-VEGF Agents for ROP

Anti-VEGF agents	Ranibizumab	Aflibercept	Brolucizumab	Faricimab	Bevacizumab
FDA approval for indication	Not approved	2023	Not approved	Not approved	Not approved
Pivotal studies	RAINBOW	BUTTERFLEYE FIREFLEYE			BEAT-ROP

- Additional approaches
  - Cryotherapy (rarely used)
  - Laser photocoagulation
  - Intravitreal anti-VEGF
  - Vitrectomy
  - Scleral buckle

Anti-VEGF is associated with ***lower rates*** *of high myopia and peripheral visual field loss.*

Aflibercept (Eylea®) PI 2023 (https://www.regeneron.com/downloads/eyleahd_fpi.pdf). Foundation ASRS. Retinopathy of prematurity (https://www.asrs.org/patients/retinal-diseases/17/retinopathy-of-prematurity). National Institutes of Health/National Eye Institute (NIH/NEI). Retinopathy of prematurity (https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinopathy-prematurity). Stahl A, et al. *Lancet*. 2019;394(10208):1551-1559. Mintz-Hittner HA, et al. *N Engl J Med*. 2011;364:603-615. Riazi-esfahani H, et al. *Int J Retina Vitreous*. 2021;7:60. URLs accessed 4/23/2024.

36

Timing of Treatment for ROP

- Threshold disease (CRYO-ROP)
  - Defined as 5 *contiguous* clock hours or 8 total *(noncontiguous)* clock hours of stage 3 in Zone I or II with plus disease
- American Academy of Pediatrics Policy Statement 2018 inclusion of prethreshold disease

Type 1 ROP (ETROP)

Zone I ROP: Any stage *with* plus disease

Zone I ROP: Stage 3, no plus disease

Zone II: Stage 2 or 3 *with* plus disease

A-ROP is considered type 1 ROP.

Chiang MF, et al. *Ophthalmology.* 2021;128(10):e51-e68. Fierson WM, et al. *Pediatrics.* 2018;142:e20183061. Foundation ASRS. Retinopathy of prematurity. (https://www.asrs.org/patients/retinal-diseases/17/retinopathy-of-prematurity). URLs accessed 4/23/2024.

Image courtesy of Dr Audina Berrocal.

37

Intervention to Avoid Blindness

- **90%** of babies will **reach threshold between 32 and 42 weeks**
- Median age at which threshold is reached is 37 weeks
  - Shifted to 34 weeks in Zone I disease (24 weeks or less/500 grams or less)
- Retinal detachment occurs at a median age of approximately 39 weeks

CRYO-ROP Cooperative Group. *Arch Ophthalmol.* 2001;119:1110-1118. Fierson WM, et al. *Pediatrics.* 2018;142:e20183061. Rivera JC, et al. *Neonatology.* 2016 (https://link.springer.com/referenceworkentry/10.1007/978-3-319-18159-2_283-1). Chang E, Capone A. Retinopathy of prematurity (ROP) (https://entokey.com/retinopathy-of-prematurity-rop/). Heidar K. Retinopathy of prematurity (https://eyewiki.aao.org/Retinopathy_of_ Prematurity). URLs accessed 4/23/2024.

Diagram courtesy of Dr Audina Berrocal.

38

Treatment Follow-Up and Complications

- Recommended follow-up in 3 to 7 days for laser and anti-VEGF treatment
  - Watching for regression and reactivation
  - With anti-VEGF, features such as retinal dilation and/or tortuosity can be reduced within a week, although late recurrences of proliferative ROP have been reported; therefore, **eyes receiving anti-VEGF need to be monitored until at least 65 weeks postmenstrual age (PMA)**
  - Monitor for endophthalmitis and other complications from injection
  - In addition to destruction of peripheral retina, complications from laser can include vitreous changes of condensation and fibrovascular traction at the ridge or optic nerve, recurrent plus disease or hemorrhage
- Even with treatment, some children will still have vision loss or blindness

Heidar K. Retinopathy of prematurity (https://eyewiki.aao.org/Retinopathy_of_Prematurity). Fierson WM, et al. *Pediatrics.* 2018;142:e20183061. NIH/NEI. At a glance: retinopathy of prematurity (https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinopathy-prematurity). NORD Rare disease database. Retinopathy of prematurity (https://rarediseases.org/rare-diseases/retinopathy-of-prematurity/). URLs accessed 4/23/2024.

39

Safety Profile of Anti-VEGF Agents

Ocular

- Retinal detachments
- Endophthalmitis
- Cataracts
- Conjunctival injection
- Eye pain
- Vitreous floaters
- Increased eye pressure

Systemic

- Nose and throat infections
- Anemia
- Nausea
- Cough

A review of numerous randomized trials suggests the systemic safety profile of bevacizumab, ranibizumab, and aflibercept appear similar.

Brolucizumab*:*
Intraocular inflammation (4%)

Aflibercept (Eylea) PI 2023 (https://www.regeneron.com/downloads/eylea_fpi.pdf). Kaiser PK, et al. *Ophthalmol Retina.* 2017;1(4):304-313. pdf). Brolucizumab (Beovu®) PI 2023 (https://www.novartis.com/us-en/sites/novartis_us/files/ beovu.pdf). URLs accessed 4/23/2024.

40

Intraocular Inflammation Safety Signal With Brolucizumab

Data from phase 3 clinical trials	HAWK			HARRIER		After rounding by the FDA, the rates in the US label are:	
	Brolucizumab 3 mg (n = 358)	Brolucizumab 6 mg (n = 360)	Aflibercept 2 mg (n = 360)	Brolucizumab 6 mg (n = 370)	Aflibercept 2 mg (n = 369)		
Patients with ≥1 ocular AE, n (%)	218 (60.9)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)		
Patients with ≥1 ocular serious AE, n (%)	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)		
Ocular AEs of potential relevance to intravitreal anti-VEGF in HAWK and HARRIER						Bro 6 mg	Afl 2 mg
Intraocular inflammation, n (%); *Pooled HAWK and HARRIER by agent/dose*	17 (4.7)	32 (8.9)	7 (1.9)	POOLED DATA		4%	1%
Retinal artery occlusion, n (%)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1%	<1%
Endophthalmitis, n (%)	3 (0.8)	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)	1%	<1%
Visual outcomes							
Patients with ≥15-letter loss from baseline at Week 96, %	8.6	8.1	7.5	7.0	7.6		

Novartis postmarketing update: A safety signal of rare AEs of retinal vasculitis and/or RVO, which may result in severe vision loss, has been identified. Typically, these events occurred in the presence of intraocular inflammation.

AE = adverse event; Afl = aflibercept; Bro = brolucizumab.

Dugel PU, et al. *Ophthalmology*. 2021;128:89-99. Brolucizumab (Beovu®) PI 2023 (www.novartis.us/sites/www.novartis.us/files/beovu.pdf). Accessed 4/23/2024.

41

Comparison of Anti-VEGF Agents

- Studies that compared the effectiveness of ranibizumab and bevacizumab found them *both* effective for treating wet AMD (CATT, LUCAS)
- The differences among ranibizumab, aflibercept, and bevacizumab have more to do with **cost, packaging, and possibly with some packaging-associated risk** (bevacizumab is compounded)
- For unknown reasons, **some patients do not respond to 1 drug but get favorable results with the other**; therefore, flexibility is needed to prescribe either medication to provide the best care

CATT Research Group. *N Engl J Med*. 2011;364:1897-1908. CATT Research Group. *Ophthalmology*. 2016;123:1751-1761. Berg K, et al. *Ophthalmology*. 2016;123:51-59. Mukamal R. Comparison of anti-VEGF treatments for wet AMD. *AAO EyeSmart*. 2020 (https://www.aao.org/eye-health/diseases/avastin-eylea-lucentis-difference). Accessed 4/24/2024.

