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Optimizing Intravitreal Pharmacotherapies for Diabetic Macular Edema

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Learning Objectives

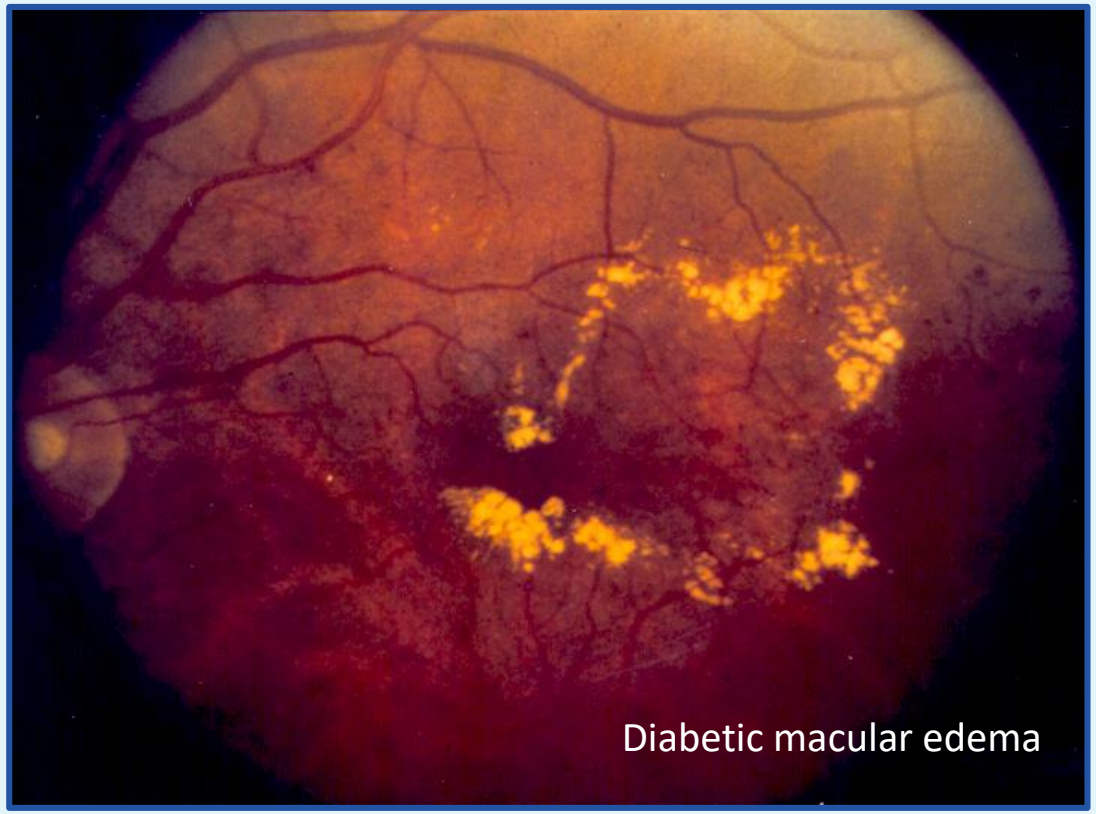
01 Describe the best approaches to treatment selection and ongoing management of diabetic macular edema (DME)

02 Explain advances in the medical treatment of DME, including emerging approaches

03 Discuss care disparities and strategies for improving vision-related outcomes in patients with DME

Introduction

- DME is a severe complication of DR that occurs as a result of inadequately treated DM[a]
  - Can occur at any stage of DR
- Manifests as retinal thickening caused by the accumulation of intraretinal fluid, primarily in the inner and outer plexiform layers[a]
  - Attributed to hyperpermeability of the retinal vasculature
- DME is the leading cause of visual impairment in patients with diabetes[b-d]
  - ~3.8% of US patients with type 2 DM have DME
  - Prevalence is expected to grow with increasing prevalence of DM
- DME may result in vision loss[e]

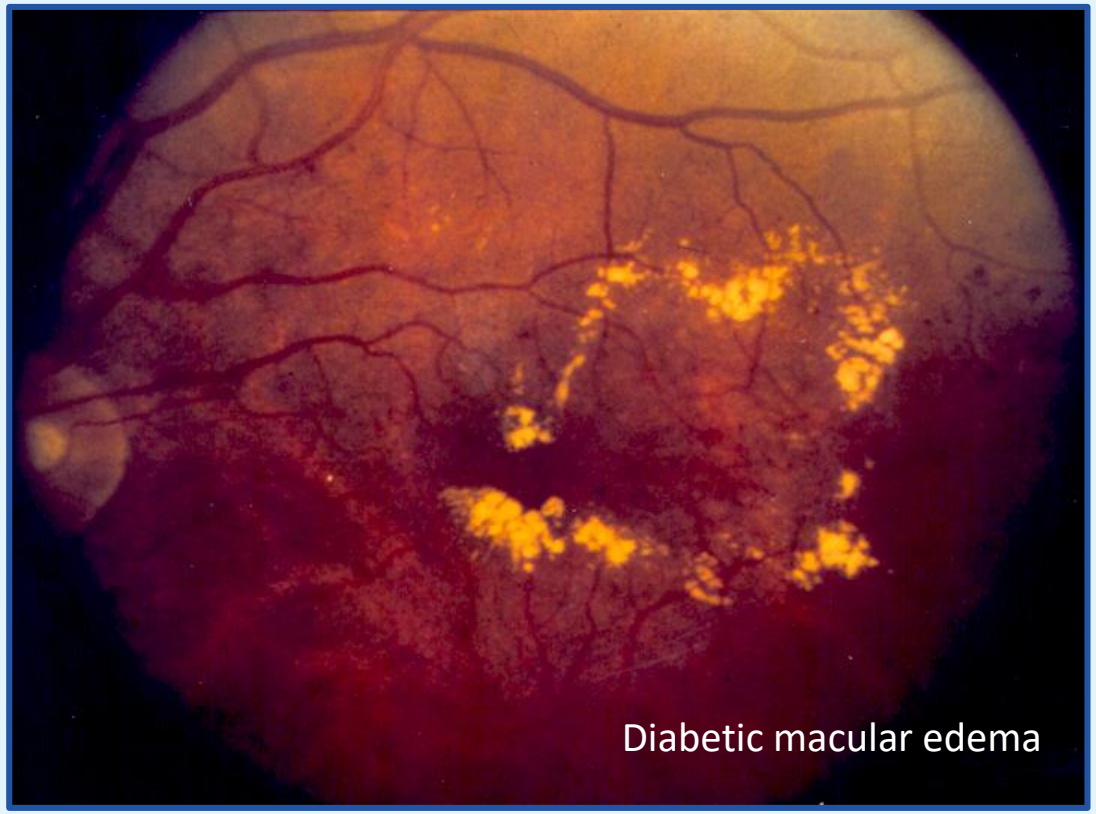

Diabetic macular edema

DM, diabetes mellitus; DR, diabetic retinopathy.

a. Musat O, et al. Rom J Ophthalmol. 2015;59:133-136; b. Holekamp NM. Am J Managed Care. 2016;22(10 suppl):s284- s291; c. Varma R, et al. JAMA Ophthalmol. 2014;132:1334-1340; d. Browning DJ, et al. Indian J Ophthalmol. 2018;66:1736-1750; e. Loftus JV, et al. Invest Ophthalmol Vis Sci. 2011;52:7498-7505.

Introduction (cont.)

- Broader insights into the pathophysiology of DME led to the advent of anti-VEGF medications[a]
- Although these treatments have improved outcomes in DME, gaps exist in their optimal utilization[a]
  - Disparities in long-term outcomes between clinical trials and real-world studies
- Corticosteroids are another important treatment option[b]
  - No clear guidelines when to switch from an anti-VEGF to a corticosteroid
  - Corticosteroids may be preferrable as the initial treatment in some patients
- New treatments are emerging that hold the promise of improving the care of larger patient subsets with DME


Diabetic macular edema

VEGF, vascular endothelial growth factor.

Sam-Oyerinde OA, et al. Ophthalmol Ther. 2023;12:809-826; b. Chawan-Saad J, et al. Taiwan J Ophthalmol. 2019;9:233-242.

DME Risk Factors

Modifiable[a-c]

- Poor glycemic control (eg, higher hemoglobin A1c)
- Hypertension
- Hyperlipidemia
- Overweight/obesity
- Nephropathy
- Anemia
- Severe obstructive sleep apnea

Nonmodifiable[c]

- Longer duration of DM
- Puberty
- Pregnancy
- History of intraocular surgery

a. Musat O, et al. Rom J Ophthalmol. 2015;59:133-136; b. Browning DJ, et al. Indian J Ophthalmol. 2018;66:1736-1750; c. Ting DS, et al. Clin Exp Ophthalmol. 2016;44:260-277; d. Diep TM, et al. Diabetes Res Clin Pract. 2013;100:298-305.

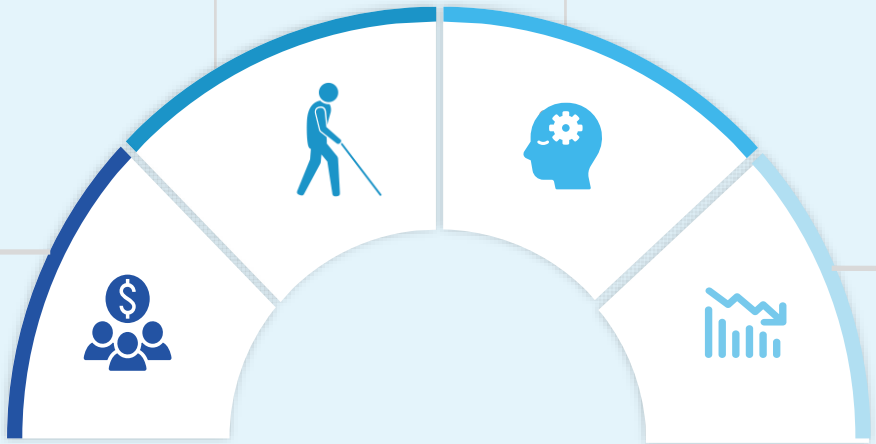
Burden of DME: Patients and Health Systems

DME has a significant impact individually and economically, posing a high treatment burden

- Patients with type 2 DM and DME have a **decreased VR-QoL** vs patients with type 1 DM and DR, glaucoma, or cataracts[a]

- DME has a **negative effect on the mental components of HR-QoL** surveys[b]

- **Healthcare resource utilization rates have been reported to be significantly higher** in patients with diabetes and DME vs diabetes alone[c]
- Working-age patients with DME averaged **25.5 healthcare visits per year** vs 15 for those with diabetes but no DME[c]



- **QoL** is greatly affected at **all stages of disease**[c]

HR-QoL, health-related quality of life; QoL, quality of life; VR-QoL, vision-related quality of life.

a. Hariprasad SM, et al. Brit J Ophthalmol. 2008;92:89; b. Loftus JV, et al. Invest Ophthalmol Vis Sci. 2011;52:7498-7505; c. Wallick CJ, et al. Ophthalmic Surg Lasers Imaging Retina. 2015;46:744-751.

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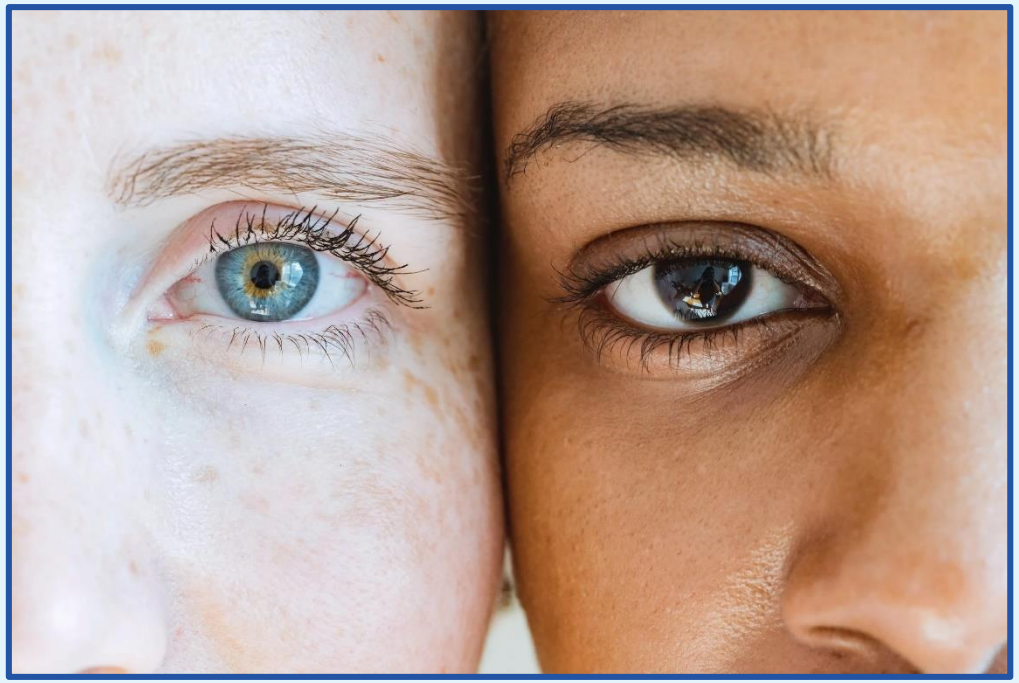
Race/Ethnicity/Gender Disparities in DR/DME

Disparities in DR/DME: Screening

- Racial and ethnic minorities are **disproportionately affected** by DR and DME at all ages but are **less likely to be screened**, even after adjusting for socioeconomic factors[a-d]
  - Risk for DME is increased 2- to 3-fold in non-Hispanic Black vs non-Hispanic White persons
- Screening disparities stem from patient, provider, and institutional barriers[a-c]
  - Examples: Screening not mentioned, difficulty accommodating appointments (eg, transportation or time issues), and perceptions of not being treated as well as or with as much respect/courtesy as other patients
- Due to screening disparities, **non-White patients often present with more advanced diabetic eye disease**[a]



a. Coney JM, et al. J Natl Med Assoc. 2022;114:171-181; b. Thomas CG, et al. JAMA Ophthalmol. 2021;139:791-795; c. Huang BB, et al. Transl Vis Sci Technol. 2023;12:14; d. Barsegian A, et al. Int J Clin Endocrinol Metab. 2017;3:34-45.

