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Advances in Retinal Disease Therapy

Where we are at, what's new and what's coming

By Luis G. León-Alvarado, MD

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About #FRI

Florida Retina Institute, a beacon of trust and innovation in vitreous and retinal ophthalmology for over 45 years, stands as the premier provider known for its compassionate care and cutting-edge expertise. With a distinguished team of 15 board-certified doctors and surgeons, state-of-the-art technology, and a commitment to clinical trials and research, patients trust Florida Retina Institute to continuously deliver the highest standard of treatment and preserve their vision.

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The most likely cause of visual loss in the aging population is cataract development.

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Learning Objectives

- **Understand Current Treatment Modalities**
  - Identify key therapies available for retinal diseases.
  - Discuss mechanisms of action and clinical outcomes.
- **Anti-VEGF Therapies**
  - Explain the role of VEGF in retinal diseases.
  - Review the function and differences among anti-VEGF agents, including Avastin(Bevacizumab), Lucentis(Ranibizumab, Eylea(Aflibercept 2mg), Beovu(Brolucizumab), Vabysmo(Faricimab), and Eylea HD(Aflibercept 8mg).

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Learning Objectives

- **Dual-Targeting Therapies**
  - Evaluate therapies that target multiple pathways, such as VEGF-A and Ang2, for enhanced efficacy.

- **Emerging Drug Delivery Systems**
  - Discuss advances in sustained drug delivery systems like PDS-Susvimo, Iluvien, and Ozurdex implants.
  - Highlight their impact on reducing treatment frequency and improving patient adherence.

Learning Objectives

- **Corticosteroid Therapies**
  - Describe corticosteroid treatments and their role in reducing inflammation and edema.
  - Evaluate different corticosteroid implants such as Ozurdex(Dexamethasone), Iluvien (Fluocinolone Acetonide), and Yutiq(Fluocinolone Acetonide).

- **Complement Inhibitors for Geographic Atrophy (GA)**
  - Define complement activation and its impact on GA.
  - Assess treatments like Syfovre (Pegcetacoplan) and Izervay (Avancipated Pegol) for slowing disease progression.

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Learning Objectives

- **Gene Therapy Approaches**
  - Understand gene therapy applications for inherited and chronic retinal diseases.
  - Explore treatments like Luxturna, ABBV-RGX-314, and Ixo-Vec for addressing genetic mutations and VEGF suppression.

- **Stem Cell Therapies**
  - Examine the potential of stem cell therapy for retinal cell replacement and function restoration.
  - Conditions like GA and Stargardt Disease.

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Learning Objectives

- **Future Directions and Innovations**
  - Recognize ongoing research trends and potential breakthroughs in retinal disease therapy.
  - Identify the challenges and opportunities in personalized treatment approaches.

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Introduction

Targeted Conditions (overview)

- Wet AMD
- Diabetic Macular Edema (DME)
- Retinal Vein Occlusion (RVO)
- Geographic Atrophy (GA)
- Inherited Retinal Disease (IRD)

Therapeutic Approaches

- Anti-VEGF Treatments
- Corticosteroid Therapies
- Gene and Stem Cell Therapies
- Eyedrops
- Emerging Drug Delivery Systems

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Wet AMD (Exudative Age Related Macular Degeneration)

- Chronic eye disorder characterized by the growth of abnormal blood vessels (choroidal neovascularization) beneath the macula
- These fragile vessels leak blood and fluid, leading to retinal damage, scarring, and rapid central vision loss if left untreated.
- Wet AMD represents approximately 10–15% of AMD cases
- Responsible for most of the severe vision loss associated with the disease.

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Wet AMD

Pathophysiology

- The hallmark of wet AMD is the overexpression of vascular endothelial growth factor (VEGF)
- Promotes angiogenesis and increased vascular permeability.
- Disrupt the normal retinal architecture, resulting in visual distortion (metamorphopsia), blurring, and central scotomas.