42

Addressing Treatment Burden: Dosing Strategies and Next-Generation Therapy

43

Animation Presentation

We will now watch a brief animation reviewing dosing strategies and second-generation anti-VEGF therapies.

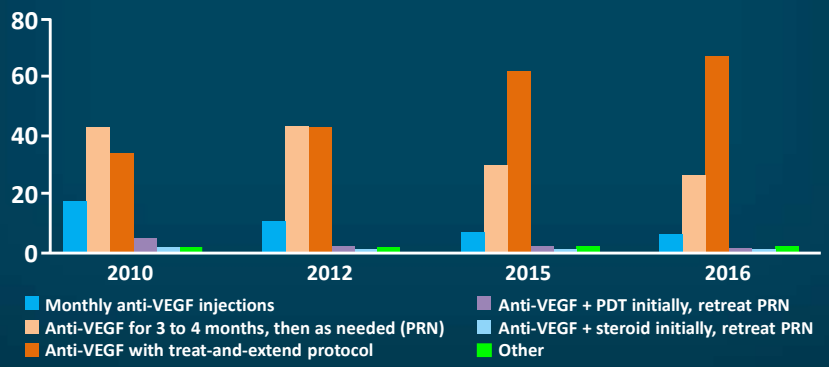
44

NEW WHITEBOARD
Dosing Strategies and Second-Generation Anti-VEGF Therapies

45

Anti-VEGF: Use of Treat-and-Extend Regimens

- Based on responses to the 2016 American Society of Retina Specialists (ASRS) Preferences and Trends survey, the number of retina specialists using a treat-and-extend (T&E) approach has been increasing, and most retina specialists would treat exudative AMD with a T&E protocol



PDT = photodynamic therapy.

ASRS. Preferences and Trends (PAT) Survey 2016. Aderman CM, Garg SJ. Intravitreal anti-VEGF injection treatment algorithm for DME. *Retina Today*. 2017 (https://retinatoday.com/articles/2017-july-aug/intravitreal-anti-vegf-injection-treatment-algorithms-for-dme). Accessed 4/23/2024.

46

Optimizing Dosing Regimens

- **Fixed dosing, PRN, and treat-and-extend**
  - Flexible dosing strategies optimize benefit-risk ratio and cost-effectiveness of anti-VEGF
  - All eyes differ in need for repeat injections, highlighting tailored approaches
- Eyes with PDR undergoing treatment with panretinal photocoagulation (PRP) have *better outcomes* when **combined** with anti-VEGF injections
- Some cases of refractory DME will have *improved responses* to a **switch** in anti-VEGF agent
- Studies underway are looking at sustained release (PAGODA, PAVILLION) and higher dosing at extended intervals (PHOTON) for management of diabetic eye disease

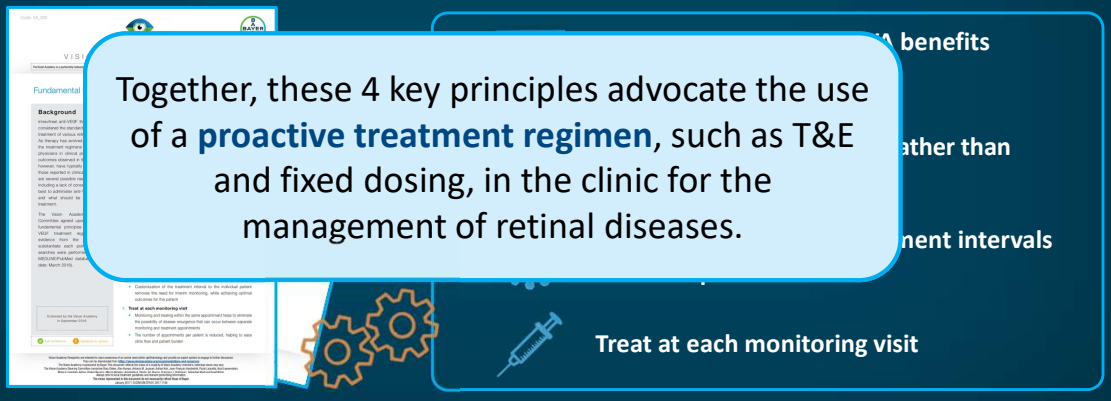
Studies underway are looking at sustained release (PAGODA, PAVILLION) and higher dosing at extended intervals (PHOTON) for management of diabetic eye disease

Freund KB, et al. *Retina.* 2015;35:1489-1506. Hendrick AM, Ip MS. *Retina Today.* 2016 (https://retinatoday.com/articles/2016-mar/managing-diabetic-eye-disease-with-intravitreal-anti-vegf-injections). Wallsh JO, Gallemore RP. *Cells.* 2021;10:1049. ClinicalTrials.gov: NCT04429503. NCT04108156. NCT04503551. Patel P, et al. *Rev Ophthalmol.* 2021 (https://www.reviewofophthalmology.com/article/a-peek-into-the-diabetic-retinopathy-pipeline). URLs accessed 4/23/2024.

47

Fundamental Principles of an Ideal Treatment Regimen

- The Steering Committee of the Bayer-supported Vision Academy identified 4 key principles for the "ideal" anti-VEGF treatment regimen[1,2*]



Together, these 4 key principles advocate the use of a **proactive treatment regimen**, such as T&E and fixed dosing, in the clinic for the management of retinal diseases.

Safety outcomes were not reported for the studies included in the reference publication (Lanzetta P, et al. *Graefes Arch Clin Exp Ophthalmol.* 2017;255(7):1259-1273).
*As an "ideal" treatment regimen, the costs of treatment (including country-specific financial drivers) were not considered.
nAMD = neovascular age-related macular degeneration; VA = visual acuity; VEGF = vascular endothelial growth factor.

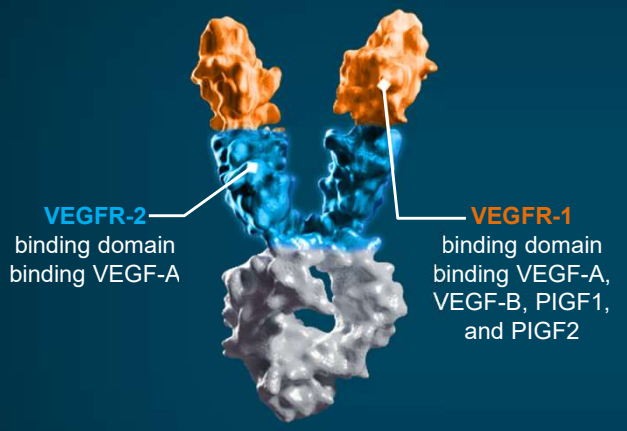
1. Lanzetta P, et al. *Graefes Arch Clin Exp Ophthalmol.* 2017;255(7):1259-1273. 2. Vision Academy. Fundamental principles of an anti-VEGF regimen (https://www.visionacademy.org/sites/g/files/vrxlpx7586/files/2020-10/vision-academy-viewpoint-fundamental-principles-of-an-anti-vegf-regimen_0.pdf). Accessed 4/23/2024.