Disparities in DR/DME: Treatment

- Non-White patients may not have the same response to DME treatment as their White counterparts
- In a study from an urban-based academic institution, Black patients had a significantly lower response to the anti-vascular endothelial growth factor (anti-VEGF) bevacizumab vs their White counterparts

	Single-Dose Analysis (N = 314)			Three-Dose Analysis (N = 151)		
	Black	Hispanic	White	Black	Hispanic	White
Total, N	146	84	84	68	42	41
% with improved VA	26.7	39.4	50.0	33.8	54.8	58.5

VA, visual acuity.

Osathanugrah P, et al. Am J Ophthalmol. 2021;222:310-317.

Disparities in DR/DME: Clinical Trials

- Women are less likely to enroll in DME clinical trials vs men[a]
  - Enrollment fraction, 3.64% vs 4.11% (OR, 1.22)
- In an assessment of 25 clinical trials for DR/DME, Black patients were significantly under-represented vs White patients[b]
  - **3.0-fold disparity in NIH trials** for DME
  - **4.5-fold disparity in industry trials** for DME
  - 2.1-fold disparity compared with disease burden in industry trials for DR

NIH-Sponsored Trials for DM, Proportion (± SD), %		Industry-Sponsored Trials for DM, Proportion (± SD), %	
Black	**White**	**Black**	**White**
12.6 ± 3.3	69.5 ± 4.4	8.6 ± 2.9	80.0 ± 2.2

NIH, National Institutes of Health; OR, odds ratio; SD, standard deviation.

a. Kuriyan AE, et al. iovs. 2022;63:2505-F0231; b. Sanjiv N, et al. J Natl Med Assoc. 2022;114:123-140.

Addressing Care Disparities

What can clinicians do to ensure more equitable care in patients with DR/DME?

Addressing Disparities in DME

- Work towards building trust with patients
- Guide patients to resources that can improve their access to care
- Consider system-level interventions (eg, patient registries, provider reminders)
- Screen patients for health literacy and provide them with appropriate education
- Strive to improve screening of at-risk patients
- Be proactive in enrolling minority populations in clinical trials

Barsegian A, et al. Int J Clin Endocrinol Metab. 2017;3:34-45.

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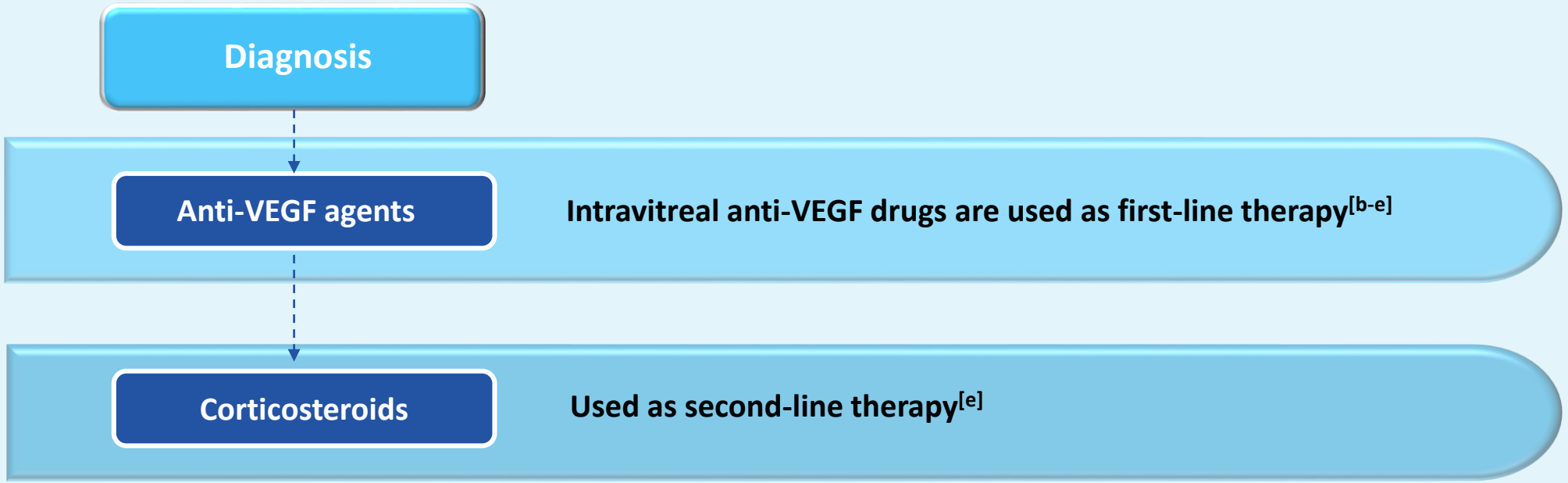
Examining the Standard of Care for DME

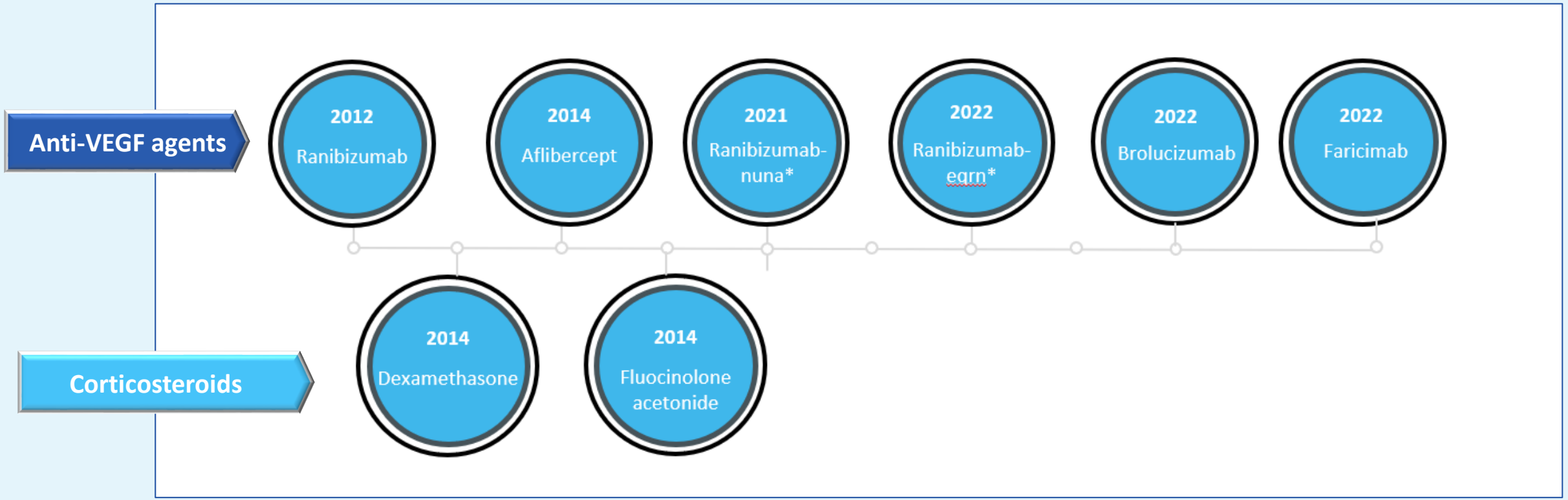
Standard of Care for DME

GOAL: Achieve best visual outcome with edema improvement while minimizing treatment burden[a]



a. Chen JT, et al. Jpn J Ophthalmol. 2020;64:235-242; b. Kim EJ, et al. Curr Diab Rep. 2019;19:68; c. Tan GS, et al. Lancet Diabetes Endocrinol. 2017;5:143–155;
d. Nicolò M, et al. Ophthalmologica. 2020;243:453-460; e. Udaondo P, et al. Ophthalmol Ther. 2022;11:489-502.

FDA-Approved Therapies in DME

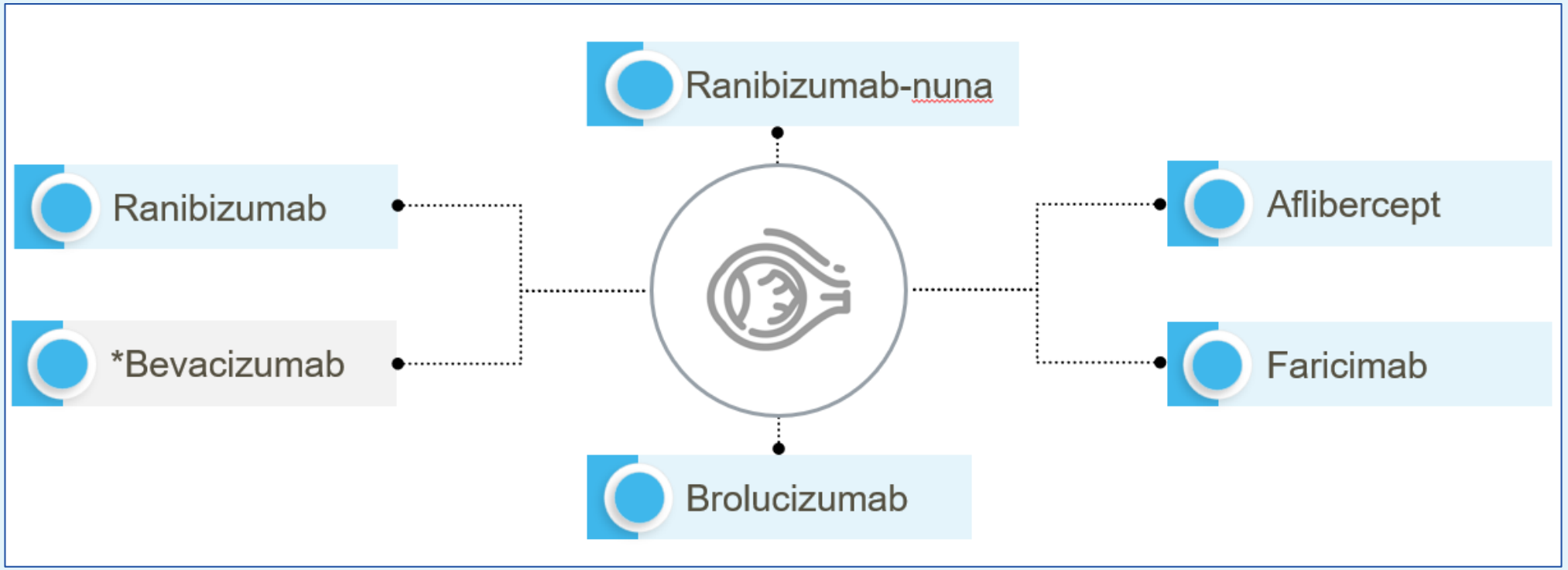


*Biosimilars of ranibizumab.

a. Chen JT, et al. Jpn J Ophthalmol. 2020;64:235-242; b. Kim EJ, et al. Curr Diab Rep. 2019;19:68; c. Tan GS, et al. Lancet Diabetes Endocrinol. 2017;5:143-155;
d. Nicolò M, et al. Ophthalmologica. 2020;243:453-460; e. Udaondo P, et al. Ophthalmol Ther. 2022;11:489-502.