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Wet AMD

Epidemiology and Demographics

- AMD is the leading cause of vision loss in individuals over the age of 50 in developed countries.
- Approximately **196 million people** worldwide were affected by AMD in 2020, a number expected to rise to **288 million by 2040** due to population aging.
- 10–15% progress to the neovascular (wet) form, but this subgroup accounts for **90% of cases of severe vision loss** caused by AMD.
- Risk increases significantly with age. Wet AMD is most common in individuals **over 60 years old**, with a prevalence of up to **12% in those over 80**.
- Some Studies indicate a slightly higher prevalence in **women** than men.
- Caucasians are at higher risk compared to African Americans or Asians.

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Wet AMD

Risk Factors

- **Genetics**: Family history of AMD significantly raises susceptibility.
- **Smoking**: Smokers have a **2-3 times higher risk** compared to non-smokers.
- **Hypertension and Cardiovascular Disease**: Associated with higher rates of progression to wet AMD.
- **Obesity and Diet**: Poor dietary intake of antioxidants and omega-3 fatty acids increases risk.
- **Environmental Factors**: UV exposure and oxidative stress contribute to retinal damage.

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Wet AMD

Current Treatment Approaches

- **Anti-VEGF Therapy**: Intravitreal injections of VEGF inhibitors Anti-VEGF agents, including Avastin(Bevacizumab), Lucentis(Ranibizumab, Eylea(Aflibercept 2mg), Beovu(Brolucizumab), Vabysmo(Faricimab), Eylea HD(Aflibercept 8mg).
- First-line treatment, effectively stabilizing or improving vision in **90%** of patients.

- **Photodynamic Therapy (PDT)**: Less commonly used but still applicable in select cases

- **Laser Photocoagulation**: Used for extrafoveal lesions but largely replaced by anti-VEGF treatments.
- **Implantable drug delivery systems**
- **Gene Therapy**

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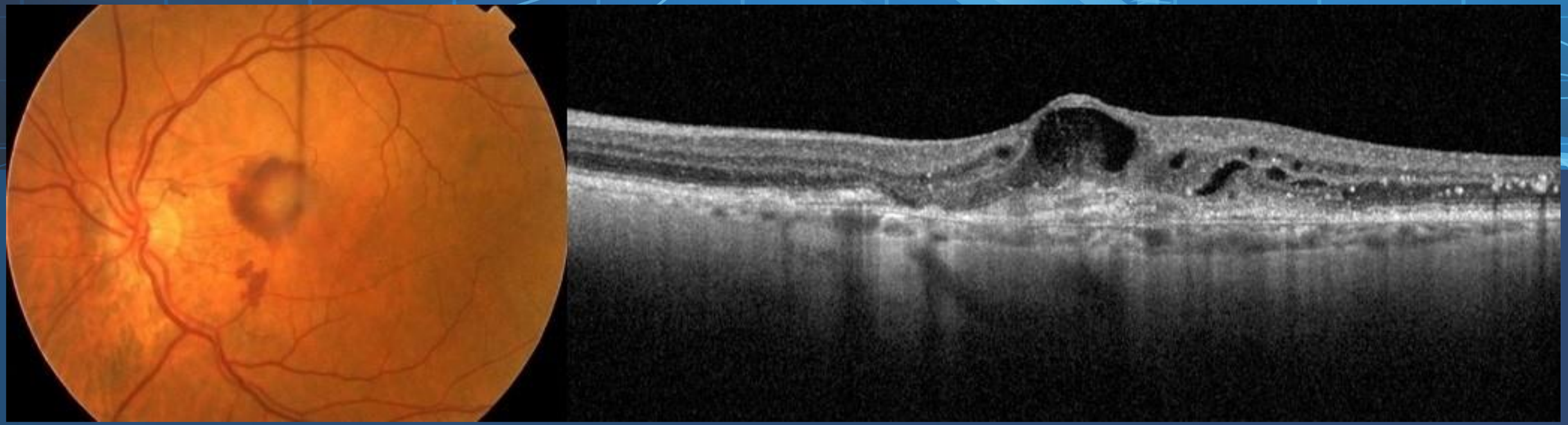
Wet AMD