48

Next-Generation Anti-VEGF

49

Aflibercept 8 mg



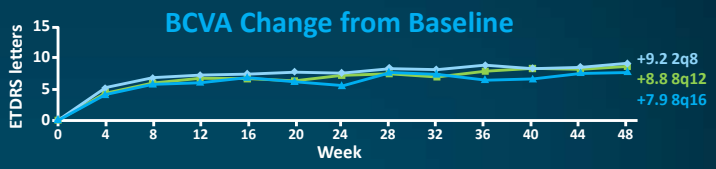
- Novel intravitreal formulation delivers 8 mg in 70 uL injection (114.3 mg/mL)
- A 4 times higher molar dose compared to aflibercept 2 mg is hypothesized to provide longer effective vitreal concentrations and enable a more sustained effect on VEGF signaling

Brown DM, Boyer DS, Do DV, et al. *The Lancet*. 2024;403(10432):1153-1163. doi:10.1016/S0140-6736(23)02577-1

50

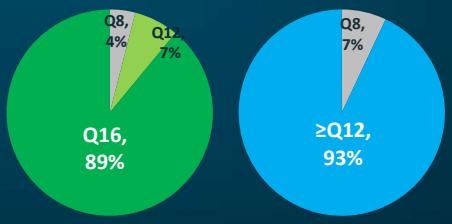
PHOTON (Phase 2/3): 8 mg Aflibercept for DME

- Higher molar dose with goal to provide longer effective vitreal anti-VEGF concentration
- N = 658
  - Aflibercept 8 mg every 12 or 16 weeks (3 initial monthly injections)
  - Aflibercept 2 mg every 8 weeks (5 initial monthly injections)
- Primary outcome
  - Mean change in BCVA (noninferiority) at Week 48
- Results
  - **Both 8 mg arms had noninferior BCVA to 2 mg every 8 weeks at Week 48** with comparable ocular/nonocular safety and randomized interval maintenance



	LS mean change from baseline at Week 48 (MMRM)	Difference in least square means vs 2q8	2-sided 95% CI	1-sided test for noninferiority at 4-letter margin
2q8	8.7			
8q12	8.1	-0.57	-2.26, 1.13	$p < .0001$
8q16	7.2	-1.44	-3.27, 0.39	$p = .0031$

93% of 8 mg patients maintained dosing intervals ≥12 weeks



8q16 (n = 156) All 8 mg (n = 456)

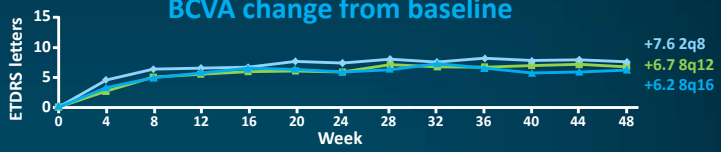
BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; MMRM = mixed models for repeated measures; q = every.

Brown DM, Boyer DS, Do DV, et al. *The Lancet*. 2024;403(10432):1153-1163. doi:10.1016/S0140-6736(23)02577-1

51

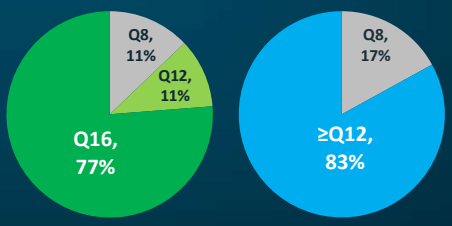
PULSAR (Phase 3): 8 mg Aflibercept for nAMD

- N = 1009 (treatment-naïve)
  - Aflibercept 8 mg every 12 or 16 weeks
  - Aflibercept 2 mg every 8 weeks
  - All arms with 3 initial monthly injections
- Primary outcome
  - Mean change in BCVA (noninferiority) at Week 48
- Results
  - **Both 8 mg arms had noninferior BCVA to 2 mg every 8 weeks at Week 48** with comparable ocular/non-ocular safety and randomized interval maintenance
  - 63% (all 8 mg arms) had *superior drying* compared to 2 mg arm (52%) at Week 16



	LS mean change from baseline at Week 48 (MMRM)	Difference in least square means vs 2q8	2-sided 95% CI	1-sided test for noninferiority at 4-letter margin
2q8	7.0			
8q12	6.1	-0.97	-2.87, 0.92	$p = .0009$
8q16	5.9	-1.14	-2.97, 0.69	$p = .0011$

83% of 8 mg patients maintained dosing intervals ≥12 weeks



8q16 (n = 312) All 8 mg (n = 628)

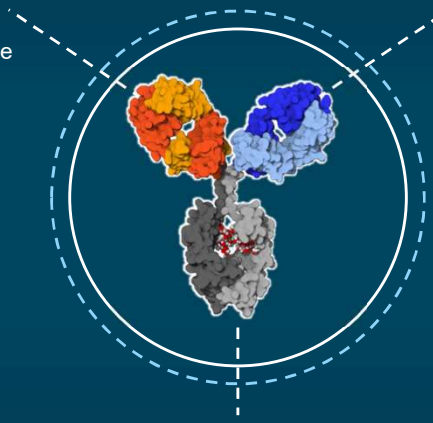
Lanzetta P, Korobelnik JF, Heier JS, et al. *The Lancet*. 2024;403(10432):1141-1152. doi:10.1016/S0140-6736(24)00063-1

52

Faricimab: Bispecific Antibody
1 Molecule, 2 Targets

Anti-Ang 2 Fab
Stabilizes vessels
Reduces vascular leakage
Reduces inflammation

Anti-VEGF A Fab
Reduces vascular leakage
Inhibits neovascularization



Modified Fc
Reduces systemic exposure
Reduces inflammatory potential

Multifactorial retinal and choroidal vascular diseases may require neutralization of more than just the VEGF pathway.

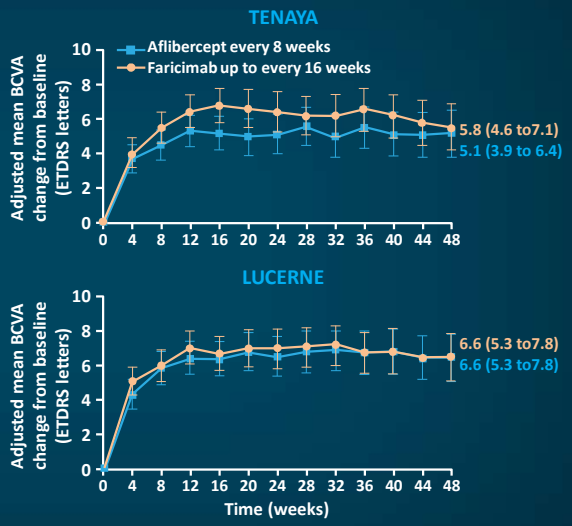
Cross monoclonal antibody (Mab) molecule representative of faricimab.
Ang 2 = angiopoietin 2; Fab = fragment antigen binding; Fc = fragment cystallizable; VEGF-A = vascular endothelial growth factor A.

Regula JT, et al. *EMBO Mol Med.* 2016;8(11):1265-1288, with correction in Regula JT, et al. *EMBO Mol Med.* 2019;11(5):e10666. Lim JI, et al. Retina Society 2022.