Anti-VEGF Overview and Administration

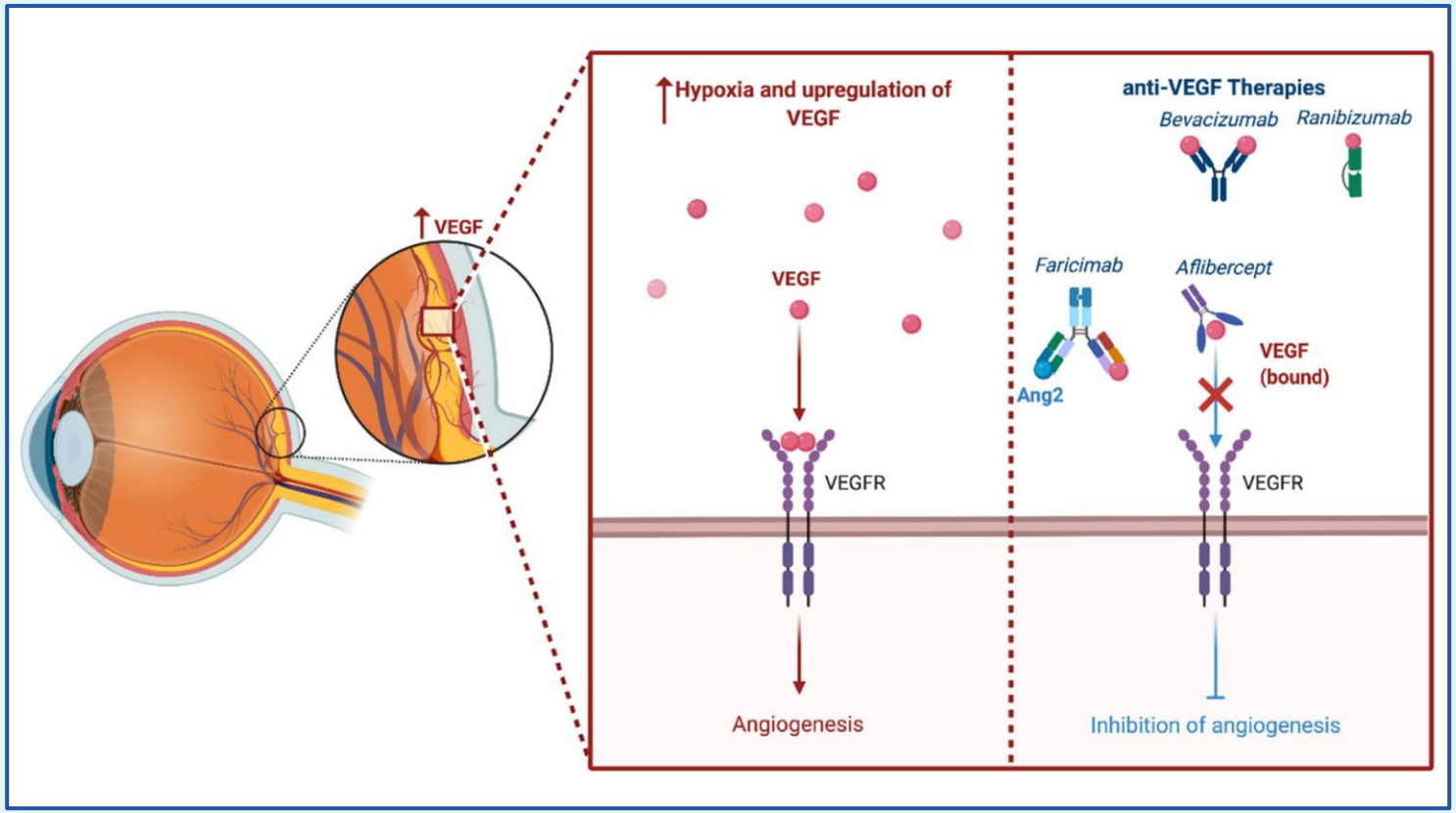
Anti-VEGF therapy is delivered via **intravitreal injection** into the vitreous cavity



*Use of bevacizumab in the eye is off-label.

Udaondo P, et al. Ophthalmol Ther. 2022;11:489-502.

Anti-VEGF Mechanism of Action



Overview[a,b]

- VEGF plays a pivotal role in the development of DME
- When VEGF binds to its receptor, a signaling cascade is initiated that promotes angiogenesis and inflammation
- Anti-VEGF agents turn off the signal mediated by VEGF by binding to its receptor

a. Chauhan MZ, et al. Cell. 2022;11:1950; b. Fogli S, et al. Pharmacol Res. 2016;103:149-157.
Image reprinted with permission from Chauhan MZ, et al. Cell. 2022;11:1950.

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Traditional Anti-VEGF Therapies

Ranibizumab: RISE and RIDE Studies

Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds human VEGF-A[a]

RISE and RIDE Efficacy and Safety[b]

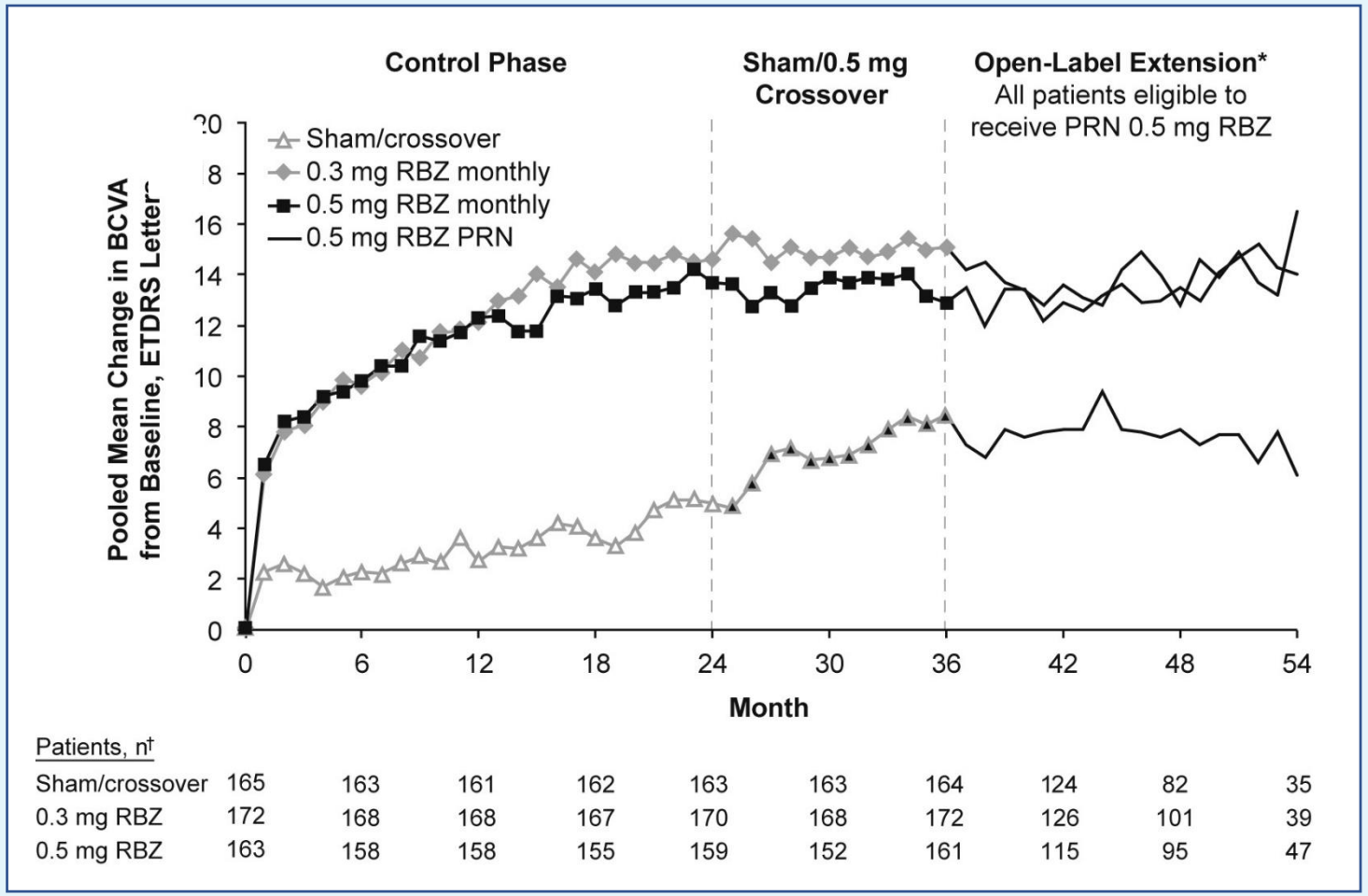
- Patients (N = 377) were randomly assigned 1:1:1 to 0.3-mg or 0.5-mg doses of ranibizumab or sham injections, all administered monthly for 24 months

24-month findings

- 18.1% of sham patients gained ≥ 15 letters vs 44.8% of 0.3-mg ranibizumab patients and 39.2% of 0.5-mg ranibizumab patients
- Both ranibizumab arms underwent significantly fewer macular laser procedures vs the sham arm
  - 0.3-0.8 vs 1.6-1.8
- Endophthalmitis occurred in 4 ranibizumab-treated patients
- Systemic vascular effects occurred in 2.4% to 8.8% of ranibizumab-treated patients and 4.9% to 5.5% of sham patients

a. NIH. Ranibizumab (Lucentis). Published August 15, 2015. Accessed May 15, 2023; b. Nguyen QD, et al. Ophthalmology. 2012;119:789-801.

RISE and RIDE: Long-Term Outcomes



As-Needed Ranibizumab

- **Vision gains** achieved after 1 or 3 yrs of monthly ranibizumab were **maintained with as-needed ranibizumab**
  - Marked reduction in treatment frequency
  - Some patients required no additional treatments
- Patients whose treatment was **deferred** by 2 yrs (randomized initially to sham) **did not achieve same BCVA gains** as those who received ranibizumab from baseline
- **No new safety concerns** identified vs core and other studies of ranibizumab

BCVA, best-corrected visual acuity.

Boyer DS, et al. Ophthalmology. 2015;122:2504-2513.e1.

VISTA and VIVID Studies: Aflibercept

Aflibercept is a fusion protein that binds with more affinity to VEGF-A vs ranibizumab and bevacizumab and binds to VEGF-B and placental growth factor[a]

148-Week Results[b]

- Patients (N = 872) were randomly assigned to IAI 2 mg every 4 weeks, IAI 2 mg every 8 weeks after 5 monthly doses, or laser control, with rescue treatment allowed after week 24
  - From week 100, laser patients who did not receive IAI rescue received as-needed IAI per treatment criteria

148-week findings*

- More IAI- vs laser-treated eyes had:
  - BCVA gains: Mean of 10.7 letters vs 1.5 letters
  - Gained ≥ 15 letters from baseline: Mean of 40.5% vs 16.3%
  - Improvement of ≥ 2 steps in the DRSS: Mean of 39.1% vs 18.8%
- No new safety concerns identified, with most frequent ocular serious AE being cataracts
  - 3.1% for 2 mg every 4 weeks, 2.1% for 2 mg every 8 weeks, and 0.3% for laser

*Mean for all IAI and laser cohorts across both studies.

IAI, intravitreal aflibercept injection.

a. Papadopoulos N, et al. Angiogenesis. 2012;15:171-185; b. Heier JS, et al. Ophthalmology. 2016;123:2376-2385.

DRCR Network Studies: Protocol T and V

The Diabetic Retinopathy Clinical Research (DRCR) Retina Network helped establish anti-VEGF therapy as a first-line treatment for vision-threatening center-involving DME (CI-DME)

Protocol T Study[a]

- A comparison of the efficacy of aflibercept, bevacizumab, and ranibizumab for CI-DME concluded:
  - Aflibercept is the most effective drug in eyes with baseline VA of 20/50 or worse
  - All 3 drugs have comparable efficacy in eyes with better baseline VA (between 20/32 and 20/40)

Protocol V Study[b]

- A comparison of aflibercept, laser photocoagulation, and observation in the initial management of patients with CI-DME and a baseline BCVA of 20/25 or better showed:
  - No significant difference
    - Suggests all 3 approaches are equally effective in eyes with mild VA loss

a. Wells JA, et al. Ophthalmology. 2016;123:1351-1359; b. Baker CW, et al. JAMA. 2019;321:1880-1894.

Biosimilars Overview

May improve cost-effectiveness of treatment

FDA-Approved and Investigational Biosimilars for DME[a]
FDA Approved *Ranibizumab biosimilars:* Ranibizumab-eqrn, ranibizumab-nuna*
In Phase 3 Trials *Ranibizumab biosimilars:* BCD100, CKD-701, LUBT010, R-TPR-024, SJP-0133 *Aflibercept biosimilars:* ABP-938, ALT-L9, CT-P42, FYB203, MYL-1701P, OT-702, SB-15, SOK583A19

*Only ranibizumab-eqrn has an interchangeability designation, allowing substitution at the pharmacy level.

Are not generics[b]

Biosimilars are **not exact copies** of biological products (ie, reference products, originators) that are no longer protected by patent, but they are **legitimate copies**

Shown to be highly similar to their originators[b,c]

To receive FDA approval, biosimilars must demonstrate **no meaningful differences** in structural or functional parameters, pharmacokinetics/pharmacodynamics, efficacy, safety, or immunogenicity vs their originators

Indications can be extrapolated[d]

Once a biosimilar receives FDA approval, it **can be used for any indications for which its originator has been approved**, provided patents for that indication have expired

a. Kapur M, et al. Int J Retina Vitreous. 2022;8:2; b. Kay J. Rheum Dis Clin North Am. 2019;45:465-476; c. Schiestl M, et al. Drug Des Devel Ther. 2017;11:1509-1515;
d. Bridges SL Jr, et al. Arthritis Rheumatol. 2018;70:334-344.