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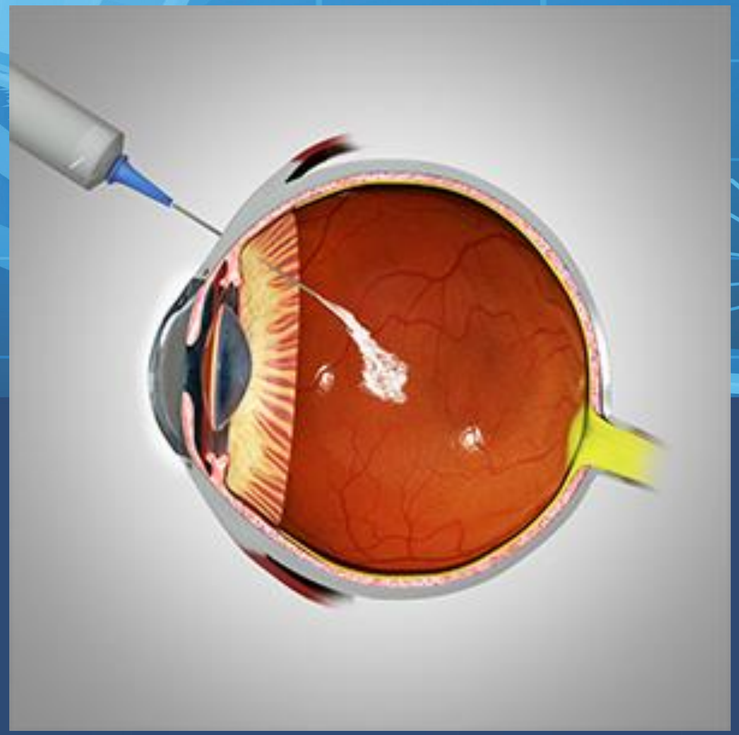
Intravitreal injections

- Intravitreal injection is the most common route of medication administration for retinal therapies.
- Usual volume administered 0.05ml
- Most common initial interval is 1 injection a month for 3 months
- Different injections protocols most widely used is treat and extend