53

TENAYA/LUCERNE: Noninferiority Trials With Faricimab* in nAMD

- N = 1329 (treatment-naive patients); phase 3
  - Faricimab 6 mg up to every 16 weeks (based on protocol-defined disease activity) or
  - Aflibercept 2 mg every 8 weeks
- Primary outcomes
  - Mean change in BCVA from baseline averaged over Weeks 40, 44, and 48
- Results
  - BCVA change from baseline with faricimab was **noninferior** to aflibercept



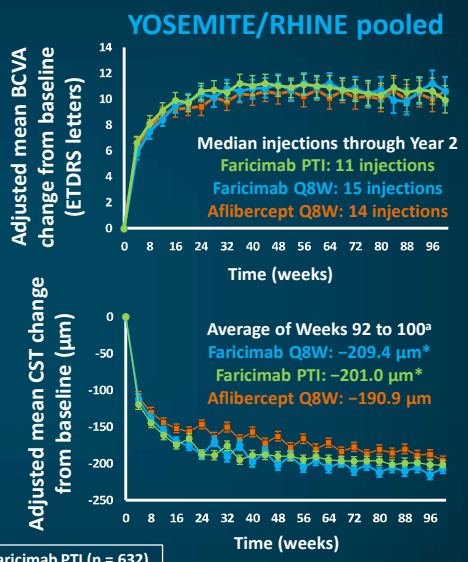
Approved indication for treatment intervals up to 16 weeks in nAMD (after initial 4 loading doses); regular assessment still indicated.

Heier JS, et al. *Lancet*. 2022;399:729-740. Faricimab (Vabysmo®) PI 2023 (https://www.gene.com/download/pdf/vabysmo_prescribing.pdf). Accessed 4/23/2024.

54

YOSEMITE/RHINE: Q8 Weeks vs T&E With Faricimab in DME

- N = 1891; phase 3
  - Faricimab 6 mg every 8 weeks, or
  - Faricimab 6 mg (personalized treatment interval), or
  - Aflibercept 2 mg every 8 weeks
- Primary outcomes
  - Mean change in BCVA and OCT, number of injections, durability, absence of fluid, and safety through Week 100
- Results
  - Clinically meaningful visual acuity (VA) gains, anatomic improvements and extended durability (up to every 16 weeks) maintained through Year 2



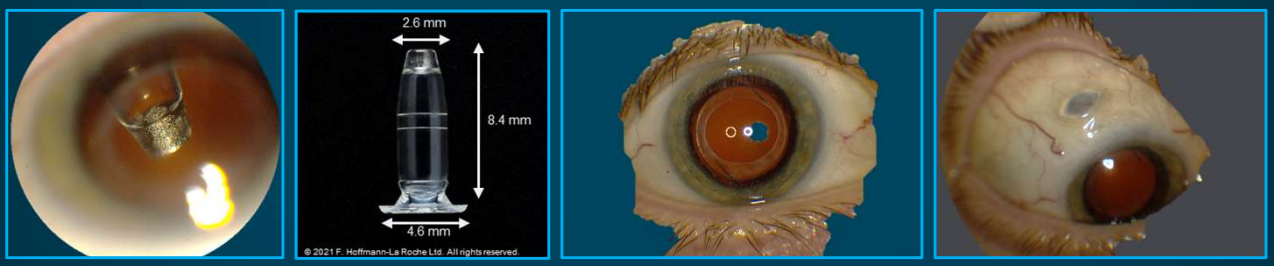
Test for superiority: *Nominal *P* < .05 vs aflibercept Q8W. *P*-values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P*-values. Clinical significance has not been established and conclusions regarding treatment effect cannot be drawn. [a] Adjusted mean change from baseline at 2 years, averaged over Weeks 92, 96, and 100.
BCVA = best-corrected visual acuity; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; PTI = personalized treatment interval; Q8W = every 8 weeks; VEGF = vascular endothelial growth factor.

Khurana RN, et al. 2022 Retina Society presentation. Wong TY, et al. *Ophthalmology.* 2023;S0161-6420(23)00933-8.

55

The Port Delivery System With Ranibizumab

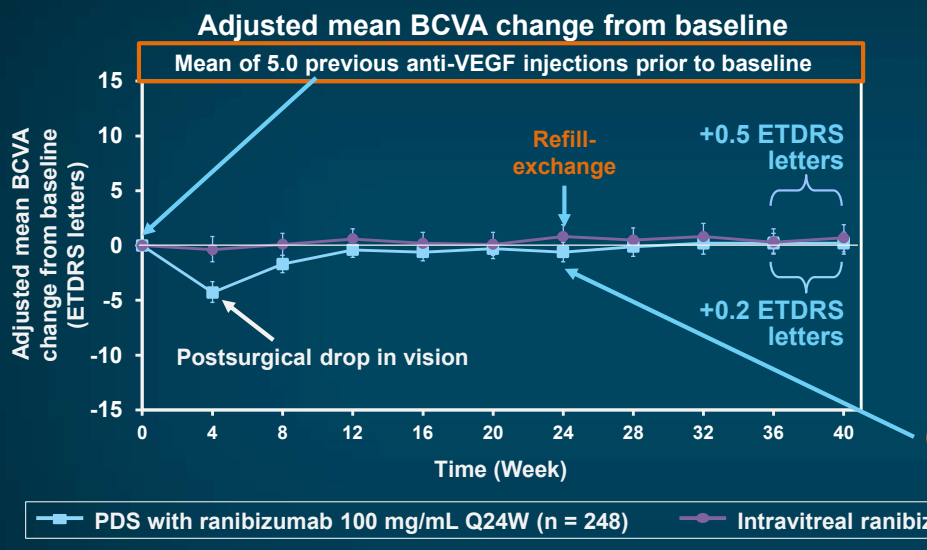
Continuous Intravitreal Delivery of a Customized Formulation of Ranibizumab



Campochiaro PA, et al. *Ophthalmology.* 2019;126:1141-1154. Ranade SV, et al. *Drug Deliv.* 2022;29:1326-1334. Rea J, et al. AAPS Pharm Sci 360. Abstract presented in 2021.

56

ARCHWAY STUDY: VA Outcomes Over 40 Weeks



Baseline		Weeks 36/40	
ETDRS	Snellen	ETDRS	Snellen
74.4	20/32	74.6	20/32
75.5	20/32	76.0	20/32

Adjusted means from an MMRM analysis and vertical bars represent 95% CI. 95% CI is a rounding of 95.03% CI; the type 1 error was adjusted for interim safety monitoring. Adjusted means estimated using an MMRM with adjustment for change from baseline in BCVA as the response and included terms for treatment group, visit, treatment-by-visit interaction, and baseline BCVA ETDRS letter score (<74 vs ≥74).
MMRM = mixed-effect model for repeated measures; Q24W = every 24 weeks.

Holekamp NM, et al. *Ophthalmology.* 2022;129:295-307.

57

Ocular AEs of Special Interest*
Through an Average of 79 Weeks of Follow-Up

MedDRA preferred term, n (%)†	PDS 100 mg/mL Q24W (n = 248)	Intravitreal Ranibizumab 0.5 mg Q4W (n = 167)	PDS 100 mg/mL Q24W (n = 248)	Intravitreal Ranibizumab 0.5 mg Q4W (n = 167)
	Overall‡		Onset After Week 40	
Overall number of AESIs	87	15	20	5
Patients with ≥1 ocular AESI	55 (22.2)	15 (9.0)	13 (5.2)	5 (3.0)
Tractional retinal detachment	0	0	0	0
Vitreous hemorrhage	15 (6.0)	6 (3.6)	2 (0.8)	2 (1.2)

October 2022
Genentech issues voluntary recall of PDS
noting 2.3% participants experienced dislocation of septum within the PDS and unsatisfactory quality control testing of repeat puncture of septum with refill needle among PDS devices manufactured for commercial use.