Fewer Treatments Over Time

Visual gains in patients with DME can be maintained over time via fewer injections—on average, 6 to 8 the first year, 2 to 3 the second year, 1 to 2 the third year, and 0 to 1 the fourth and fifth years.

Stuart A. AAO.org. Published May 2016. Accessed May 22, 2023.

Selection and Response

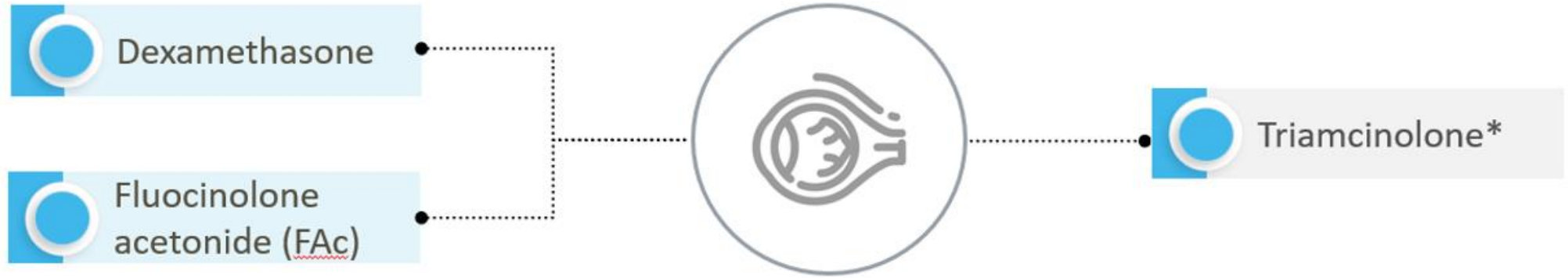
How do you decide between ranibizumab, including available biosimilars, aflibercept, and off-label use of bevacizumab?

What do you do if someone fails to respond to one of these anti-VEGF-A therapies?

FDA-Approved Corticosteroids

Corticosteroid Overview and Administration

- Corticosteroids are delivered via **intravitreal implants**[a,b]
- Steroids have potent **anti-edematous** and **anti-inflammatory** properties because they inhibit many pro-inflammatory mediators (eg, IL-1B, IL-6, IL-8, MCP-1, IP-10)[c]



*Use of triamcinolone acetonide is off-label for DME.

IL, interleukin; IP-10, interferon gamma-induced protein-10; MCP-1, monocyte chemoattractant protein-1.

a. Udaondo P, et al. Ophthalmol Ther. 2022;11:489-502; b. Ehlers JP, et al. Ophthalmology. 2022;129:88-99; c. Whitcup SM, et al. iovs. 2018;59:1-12.

Corticosteroids: Rationale/Limitations

Rationale for Use[a-c]

- Non-VEGF mediators are urgently needed for the ~40% of patients with DME who do not respond to anti-VEGF drugs
- Persistent, chronic DME in the setting of optimized anti-VEGF therapy may signal a more inflammatory-driven DME phenotype
  - Intravitreal corticosteroid therapy provides a way to control this inflammation
- Have a longer duration of action

Considerations/Limitations[a,d,e]

- Common AEs associated with corticosteroids include cataract formation, cataract progression, and ocular hypertension
  - Limit the use of corticosteroids

a. Chawan-Saad J, et al. Taiwan J Ophthalmol. 2019;9:233-242; b. Elyasi N, et al. AAO.org. Published May 2021. Accessed May 22, 2023; c. Simó R, et al. 2014;37:893-899;
d. Gao L, et al. Eye Vis (Lond). 2021;8:35; e. Ehlers JP, et al. Ophthalmology. 2022;129:88-99.

MEAD Study: DEX Implants

As a second-line pharmacologic agent for DME, intravitreal corticosteroid implants have been associated with variable outcomes

3-Year Results

- Patients were randomized in a 1:1:1 ratio to study treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or sham procedure and followed for 3 years

Findings

- Both DEX implants met the primary efficacy endpoint for improvement in BCVA
  - 22.2% and 18.4% with DEX 0.7 mg and 0.35 mg, respectively, vs 12.0% for sham
- Mean average reduction in CRT from baseline was greater with both DEX implants vs sham
  - -111.6 µm and -107.9 µm with DEX 0.7 mg and 0.35 mg, respectively, vs -41.9 µm for sham
- The safety profile was acceptable and consistent with previous reports
  - Rates of cataract-related AEs in phakic eyes were 67.9%, 64.1%, and 20.4% in the DEX 0.7 mg, DEX 0.35 mg, and sham arms, respectively

CRT, central retinal thickness; DEX, dexamethasone.

Boyer DS, et al. Ophthalmology. 2014;121:1904-1914.

Real-World Data: FAc Implant

A 2021 systematic review assessed the safety and efficacy of the FAc intravitreal implants using data from 22 observational, real-world studies that collectively included 1880 eyes with DME

Findings

Efficacy

- Mean peak visual gain was +8.7 letters (11.3 months post-FAc injection), with greater gains for lower baseline BCVA and for more recent DME
- Mean baseline CRT was 516 µm, which decreased to a minimum of 332 µm
- Maximum CRT decrease of −34.3% from baseline was observed at 16.6 months, with a greater percentage of CRT decrease observed for thicker vs thinner baseline CRT

Safety

- 20% of patients developed FAc-induced ocular hypertension during the follow-up period
- Lens opacification occurred in 31.4% of phakic patients and 43.2% required cataract surgery

CRT, central retinal thickness; FAc, fluocinolone acetonide.

Kodjikian L, et al. Pharmaceutics. 2021;13:72.

DRCR Protocol U: DEX + Ranibizumab

Phase 2 RCT comparing continuing intravitreous ranibizumab alone vs combining with an intravitreous DEX implant in eyes with persistent DME

3-Year Results

- 129 eyes from 116 adults with persistent DME with visual acuity of 20/32 to 20/320 after ≥ 3 anti-VEGF injections before a run-in phase (ie, additional 3 monthly 0.3-mg ranibizumab injections)
- Following run-in, study eyes with persistent DME were randomly assigned to receive 700 µg of DEX (n = 65) or sham treatment (n = 64 eyes) in addition to continued 0.3-mg ranibizumab in both treatment arms as often as every 4 weeks based on a structured re-treatment protocol

Findings

- Patients with persistent DME who received intravitreal DEX implants in combination with ranibizumab had decreased retinal thickening on OCT, but BCVA did not improve vs continuing ranibizumab alone
- 29% of patients in the combination group vs 0% in the ranibizumab monotherapy group experienced increased IOP necessitating treatment with antihypertensive drops

OCT, optical coherence tomography.

Maturi RK, et al. JAMA Ophthalmol. 2018;136:29-38.

Selecting Between Corticosteroids

Which patients have you found to be the best candidates for corticosteroids, and do you ever use them in the frontline?

When selecting between available corticosteroids, how do you decide which agent to select?

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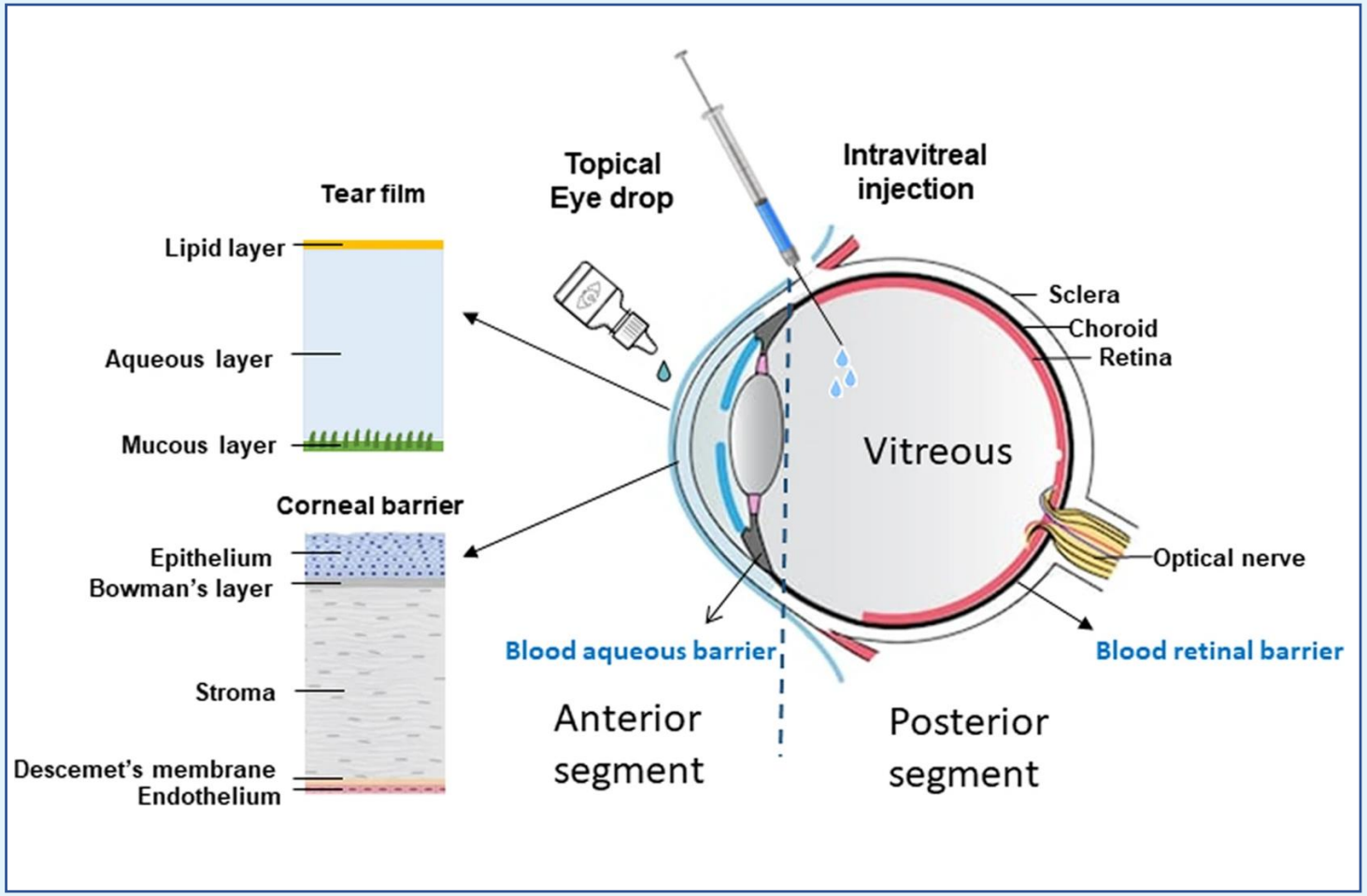
Unmet Need and Barriers With Current Disease Management

Anti-VEGF Administration Challenges



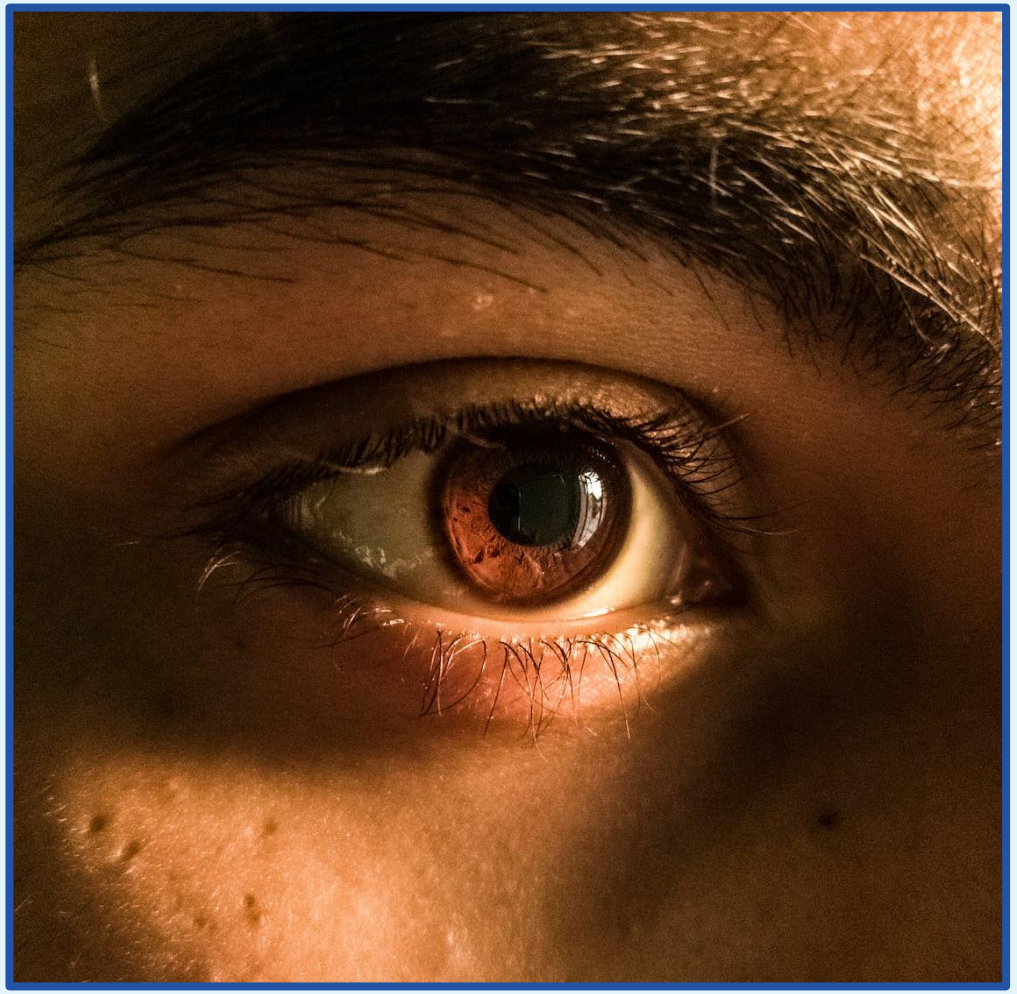
Challenges

- Topical administration is ineffective in reaching the retina, making intravitreal delivery necessary
- Multiple intravitreal injections are needed to achieve optimal and continued effect
- Administration requirements can be burdensome to patients, resulting in compliance challenges
- Intravitreal injections can lead to ocular complications, ranging from subconjunctival hemorrhage and raised intraocular pressure to sight-threatening endophthalmitis and retinal detachment

Seah I, et al. Eye (Lond). 2020;34:1341-1356.