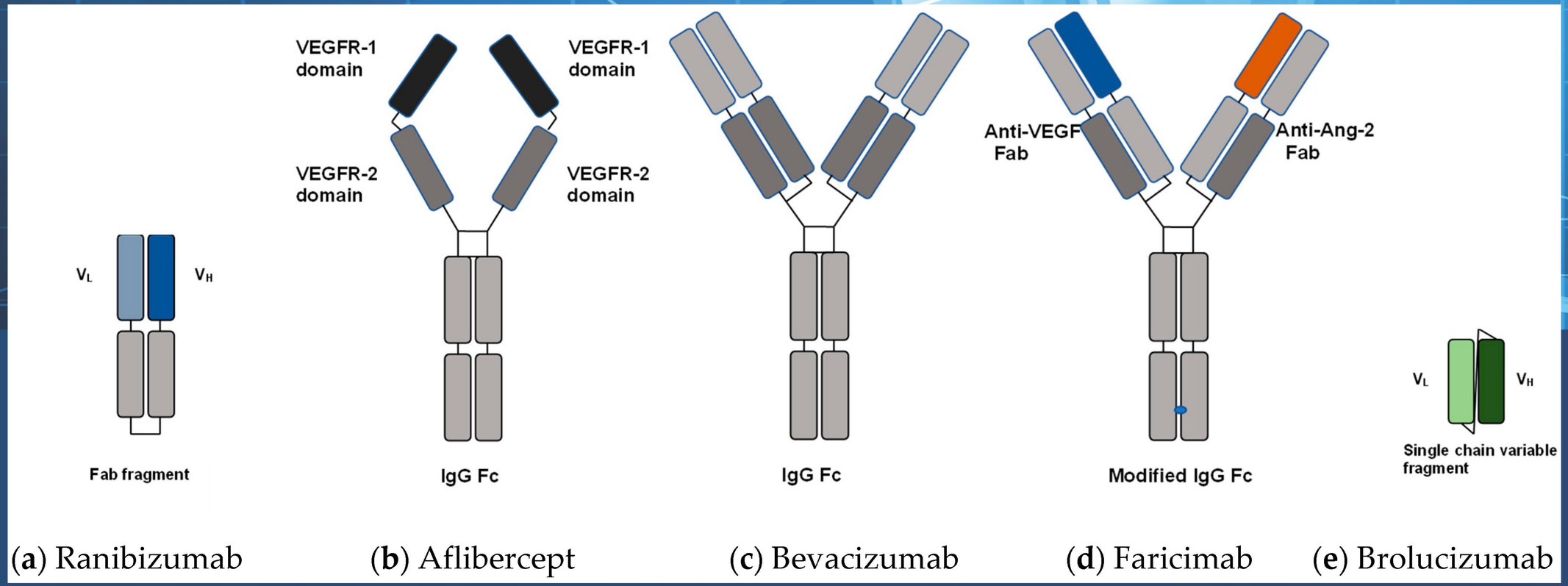
Avastin (Bevacizumab) 2005

Mechanism: VEGF-A binding to reduce vascular leakage.
- CATT (Phase III): Showed non-inferiority to Lucentis for vision stabilization.
- Limitations: Off-label use; requires frequent dosing.
Advantages: Cost-effective alternative.



Lucentis (Ranibizumab) 2006

- Mechanism: High-affinity VEGF-A inhibition for reducing edema.
- First FDA approved intravitreal medication for WET AMD
- MARINA (Phase III): Significant improvement in visual acuity.
- ANCHOR (Phase III): Compared favorably with photodynamic therapy.
- Advantages: FDA-approved; lower systemic exposure.



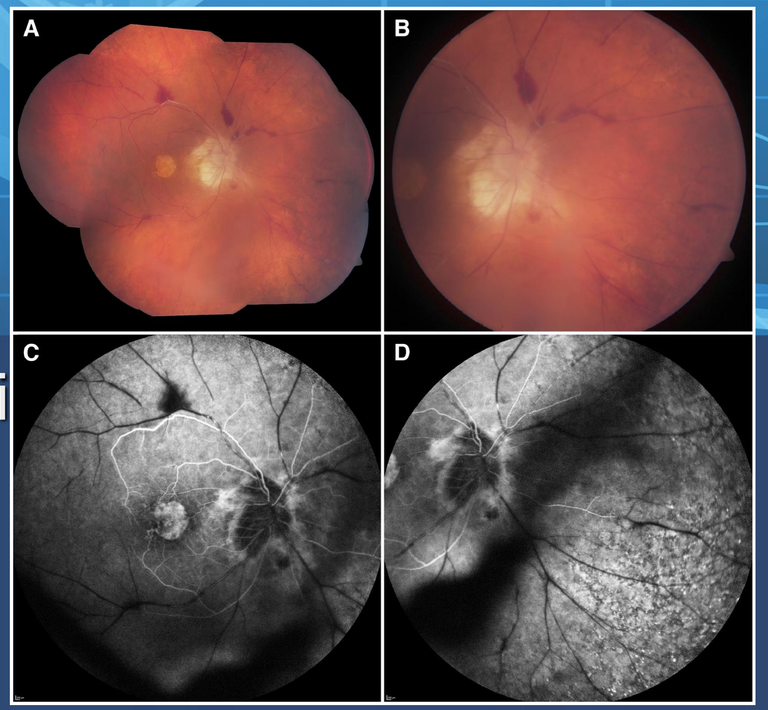
(**a**) Ranibizumab (**b**) Aflibercept (**c**) Bevacizumab (**d**) Faricimab (**e**) Brolucizumab