- 3 PDS-treated patients experienced implant dislocation; 2 had onset after Week 40
- 1 of 248 PDS-treated patients had irreversible vision loss due to an AE (*Enterococcus faecalis* endophthalmitis); no new events after Week 40

*Protocol-defined ocular AESIs potentially related to the PDS implant or implant insertion procedure. †Frequency counts by MedDRA Preferred Term. Multiple occurrences of the same AE in an individual are counted only once for each column. ‡All data through the 9/11/2020 clinical cutoff date. §Includes the following terms: Cataract, cataract nuclear, cataract cortical, cataract subcapsular. Observed data, all treated patients who received ≥1 dose of study drug according to the actual treatment. Month 1 visit includes data up to 37 days (monthly study visit + 7 days).
Clinicaltrial.gov: NCT03677934. Holekamp N, et al. *Ophthalmology.* 2022;129:295-307.
AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities.

Awh CC, et al. Updated safety and efficacy results from the Archway phase III trial of the port delivery system with ranibizumab (PDS) for neovascular AMD. ASRS 2021. Genentech. News release 10/2022.

58

Who Would Benefit From Anti-VEGF?

59

Factors That Affect Use of Anti-VEGF and Therapy Choice

- Patient-related factors
  - Personal preferences
  - Ability to adhere to required follow-up schedule
- Disease-related factors
  - Extent/severity
  - Risk of progression to vision threatening complications
- Treatment-related factors
  - Treatment burdens and requirements for follow-up
  - Potential side effects
- Payor restrictions/step therapy

Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P1-P65.

60

Present the Options to Your Patient—Both Work

Desired Frequency for Office Visits and Number of Injections

1. **PRN: 24 office visits (monthly) over 2 years, with ≈14 injections**
   - 25% of patients on PRN regimens may require ≤9 injections, *and PRN permits identification of these individuals and avoids overtreatment*
   - Every patient following a PRN regimen still needs to return 24 times over 24 months—little risk of vision loss from undertreatment

2. **T&E: ≈11 to 18 office visits, with injections at each visit**
   - The average number of injections will be 18 instead of 14, but the average number of visits also will be 18 over 2 years
   - Monthly returns may not be necessary over 2 years—risk of vision loss from undertreatment

Ross AH, et al. *Eye (Lond)*. 2020;34:1825-1834. CATT Research Group. *Ophthalmology*. 2012;119:1388-1398. Berg K, et al. *Ophthalmology*. 2016;123:51-59.

61

Vision Outcomes in Clinical Trials and Real-World Studies May Be Tied to the Number of IVT Anti-VEGF Injections Received per Year

Results from 1 year of IVT anti-VEGF monotherapy[1-11]

		Clinical trial data[a]	Real-world data[a]
nAMD	Mean change in BCVA from baseline (ETDRS letters)	6.6–11.3	0.4–1.1
	Mean # of injections/year	7.5–12.5	6.0–7.6
DME	Mean change in BCVA from baseline (ETDRS letters)	10.7–12.5	4.2
	Mean # of injections/year	8.4–12.2	6.4

[a]Table includes data from patients with nAMD and DME previously enrolled in clinical and real-world trials who received fixed and PRN dosing intervals of aVEGF monotherapy. These trials were conducted at different time periods.

BCVA = best-corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; IVT = intravitreal injection; PRN = "pro re nata" or "as needed."

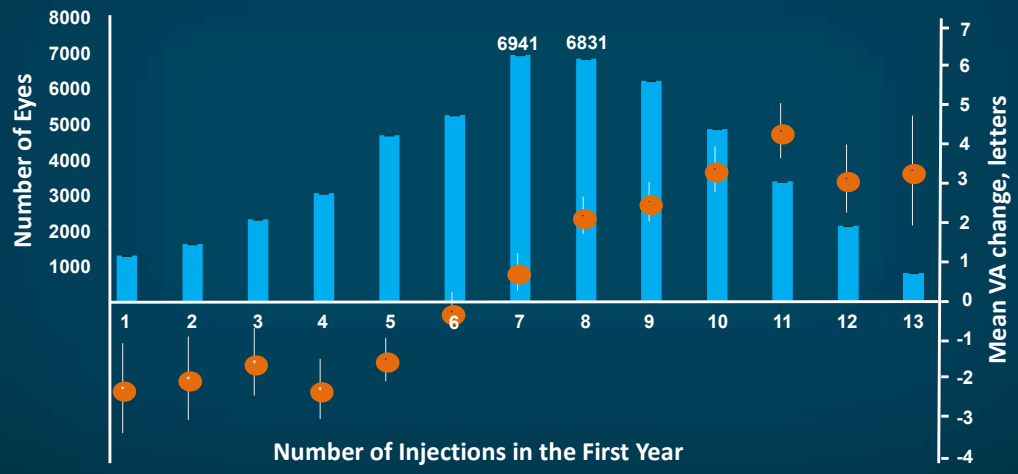
1. Brown DM, et al. *N Engl J Med*. 2006;355:1432-1444. 2. Busbee BG, et al. *Ophthalmology*. 2013;120:1046-1056. 3. Heier JS, et al. *Ophthalmology*. 2012;119:2537-2548. 4. Rosenfeld PJ, et al. *N Engl J Med*. 2006;355:1419-1431. 5. Dugel PU, et al. *Ophthalmology*. 2020;127(1):72-84. 6. Martin DF, et al. *N Engl J Med*. 2011;364(20):1897-1908. 7. Khanani AM, et al. *Ophthalmol Retina*. 2020;4(2):122-133. 8. Kiss S, et al. *Ophthalmology*. 2020;127(9):1179-1188. 9. Ciulla TA, et al. *Ophthalmol Retina*. 2020;4(1):19-30. 10. Korobelnick JF, et al. *Ophthalmology*. 2014;121(11):2247-2254. 11. Ciulla TA, et al. *Br J Ophthalmol*. 2021;105(2):216-221.

62

Real-World Data Show a Relationship Between Vision Outcomes for Patients With nAMD and Number of IVT Anti-VEGF Monotherapy Injections

Retrospective study of US electronic medical records (2012–2016)

Patients with treatment-naive nAMD (n = 49,485 eyes) who underwent anti-VEGF monotherapy injections[a]



VA = visual acuity.

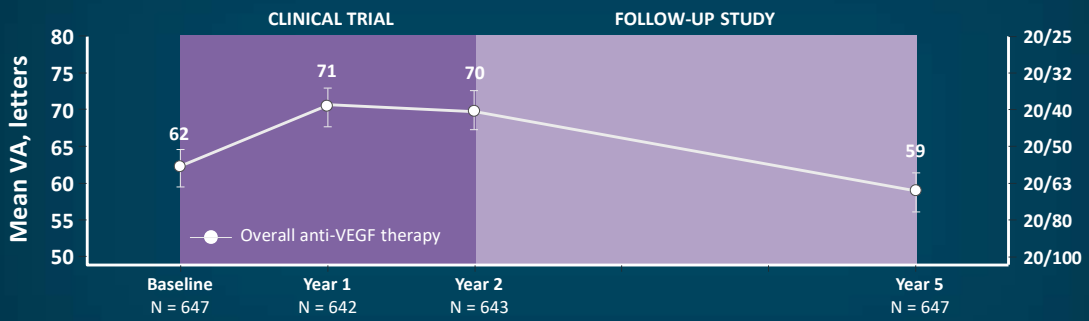
[a]This retrospective study assessed anti-VEGF therapy intensity and its relationship with VA change in real-world patients with nAMD (N = 49,485 eyes). The analyses were performed on a large database of aggregated, longitudinal medical records of treatment-naive patients with nAMD who underwent anti-VEGF injections between January 2012 and October 2016.