Clinical Practice Challenges

- Real-world evidence suggests the **burden of treatment** on patients, caregivers, and the health care system reduces patients' ability to follow their treatment management plan as recommended[a-d]
- On average, including travel time, each intravitreal injection appointment takes ~4.5 hours[e]
  - Equates to a treatment burden over 6 months of 20 hours
- Even when adequately treated, a subset of DME patients **do not respond** to current anti-VEGF treatment[f]



a. Holekamp NM, et al. Am J Ophthalmol. 2018;191:83-91; b. Ciulla TA, et al. Br J Ophthalmol. 2021;105:216-221; c. Holekamp NM. Am J Manage Care. 2019;25(10 suppl):S172-S181; d. Dervenis N, et al. Adv Ther. 2017;34:1270-1282; e. Sivaprasad S, et al. Clin Ophthalmol. 2016;10:939-946; f. Bressler NM, et al. Am J Ophthalmol. 2018;195:93-100.

Gaps and Treatment Barriers: Patient and HCP

Real-world studies have highlighted undertreatment of DME patients, due to the high treatment burden associated with frequent anti-VEGF injections

Patient Education

- Failure to recognize symptoms of DME
- Lack of understanding of risk diabetes poses to eyesight
- Noncompliance with recommendation to have a yearly dilated eye exam

PATIENT

Undertreatment

- Real-world patients have been observed to receive fewer intravitreal injections over the first year of treatment, are monitored less frequently, and achieve inferior vision outcomes
- Patients are at high risk of being lost to follow-up

HCP

Underdiagnosis

- Time constraints
- Insidious nature of both DR and DME

HCP

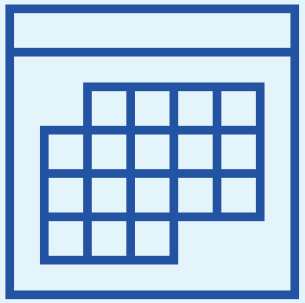
Patient Outcomes

- Recognize treatment challenges
- Decrease treatment burden

PATIENT

Holekamp NM et al. Am J Ophthalmol. 2018;191:83-91; Chou CF, et al. Diabetes Care. 2014;37:180-188.

Addressing Treatment Challenges



Extended Dosing Strategies

- ***Pro re nata* (PRN)** is an as-needed approach that was developed to decrease the number of injections while maintaining a fixed follow-up schedule to closely monitor treatment responses
- **Treat and extend (T&E)** is a regimen whereby the anti-VEGF treatment interval is gradually extended or reduced until the ideal interval for that patient is established, as evidenced by stability of vision and/or retinal anatomy on OCT

Novel Treatments

- Novel delivery methods and agents aim to extend treatment intervals for anti-VEGF-A therapy, provide broad-spectrum VEGF inhibition, and target alternative pathways and mechanisms involved in the pathogenesis of DME
- These treatment modalities ultimately aim to decrease treatment burden or improve disease control, aiming to improve real-world outcomes for patients with DME

Ahmed AA, et al. Retinal Physician. Published September 1, 2022. Accessed May 8, 2023; Sivaprasad S, et al. Clin Ophthalmol. 2016;10:939-946.

Treatment Barriers in Clinical Practice

What barriers to optimal treatment do you encounter in clinical practice and what strategies do you use to overcome these barriers?

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Novel Recently Approved DME Treatments

Opportunity to Mitigate Treatment Burden?

Faricimab[a]

FDA approved for DME and nAMD

Administration: 1 of 2 dosing regimens recommended

Regimen 1: 6 mg every 4 weeks (~28 days ± 7 days apart, monthly) for at least 4 doses, after which the dosing interval can continue every 4 weeks or be extended up to 8 weeks, provided resolution was observed on CST of the macula via OCT following the initial 4 treatments and follow-up evaluations support interval extension

Regimen 2: 6 mg every 4 weeks for the first 6 doses, followed by 6-mg doses administered at intervals of every 8 weeks

Brolucizumab[b]

FDA approved for DME and nAMD

Administration: 6 mg every 6 weeks (~39-45 days apart) for the first 5 doses, followed by 1 dose of 6 mg every 8 to 12 weeks

Dosing intervals shorter than 8 weeks after initial treatment should not be used due to a risk of retinal vasculitis and/or retinal vascular occlusion

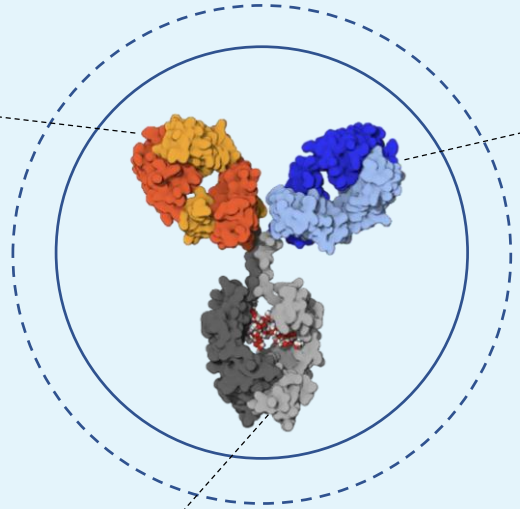
CST, central subfield thickness; nAMD, neovascular age-related macular degeneration.

a. Faricimab-svoa [prescribing information]. Approved 2022. Revised January 2023; b. Broculizimab-dbll [prescribing information]. Approved 2019. Revised December 2022.

Faricimab Mechanism of Action

- Faricimab is the **first bispecific antibody** deigned for intraocular use: 1 molecule, 2 targets
- **Simultaneous inhibition** of Ang-2 and VEGF-A

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



Anti–VEGF-A Fab
- Reduces vascular leakage
- Inhibits neovascularization

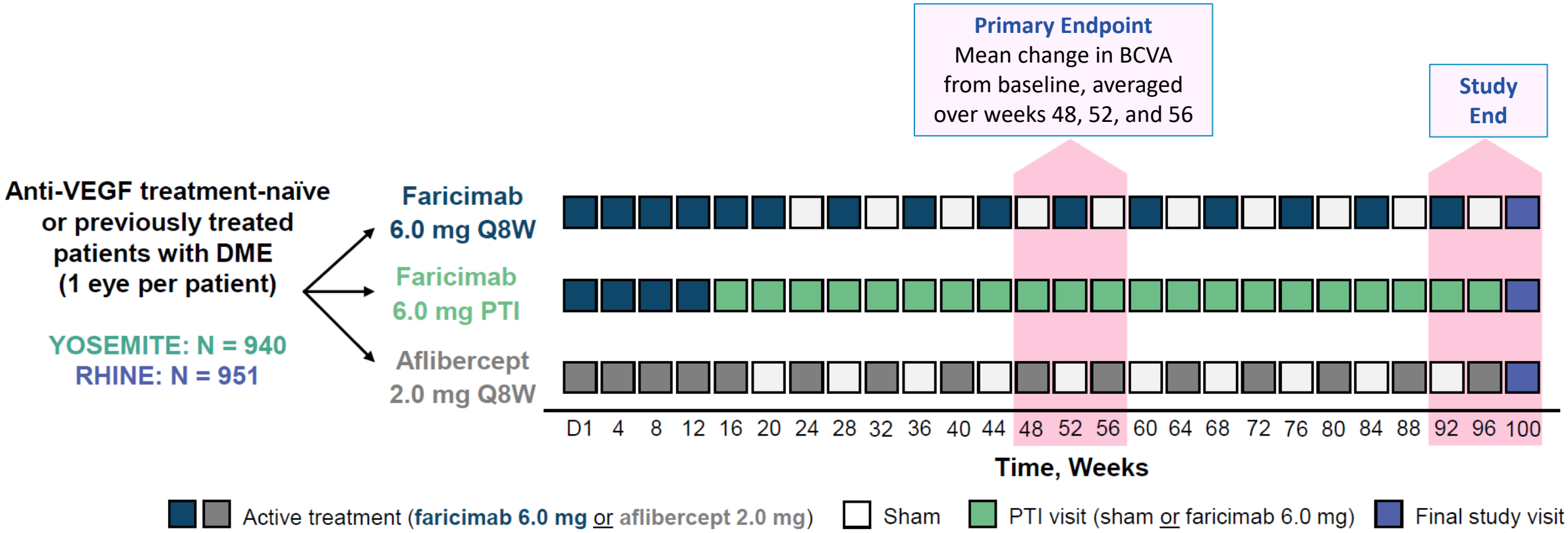
Modified Fc
- Reduces systemic exposure
- Reduces inflammatory potential

Ang-2, angiopoietin-2.

Sahni J, et al. Ophthalmology. 2019;126:1155-1170.

Faricimab: YOSEMITE and RHINE Study Design

- Phase 3, randomized, double-masked, active comparator-controlled trials
- 1891 patients with center-involving DME (CST ≥ 325 µm) and BCVA of 25 to 73 ETDRS letters