Eylea (Aflibercept) 2011

- Mechanism: VEGF-A and PlGF inhibition for prolonged suppression.
- VIEW 1 and VIEW 2 (Phase III): Comparable efficacy to Lucentis with fewer injections.
- Advantages: Prolonged dosing intervals; reduced injection burden.
- Currently most preferred intravitreal VEGF inhibitor in ophthalmology

Beovu (Brolucizumab) 2019

- Mechanism: Single-chain antibody targeting VEGF-A.
- HAWK and HARRIER (Phase III): Prolonged dosing intervals.
- Challenges: Associated with inflammation and vasculiti
- Benefits: High potency and better tissue penetration.
- Rarely used now due to potential side effects



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New and upcoming therapies

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Vabysmo (Faricimab) 2022

- Mechanism: Dual inhibition of VEGF-A and Ang2.
- TENAYA and LUCERNE (Phase III): Extended durability and vessel stability.
- Benefits: Effective dual-target approach and longer-lasting outcomes.

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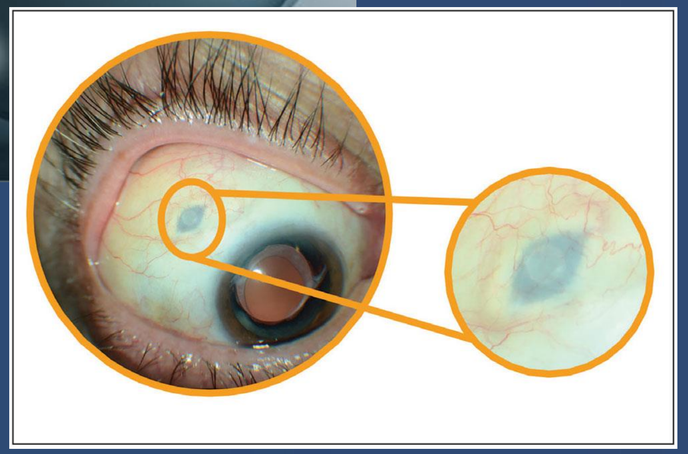
Eylea HD 8mg

- Higher dose and higher injected volume than Eylea.
- Most recent FDA approved medication for Wet AMD
- Extended Dosing Intervals: Up to 16 weeks after three initial monthly doses, potentially reducing the frequency of injections for patients.
- PULSAR Trial: This pivotal study evaluated EYLEA HD in patients with wet AMD. Results showed that 79% and 77% of patients maintained 12- and 16-week dosing intervals, respectively, through 48 weeks, with vision gains comparable to the standard EYLEA regimen.

PDS-Susvimo (Ranibizumab Implant)

- Mechanism: Refillable implant for ranibizumab (Lucentis) delivery. Q6 months refill
- ARCHWAY and PORTAL (Phase III): Effective and reduces treatment burden.
- Challenges: Risk of device-related complications.



Gene Therapy: ABBV-RGX-314

- Mechanism: Continuous VEGF suppression using AAV8 vector.
- ATMOSPHERE (Phase II/III): Long-term suppression with reduced injection frequency.
- Challenges: Surgical delivery method.
- Prospects: Long-term relief with single-dose therapy.