Ciulla TA, et al. *Ophthalmol Retina*. 2020;4:19-30.

63

Long-Term Vision Outcomes With IVT Anti-VEGF Monotherapy Have Also Been Investigated in Real-World Patients With nAMD

5-year CATT follow-up study (n = 647)[a]



	Year 3	Year 4	Year 5
Mean # of injections (SD)	4.8 (4.0)	4.5 (3.8)	4.0 (3.6)

CATT = Comparison of Age-Related Macular Degeneration Treatment Trials; SD = standard deviation.

[a]The aim of the CATT trial was to evaluate 5-year, follow-up outcomes in nAMD patients who received anti-VEGF monotherapy with a monthly or as needed dosing regimen for 2 years.

CATT Research Group. *Ophthalmology*. 2016;123:1751-1761.

64

Individualizing Treatment in Retinal Disease

65

Individualizing Treatment

- **Consider anti-VEGF *while visual acuity is still good***
- The role of VEGF and/or the inflammatory response is not the same for every patient
- It is not as simple as patients either responding or not responding; they can exhibit a range of responses to therapy

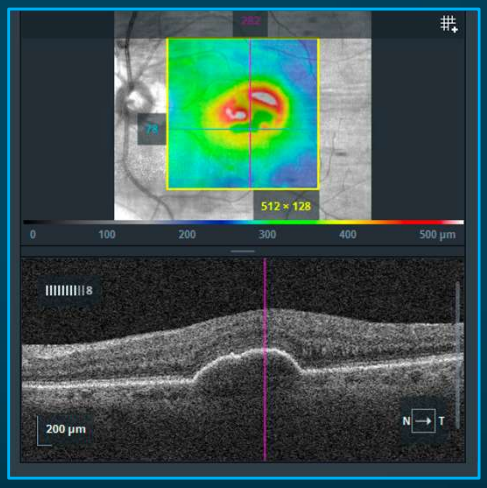
A case-by-case approach that considers factors relating to each individual patient's clinical features, needs, and preferences drives the choice of which agent or agents to use and how often to use them.

Wykoff CC, et al. *J Manag Care Spec Pharm*. 2018;24:S2a.

66

Case 1: Patient With AMD

- A 72-year-old patient with nAMD treated with bevacizumab
- Patient lives in a rural area and must travel 2 hours for visits
- June = CSF 350 µm



CSF = central subfield.

Images courtesy of Dr Rishi Singh.

67

5WH0

Case 1: Question 1

When determining initial treatment options for this patient, you would consider all the following factors EXCEPT?

a) Anti-VEGF agents with potential extended dosing intervals based on response
b) Anti-VEGF agents with monthly injections +/- treatment based on response
c) Next-generation anti-VEGF agents

68

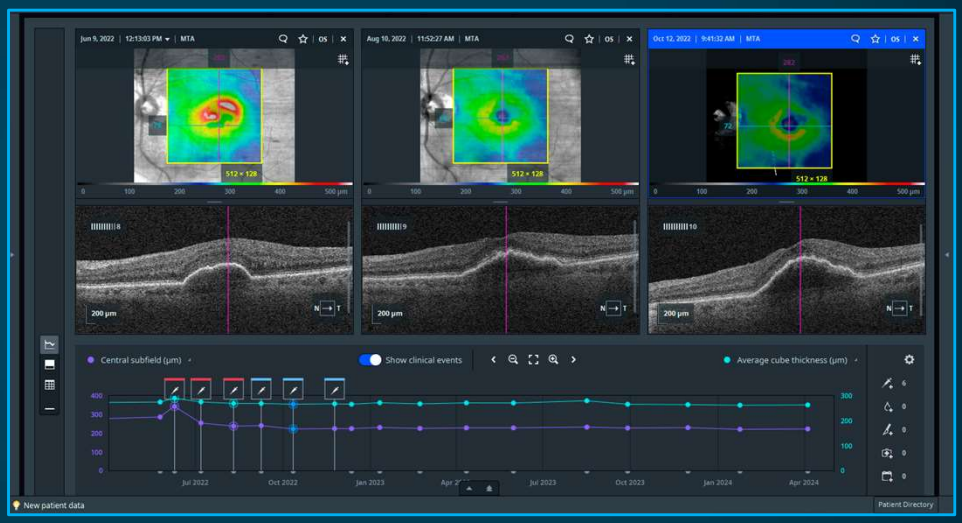
Slide 68

SWH0 Answer: b

Sharon Windsor Harker, 2024-04-17T16:29:59.701

Case Study 1: Patient With nAMD

- **Initial response**
  - **June = CSF 350 µm**
    - ***Bevacizumab***
  - **July = CSF 280 µm**
  - **August = CSF 260 µm**
    - *Inability to extend treatment intervals*
    - ***Aflibercept 2 mg***



Bevacizumab 25 mg/0.05 mL

Aflibercept 2 mg

Images courtesy of Dr Rishi Singh.

69

Case 1: Question 2

Despite switching to an alternative agent, longer dosing intervals were not able to be achieved. What steps in management would you consider next?

a) Switch to ranibizumab
b) Switch to faricimab
c) Switch to aflibercept 8mg
d) Switch to brolucizumab
e) A and D
f) B and C
g) All the above

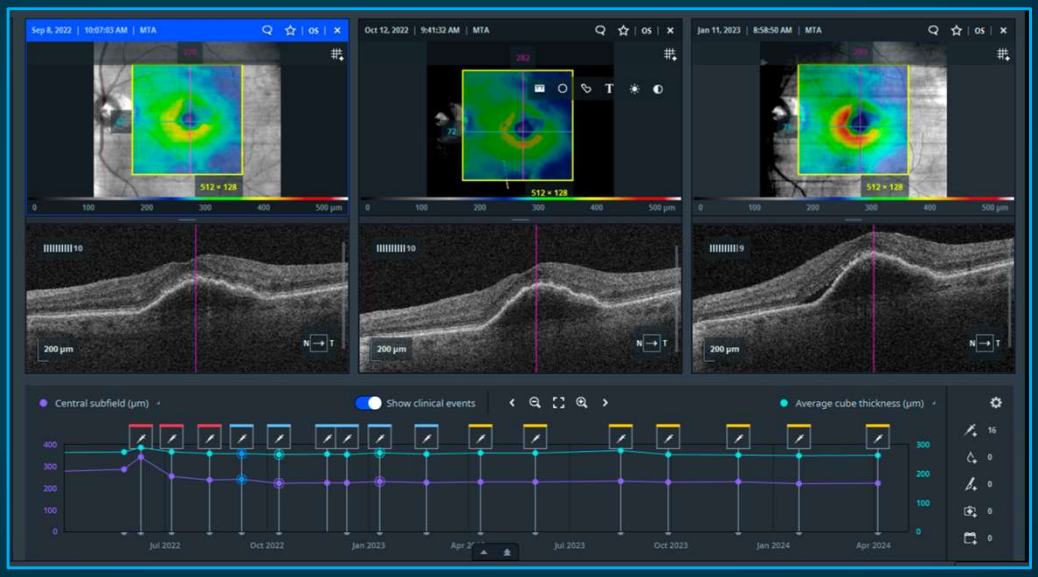
70

Slide 70

0 answer is F
, 2024-04-18T19:57:51.586

Case Study 1: Switch to Aflibercept 8 mg

Bevacizumab 25 mg/0.05 mL
Aflibercept 2 mg
Aflibercept 8 mg



Images courtesy of Dr Rishi Singh.