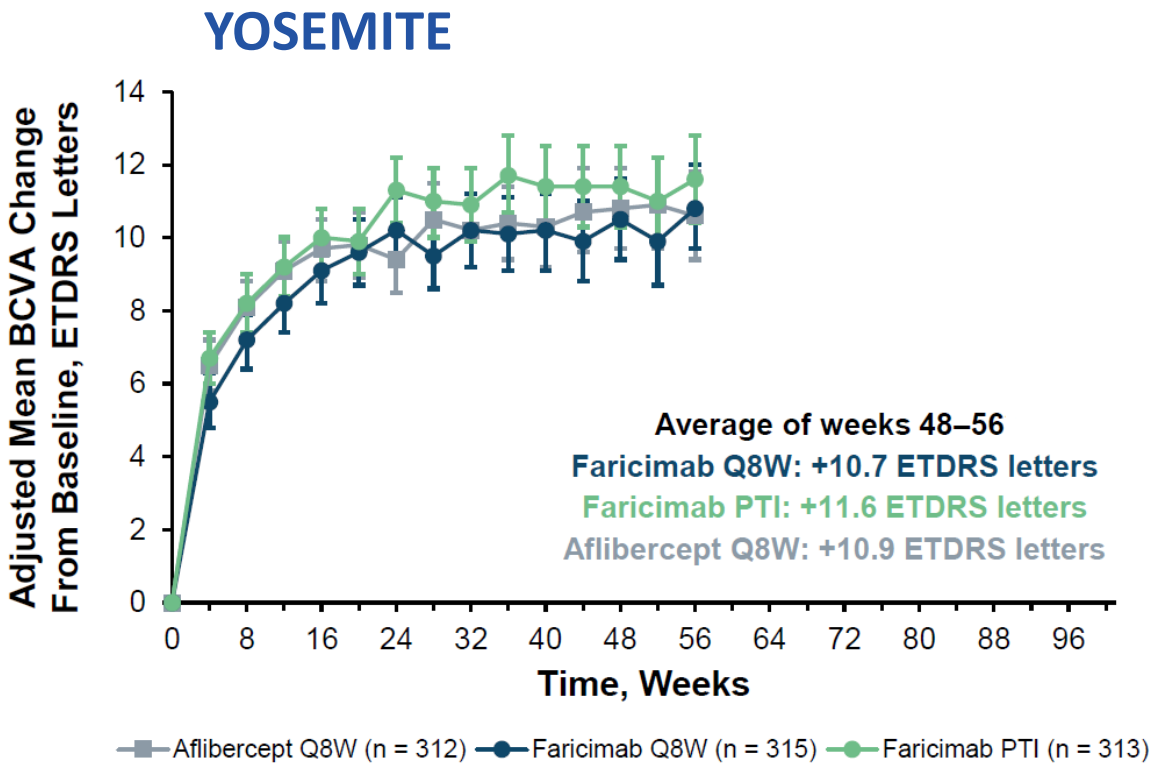


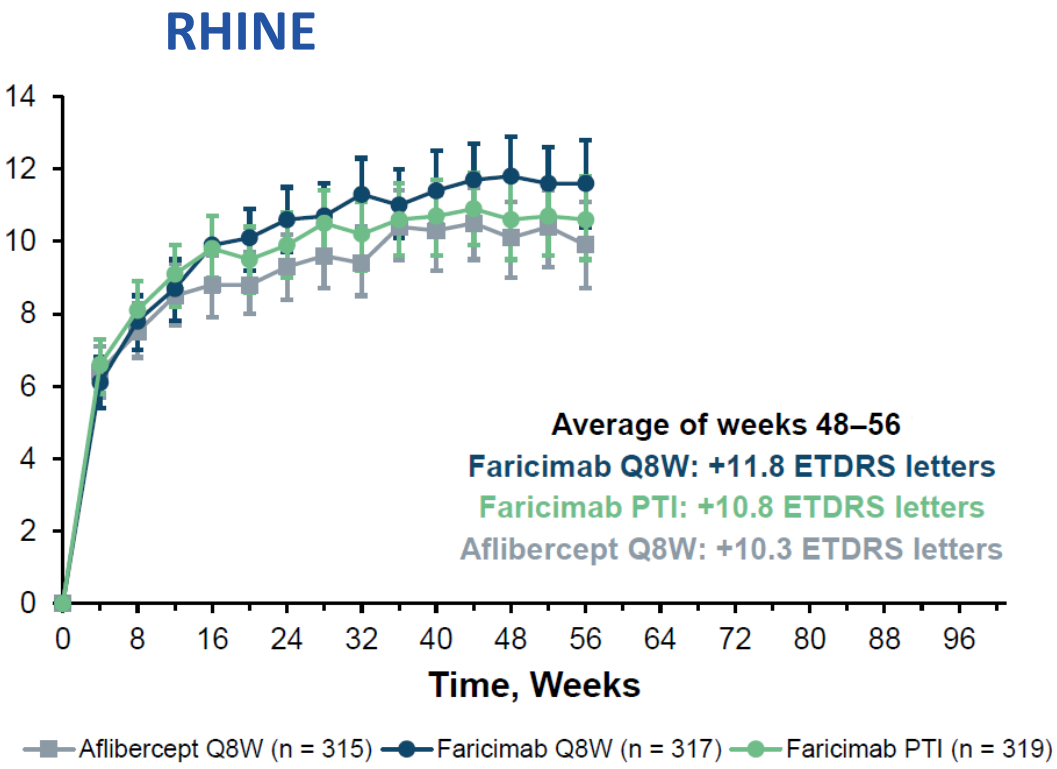
CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalized treatment interval.

Eter N, et al. Ophthalmol Sci. 2021;2:100111.

YOSEMITE and RHINE: 1-Year Efficacy

BCVA gains with both faricimab dosing strategies were noninferior to aflibercept administered every 8 weeks



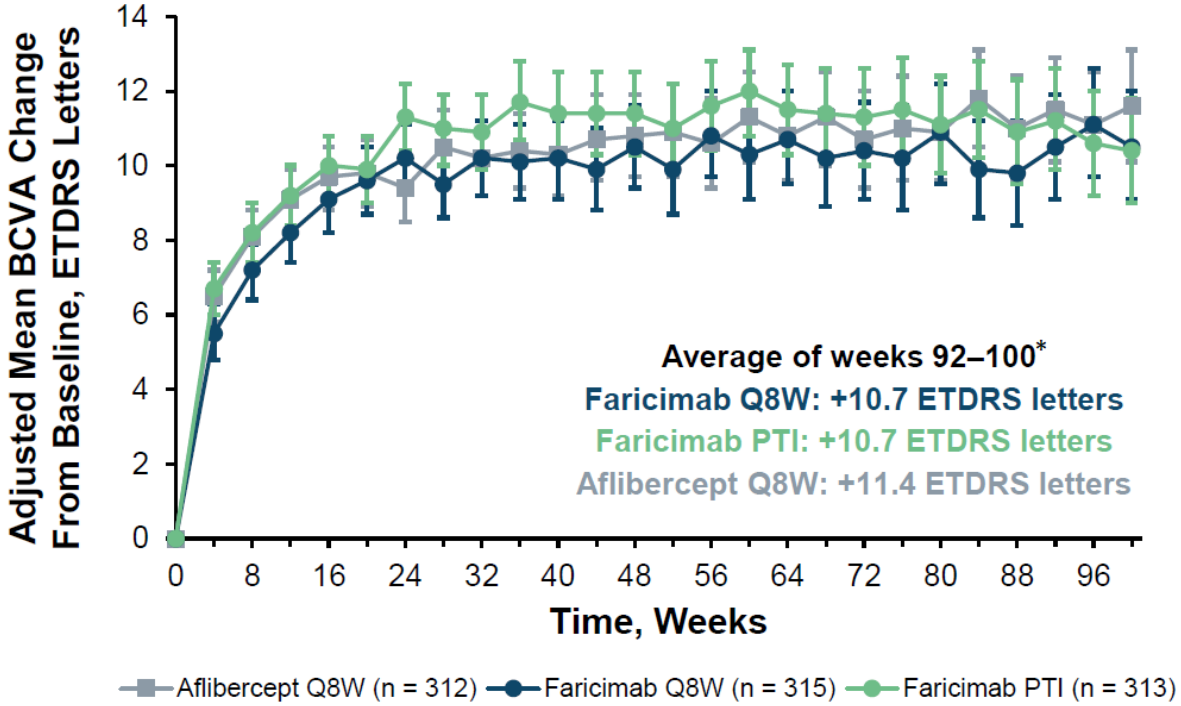


Wykoff CC, et al. Lancet. 2022;399:741-755.

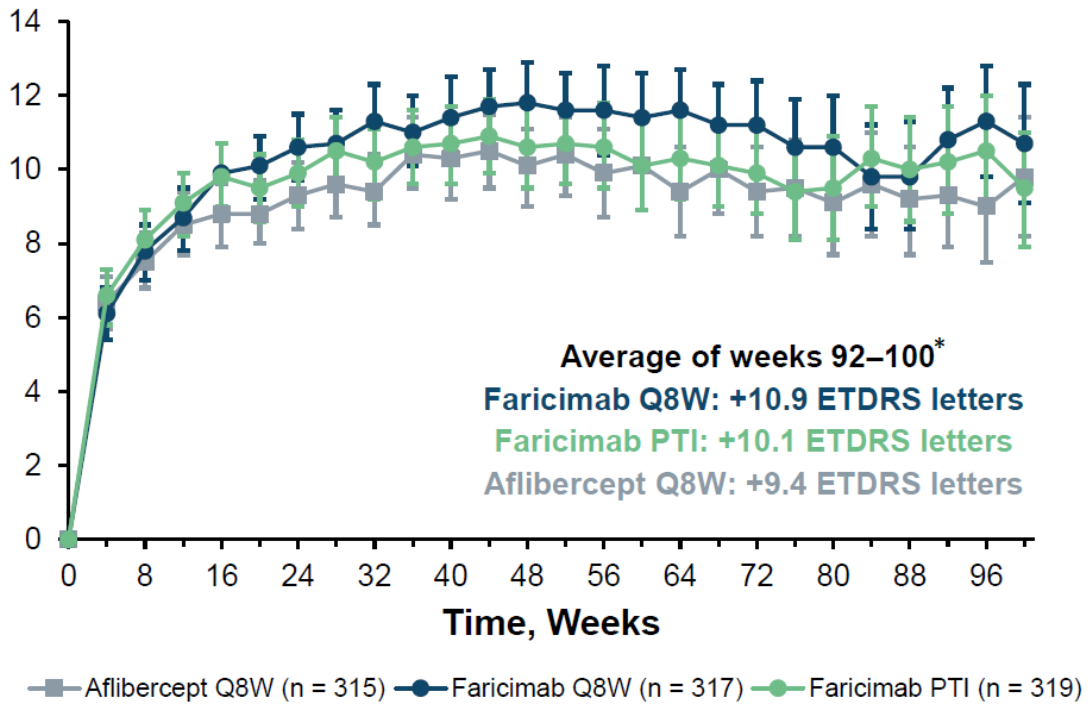
YOSEMITE and RHINE: 2-Year Efficacy

BCVA gains with both faricimab dosing intervals at 1 year remained noninferior to aflibercept and were maintained through year 2

YOSEMITE



RHINE



*Adjusted mean BCVA change from baseline at 2 years, averaged over weeks 92, 96, and 100

Wells JA, et al. Presented at: Angiogenesis, Exudation, and Degeneration 2022 Virtual Congress; February 11-12, 2022.

YOSEMITE and RHINE: Disease Control/Dosing

Disease Control

- Improved anatomic outcomes were observed with faricimab administered up to every 16 weeks vs aflibercept administered every 8 weeks, with results maintained through year 2
  - Change in CST favored faricimab
  - More patients treated with faricimab vs aflibercept achieved absence of DME and absence of intraretinal fluid

Dosing

- 79% of patients who achieved a faricimab dosing interval of every 12 to 16 weeks at week 52 maintained a dosing interval ≥ 12 weeks through week 96
- 76% of patients who achieved a faricimab dosing interval of every 16 weeks at week 52 maintained this dosing interval through week 96

Wells JA, et al. Presented at: Angiogenesis, Exudation, and Degeneration 2022 Virtual Congress; February 11-12, 2022.

YOSEMITE and RHINE: Safety

Faricimab was well tolerated

No cases of retinal vasculitis or occlusive retinal vasculitis

Events Per 100 Patient Years

Ocular AEs	• 58.65 faricimab Q8W • 55.13 faricimab PTI • 43.58 aflibercept Q8W
Serious Ocular AEs	• 2.99 faricimab Q8W • 3.72 faricimab PTI • 1.93 aflibercept Q8W
Intraocular Inflammation Events	• 0.88 faricimab Q8W • 1.38 faricimab PTI • 0.88 aflibercept Q8W

PTI, personalized treatment interval; Q8W, every 8 weeks.

Wells JA, et al. Presented at: Angiogenesis, Exudation, and Degeneration 2022 Virtual Congress; February 11-12, 2022.

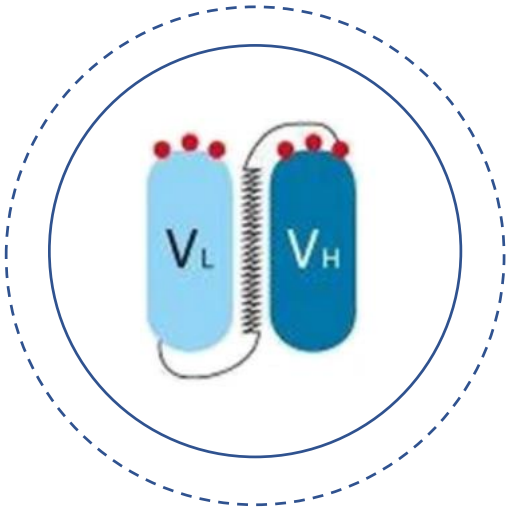
Faricimab: Rhone-X

- Faricimab is currently being studied in the phase 3 Rhone-X study
- Will provide safety and efficacy data for up to 4 years of faricimab treatment

ClinicalTrials.gov. NCT04432831. Accessed May 23, 2023.