71

Case 1: Question 3

After switching to another next-generation anti-VEGF, therapeutic efficacy was maintained while increasing the treatment interval. What factors should be considered to help improve potential outcomes for this patient?

a) Consider patient's ability to adhere to treatment schedule
b) Consider patient's personal preferences, such as less frequent trips
c) Earlier consideration of next generation therapy
d) A and C
e) All the above

72

Switching to an Alternate Anti-VEGF Agent

When to consider adjusting current anti-VEGF regimen

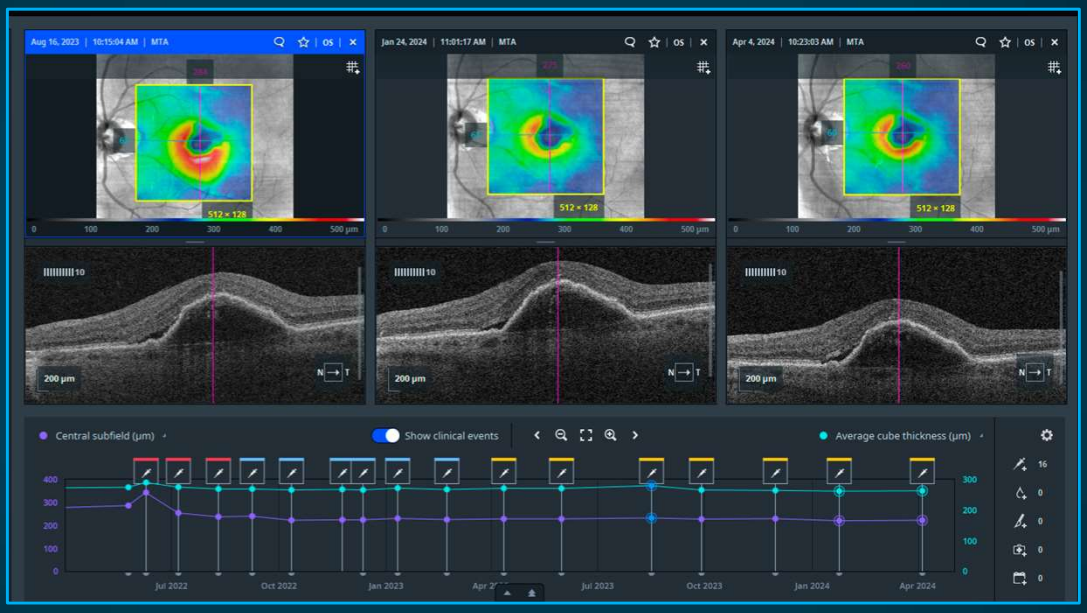
- When there is persistent fluid
  - OCT is helpful to distinguish between true nonresponder and inadequate response (dosing interval)
- With new fluid accumulation
- Desire to achieve increased treatment intervals between injections

Jaffe GJ, et al. *Ophthalmology*. 2016;123(9):1856-1864. Dugel PU, et al. *Ophthalmology*. 2017;124(9):1296-1304. Madjedi K, et al. *Surv Opthalmol*. 2022;67:1364-1372. Gallego-Pinazo R, et al. Switching anti-VEGF agents in eyes with treatment resistant neovascular AMD. 2014 (https://www.retinalphysician.com/issues/2014/may-2014/switching-anti-vegf-agents-in-eyes-with-treatment). Accessed 4/23/2024.

73

Case Study 1

Bevacizumab 25 mg/0.05 mL
Aflibercept 2 mg
Aflibercept 8 mg



Images courtesy of Dr Rishi Singh.

74

Personalizing Treatment by Risks and Preferences

Consider

- Disease severity
- Adherence
- Cost
- Patient preference
- Treatment-associated risks

Rapport with the patient is key

- Rapport begins with education

The most important element for the patient with retinal disease is

THE PATIENT MUST COME BACK!

Patients with retinal disease who are lost to follow-up after anti-VEGF treatment have worse anatomic and visual outcomes and may suffer from complications resulting in irreversible vision loss.

TRD = tractional retinal detachment.

Weng C. *Retinal Physician*. 2020 (https://www.retinalphysician.com/issues/2020/september-2020/the-expanding-role-of-anti-vegf-in-the-management). Accessed 4/23/2024. Maturi RK, et al. *JAMA Ophthalmol*. 2021;139:701-712; Almony A. *Am J Manag Care*. 2023;29(suppl 6):S81-S89.

75

Incorporating Safety Data Into Treatment Decisions

- Risk vs benefit assessment
- **Anti-VEGF drugs can penetrate into the systemic circulation and alter systemic VEGF**
  - While there appears to be some differential in the magnitude of systemic VEGF suppression between agents, studies have not demonstrated differential rates of thromboembolic events or mortality when comparing anti-VEGF therapies
- Consider at-risk patients (cardiovascular/cerebrovascular disease)—systemic administration in oncology included thromboembolic events
- Intraocular inflammation with brolucizumab

Baumal CR, et al. *Ophthalmology*. 2020;127:1345-1359. Modi YS, et al. Drug Saf. 2015;38(3):279-293.

76

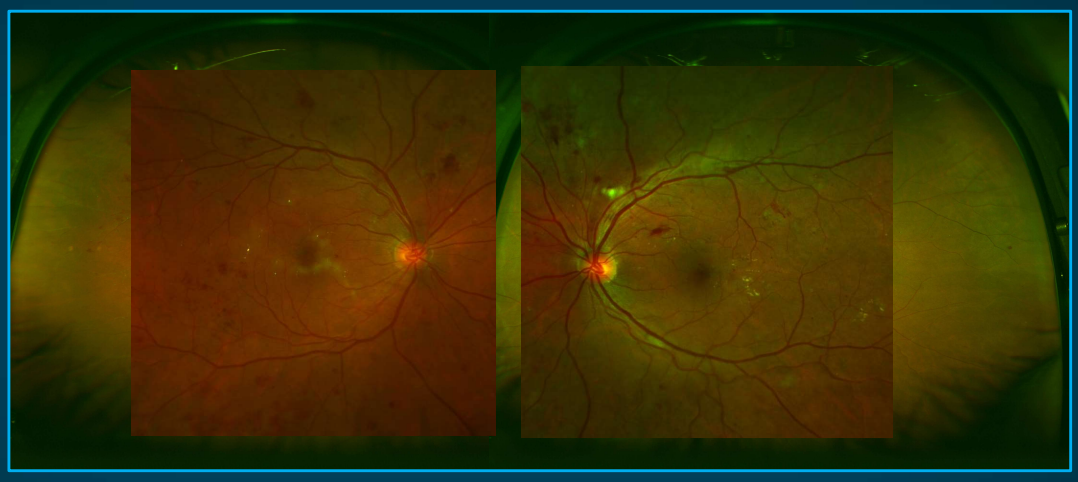
Case 2: Patient With DR, PDR, and DME

- A 65-year-old patient with DR, PDR, and DME
- Patient treated with 4 loading doses of next-generation anti-VEGF therapy Q1M

DME = diabetic macular edema; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy.

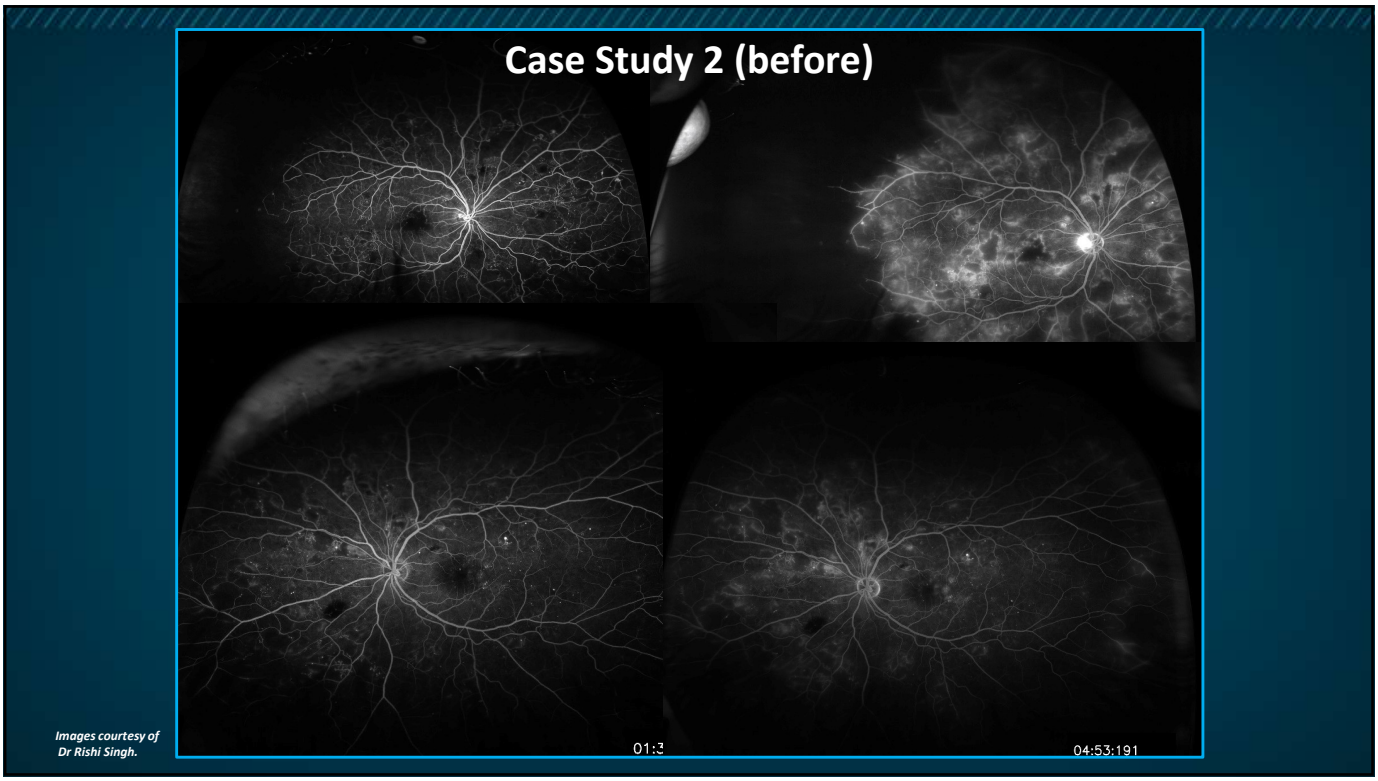
77

Case Study 2 (before)



Images courtesy of Dr Rishi Singh.

78

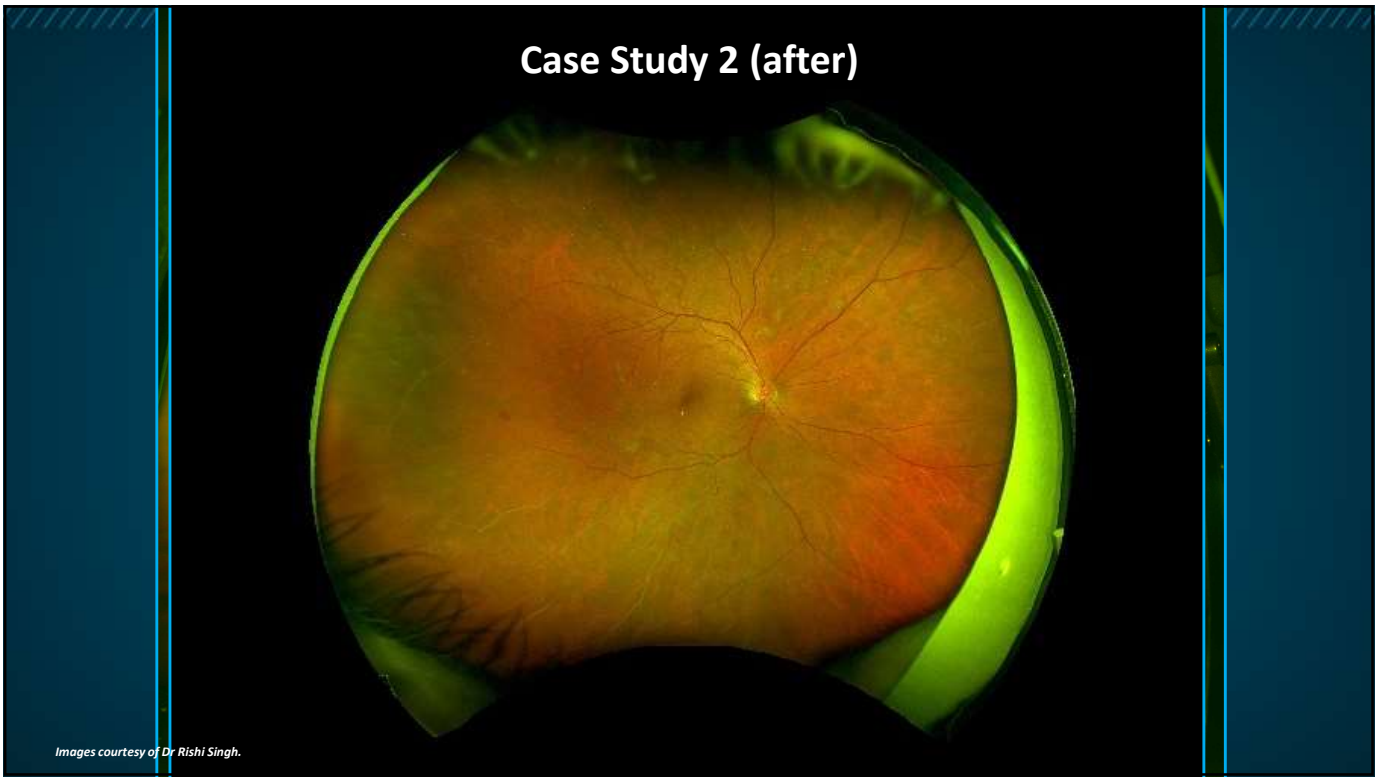

Case Study 2 (before)
Images courtesy of Dr Rishi Singh.
01:3
04:53:191

79


Case Study 2 (after)
Images courtesy of Dr Rishi Singh.

80

Case Study 2 (after)



Images courtesy of Dr Rishi Singh.

81

Conclusions

- Anti-VEGF therapy has revolutionized the care of the most common retinal diseases, including AMD, DR, DME, ROP, and RVO, and identifying patients who could benefit from these treatments is important
- Overall safety, tolerability, and immunogenicity profile of anti-VEGF therapy is acceptable (with exception of brolucizumab)
- Therapy can be individualized with drug selection, dosing regimen, and follow-up schedules
- More durable options with next-generation therapies can impact treatment burden and improve outcomes

82

Thank you!

83