Brolucizumab Mechanism of Action

- Binds to the 3 major isoforms of VEGF-A: VEGF110, VEGF121, and VEGF165[a]
- Binding suppresses endothelial cell proliferation, neovascularization, and vascular permeability[a]



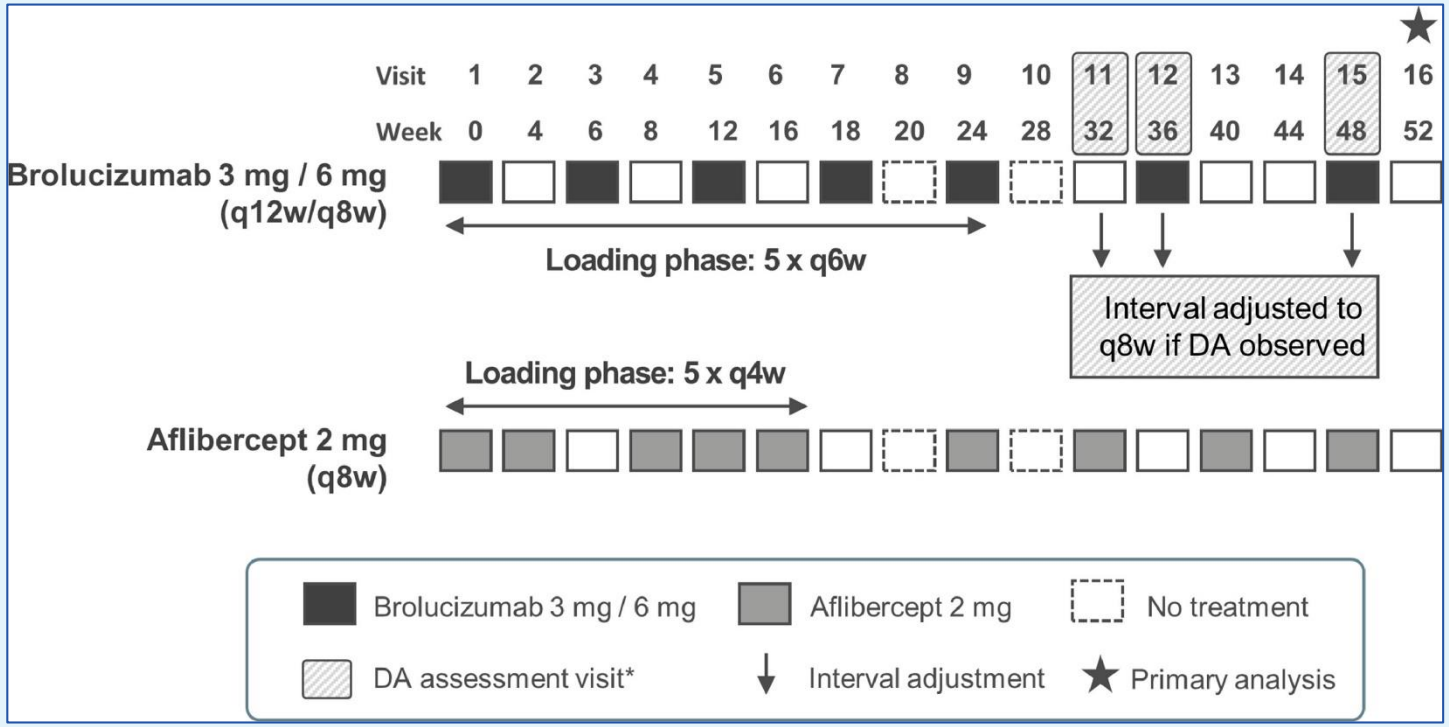
scFv composed of 2 complementarity-determining regions of the anti-VEGF molecule grafted to a human scFv scaffold[b]

scFv, single-chain antibody fragment.

a. Broculizimab-dbll [prescribing information]. Approved 2019. Revised December 2022; b. Moret E, et al. Graefes Arch Clin Exp Ophthalmol. 2022;260:1005-1014.

Brolucizumab: KESTREL and KITE Study Design

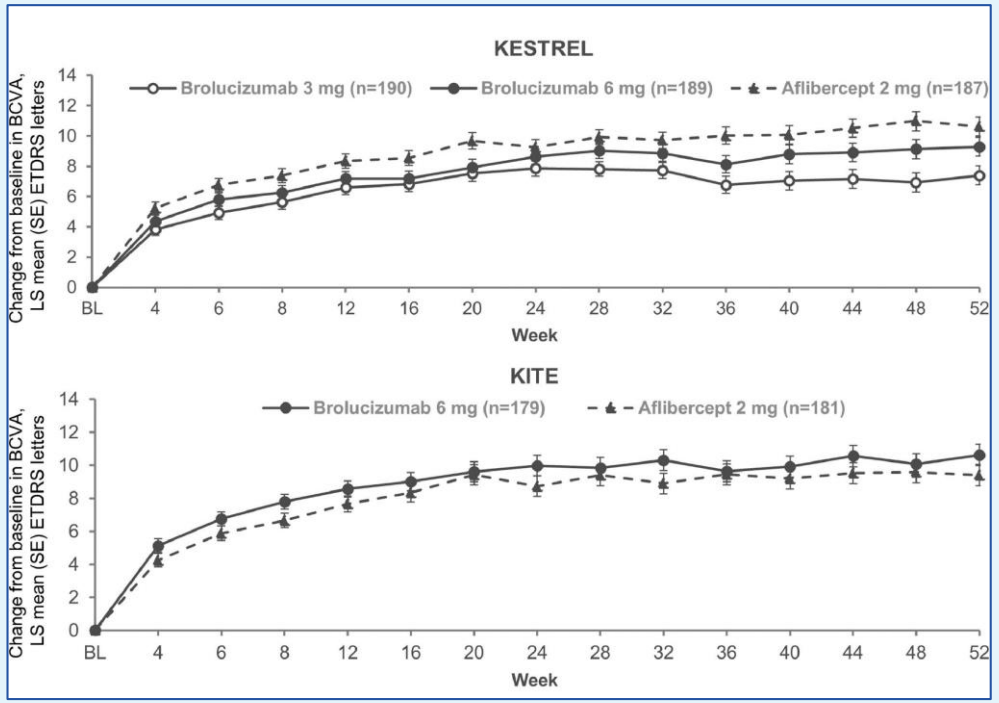
- Phase 3, 100-week, randomized, double-masked, active-controlled, multicenter trials
- Primary endpoint: BVCA change from baseline at week 52

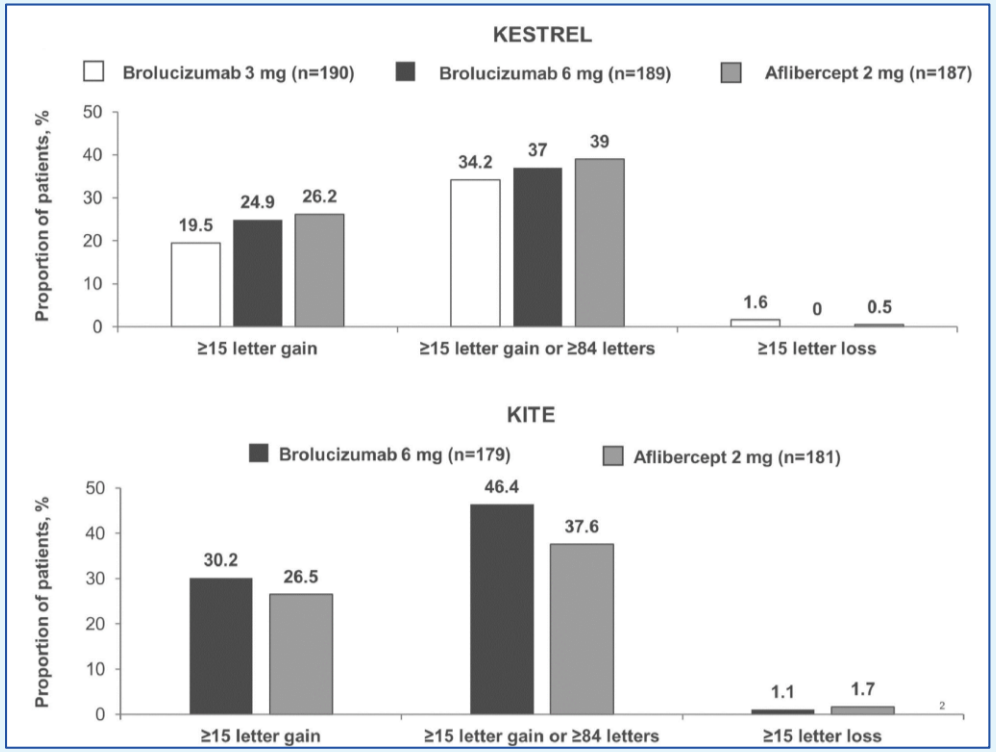


Brown DM, et al. Am J Ophthalmol. 2022;238:157-172.

KESTREL and KITE: 1-Year Efficacy

Brolucizumab 6 mg was noninferior to aflibercept in mean change in BCVA from baseline





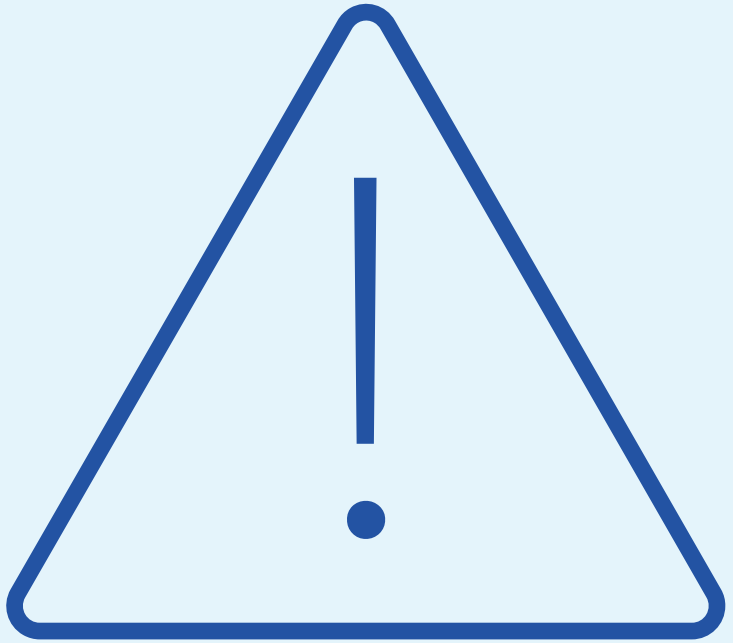
Brown DM, et al. Am J Ophthalmol. 2022;238:157-172.

Brolucizumab Safety: MERLIN Study

Dosing intervals after initial treatment should not be shorter than 8 weeks

2-year, phase 3 study assessing brolucizumab 6 mg or aflibercept 2 mg every 4 weeks in patients with nAMD

- **9.3%** of patients treated with brolucizumab developed **intraocular inflammation**
  - Included **retinal vasculitis** and **retinal vascular occlusion**
- Based on these safety risks, MERLIN and other studies assessing shorter brolucizumab dosing intervals, including RAPTOR and RAVEN, were **terminated early**



Coney JM, et al. AAO EyeWiki. Updated April 12, 2023. Accessed May 24, 2023.

Use in Clinical Practice

When do you use faricimab vs one of the historically used anti-VEGF therapies?

With safety concerns regarding brolucizumab, when might you consider using this agent in clinical practice?

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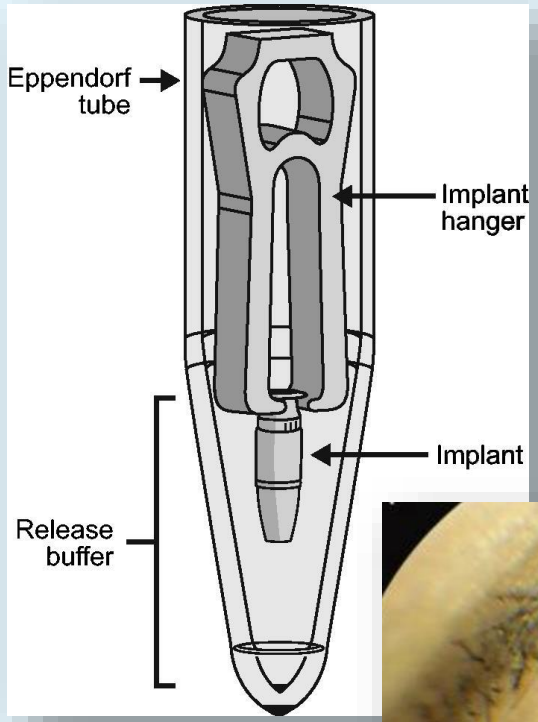
Emerging Treatments for DME

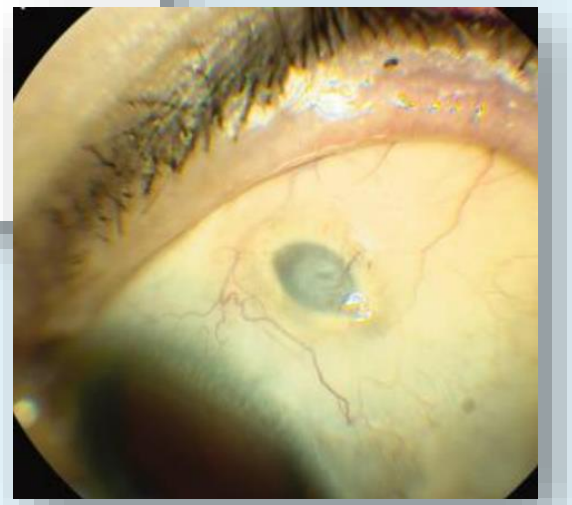
Ranibizumab Via Port Delivery System

- Innovative intraocular drug delivery system designed to provide continuous delivery of ranibizumab into the vitreous for ≥ 6 months[a]
- FDA approved in 2021 for nAMD[a]
- Currently being assessed in DME in the phase 3 Pagoda study[b]
  - Comparing ranibizumab via PDS every 24 weeks vs intravitreal administration every 4 weeks

Pagoda Findings[c]

- Met its primary endpoint, showing the PDS to be noninferior to monthly intravitreal injections through week 64
- > 95% of patients did not require supplemental treatment through each refill-exchange interval
- No new AEs identified and no cases of endophthalmitis or retinal detachment were observed, but PDS has been associated with a 3-fold increased risk of endophthalmitis





PDS, port delivery system.

a. Ranade SV, et al. Drug Deliv. 2022;29:1326-1334; b. Clinical Trials.gov. NCT04108156. Accessed May 24, 2023; c. Khanani AM, et al. Presented at Angiogenesis, Exudation, and Degeneration 2023 Virtual Congress; February 10-11, 2023.

High-Dose Aflibercept: Photon Trial

Some patients produce such large quantities of VEGF due to their underlying disease that even the strongest treatments have lacked efficacy, or they required more frequent injections[a]

Design[b]

- Phase 3 trial in patients with DME comparing 3 monthly loading doses of 8 mg of aflibercept followed by every 12 or 16 weeks with the current standard of 5 doses of 2-mg aflibercept monthly followed by every 8 weeks
- Primary endpoint was mean change in BCVA (noninferiority)

Findings[b]

- 8-mg aflibercept every 3 to 4 months was noninferior to 2-mg aflibercept every 2 months
- > 90% of patients stayed on ≥ 12-week dosing and > 80% stayed on 16-week dosing
- No cases of endophthalmitis, occlusive retinal vasculitis, or clinically relevant change in intraocular pressure were observed
- No increase in systemic toxicity

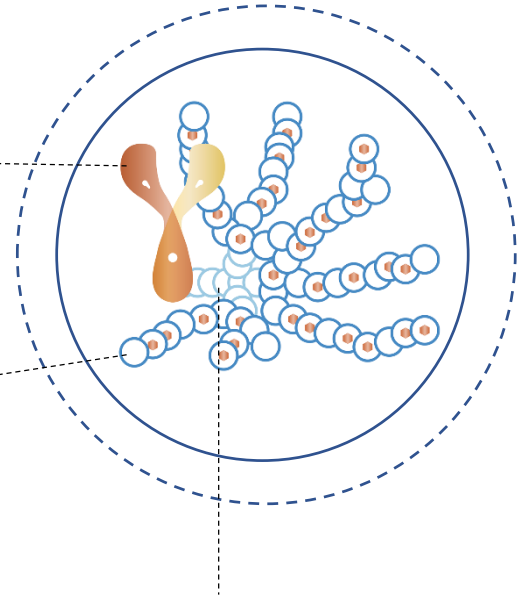
Similar findings were observed in the phase 3 PULSAR trial, which evaluated the same dosing strategy for nAMD

a. Modi Y, et al. Retinal Physician. Published January 1, 2023. Accessed May 24, 2023; b. Brown DM, et al. Presented at: Retina Society 2022; November 2-5, 2022.

Tarcocimab Tedromer (KSI-301)

IgG1 antibody
- Binds to 1 or 2 targets with high specificity
- Immune silent

Biopolymer
- Optically clear, branched, high molecular weight phosphorylcholine polymer
- Binds to water to create protective boundary, shielding antibody from nonspecific interactions that detract from target action



Stable linkage
- Site-specific linkage that is nondegradative and nonerodable
- Exits eye intact with no residual material

Overview[a]

- Investigational anti-VEGF inhibitor designed to improve bioavailability and intraocular half-life using a proprietary antibody biopolymer conjugate platform
- Administered via 5 mg intravitreal injection

Phase 3 Clinical Trials in DR or DME

- **GLOW:** Assessing twice-yearly dosing in patients with treatment-naive, moderately severe to severe nonproliferative DR without DME[b]
  - Comparing with sham treatment
- **GLEAM:** Assessing once every 4 weeks for 3 monthly doses followed by an individualized dosing regimen (every 8 to 24 weeks) via intravitreal injection from Week 16 to Week 100[c]
  - Comparing with aflibercept

a. Regillo C. Presented at: Association for Research in Vision and Ophthalmology 2022 Annual Meeting; May 3, 2022; b. ClinicalTrials.gov. NCT05066230. Accessed May 25, 2023; c. ClinicalTrials.gov. NCT04611152. Accessed May 25, 2023.

Investigational Corticosteroids

AR-1105[a,b]	• DEX extended-release biodegradable intravitreal implant • Has dose-sparing, linear release rate • Preparations for phase 3 trial are underway
IBE-814[a,c]	• Intravitreal DEX implant • Designed to deliver a low, sustained dose of DEX for ~6 months, without the use of polymeric carriers or excipients • Phase 2 trial ongoing
OCS-01[a,d]	• Topical formulation of a high-concentration, preservative-free DEX • Phase 2/3 trial ongoing

a. Kirkner RM, et al. Retina Specialist. Published February 14, 2023. Accessed May 25, 2023; b. Tully J, et al. iovs. 2018;59:5673; c. ClinicalTrials.gov. NCT04576689. Accessed May 25, 2023; d. ClinicalTrials.gov. NCT05066997. Accessed May 25, 2023.

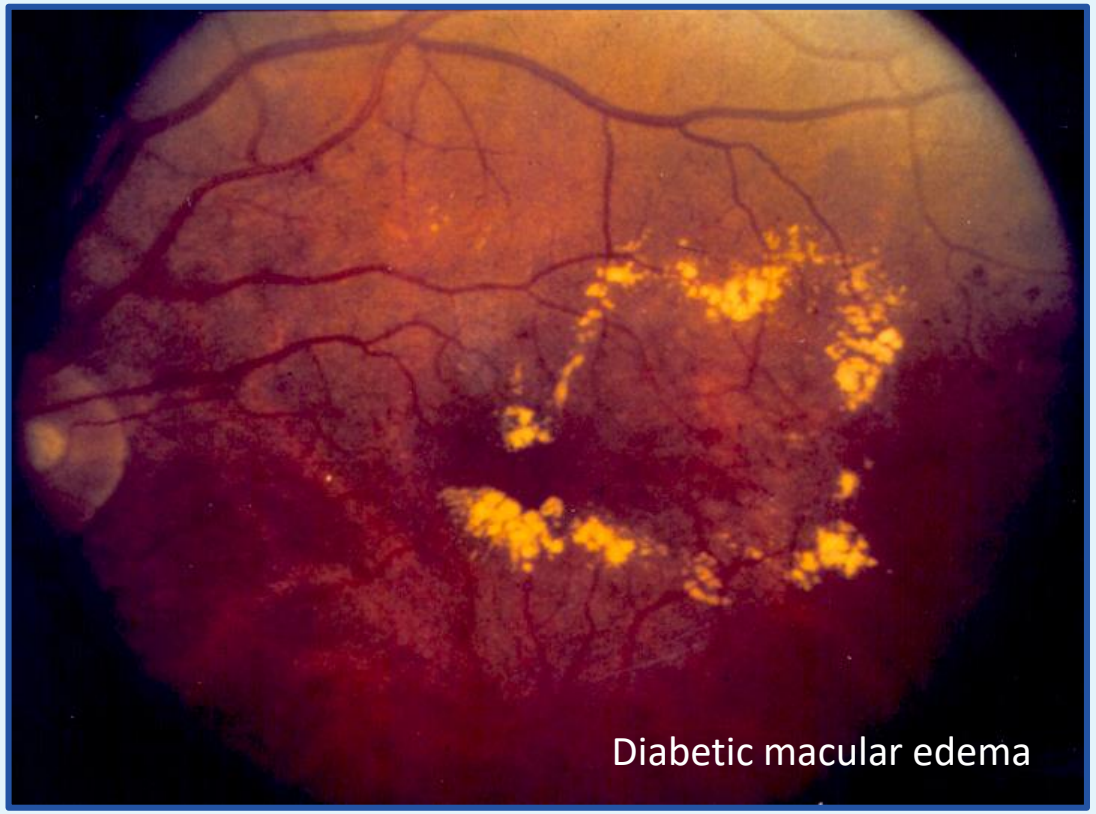
Investigational Gene Therapies in DR/DME

Gene Therapy	Overview
RGX-314[a-c]	• NAV AAV8 vector that spurs production of a ranibizumab-like molecule • Can be delivered suprachoroidally or subretinally • Phase 2 ALTITUDE study ongoing in DR without center-involved DME ▪ Interim data show clinically meaningful improvement in disease severity vs observational control
4D-150[d]	• AV-based gene therapy comprised of miRNA targeting VEGF-C and codon-optimized sequence encoding aflibercept • IND application filed
EXG102-031[d]	• Recombinant adeno-associated virus-based therapy targeting VEGF and Ang-2 • IND application accepted and phase 1 trial pending
ADVM-022[e]	• Halted as a treatment for DME after several patients in the high-genomic load group developed significant intraocular inflammation • Investigation as a potential treatment for nAMD is continuing

a. Hutton D. Ophthalmology Times. Published November 3, 2022. Accessed June 2, 2023; b. Joszt L. American Journal of Managed Care. Published February 11, 20023. Accessed June 2, 2023; c. ClinicalTrials.gov. NCT04567550. Accessed June 1, 2023; d. Kirkner RM, et al. Retina Specialist. Published February 14, 2023. Accessed May 25, 2023; e. Quin LG. Retina Specialist. Published April 6, 2022. Accessed May 25, 2023.

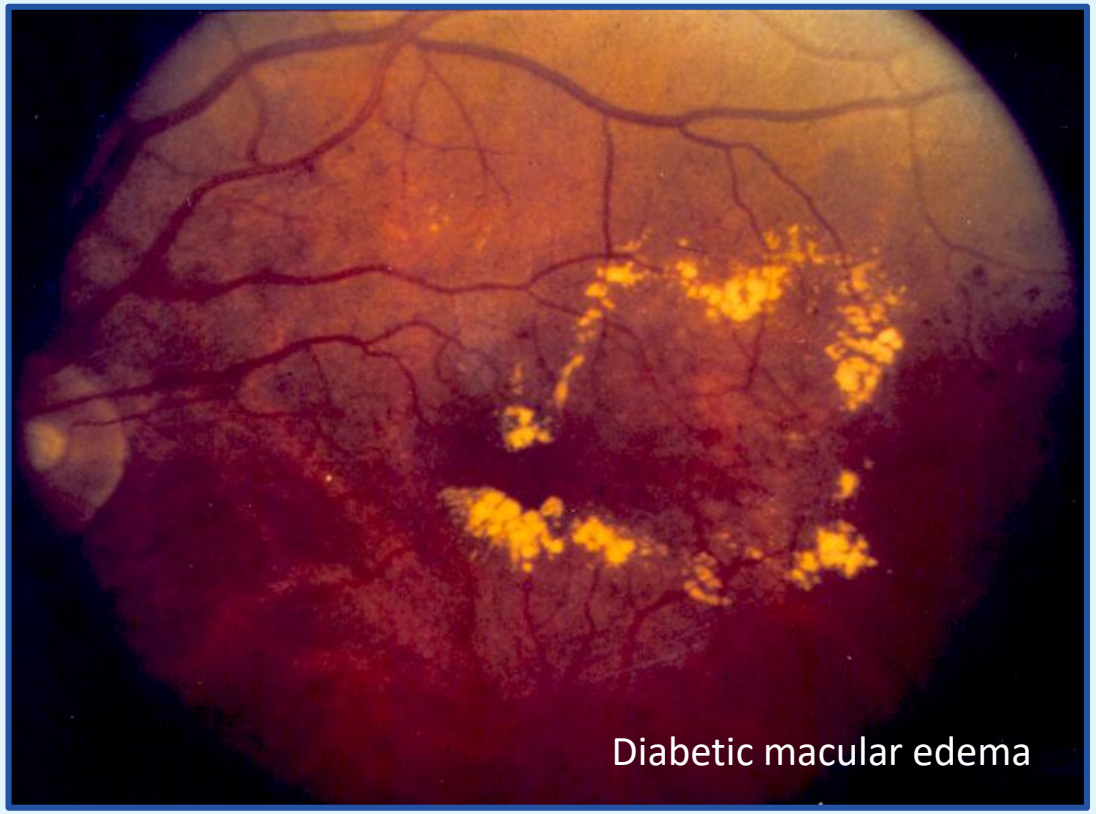
Concluding Remarks

- DME is a severe complication of DR that requires early and ongoing treatment to prevent vision loss
- The standard of care is anti-VEGF therapy, which is administered via intravitreal injection
- Although anti-VEGF treatments are highly effective and have revolutionized the treatment of DME, some patients are poor responders or do not adhere to treatment because of the burden of frequent injections, particularly in the first year of treatment
- When anti-VEGF fails, corticosteroid implants can be considered
- Corticosteroids can also be considered as a first-line treatment in some patient populations, including those with more inflammatory disease


Diabetic macular edema

Concluding Remarks (cont.)

- To improve outcomes, patients must comply with their treatment regimens
- Compliance can be improved by identifying and addressing, to the extent possible, any patient, provider, and institutional barriers
- Despite many treatments being available for DME, significant unmet need remains
- However, several new anti-VEGF treatments were recently approved, and other anti-VEGF medications, corticosteroids, and other treatments are under investigation
- New delivery methods, such as via PDS or topical instillation, are also under investigation
- Collectively, these developments have the potential to help fill some of the unmet needs in DME


Diabetic macular edema

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