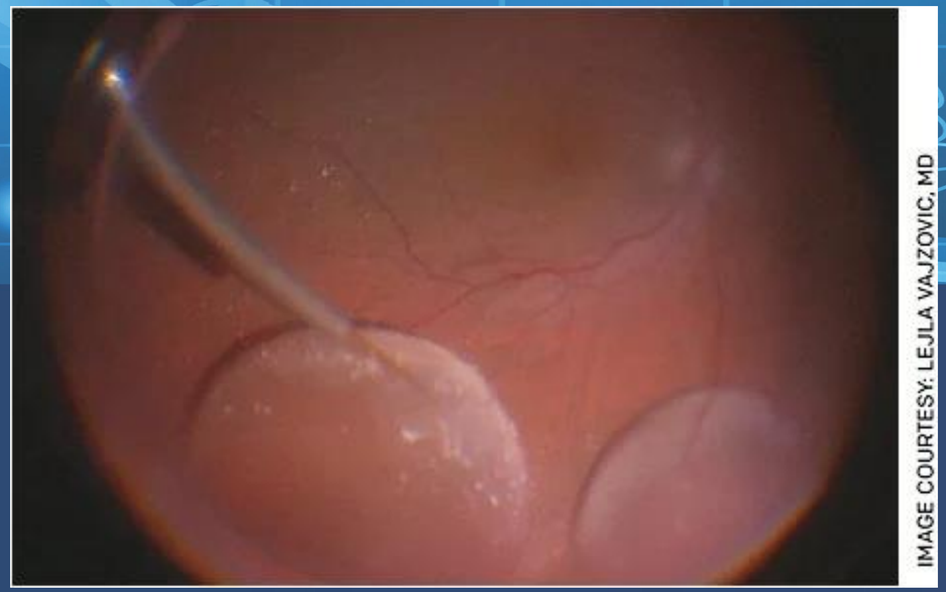


IMAGE COURTESY: LEJLA VAJZOVIC, MD

Gene Therapy: Ixo-Vec

- Mechanism: Intravitreal delivery of anti-VEGF genes.
- OPTIC (Phase I/II): Sustained suppression of VEGF activity.
- Advantages: Single-dose therapy potential with minimal follow-ups.
- Potentially proinflammatory, patients need steroid treatment

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OTX-TKI (AXPAXLI)

Intravitreal implant that aims to treat wet age-related macular degeneration

- **SOL-1**: A superiority study that compares a single AXPAXLI implant to a single aflibercept injection. The primary endpoint is the proportion of subjects who maintain visual acuity at Week 36.
- **SOL-R**: Compares AXPAXLI dosed every 6 months to aflibercept dosed every 8 weeks, also includes a third arm evaluating 8 mg aflibercept dosed every 6 months.

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Next Up

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Diabetic Macular Edema (DME)

- Complication of **diabetic retinopathy** characterized by the accumulation of fluid in the **macula**
- This fluid buildup occurs due to **leakage from damaged retinal capillaries** caused by prolonged **hyperglycemia** and subsequent **microvascular damage**.

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DME

Demographics and Epidemiology:

- **Prevalence:**
  - DME is a leading cause of vision loss in diabetic patients worldwide.
  - **Most common cause of visual loss in NPDR patients**
  - Approximately **6–10% of diabetics** develop DME.
  - More common in **type 2 diabetes mellitus (T2DM)** compared to type 1.
- **Demographics:**
  - Affects all ethnicities but may have **higher prevalence** in African American and Hispanic populations.
  - Older age groups and longer diabetes duration are more prone to DME.
  - Men may have a **slightly higher risk** than women.

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DME

- **Chronic Hyperglycemia:**
  - Leads to **microvascular damage** in the retina.
  - Promotes **capillary endothelial dysfunction, pericyte loss**, and **breakdown of the blood-retinal barrier (BRB)**.

- **Key Mechanisms:**
  - **Vascular Leakage:** Breakdown of the BRB results in the accumulation of extracellular fluid in the macula.
  - **Inflammation:** Increased levels of inflammatory cytokines (e.g., **VEGF**, TNF-α) contribute to vessel permeability.
  - **Retinal Thickening:** Fluid accumulation causes retinal thickening and distortion of photoreceptors.
  - **Ischemia and Hypoxia:** Capillary closure and hypoxia upregulate **VEGF**, which exacerbates permeability and edema.

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DME

- Systemic Risk Factors:
  - Duration of Diabetes: Longer disease duration increases risk.
  - Poor Glycemic Control (HbA1c): Higher levels are strongly associated with DME.
  - Hypertension and Dyslipidemia: Elevated blood pressure and cholesterol.

- Ocular Risk Factors:
  - Diabetic Retinopathy Severity: More advanced retinopathy correlates with higher DME incidence.

- Lifestyle Factors:
  - Obesity, Smoking, and Sedentary Lifestyle are associated with increased risk due to systemic vascular effects.

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DME

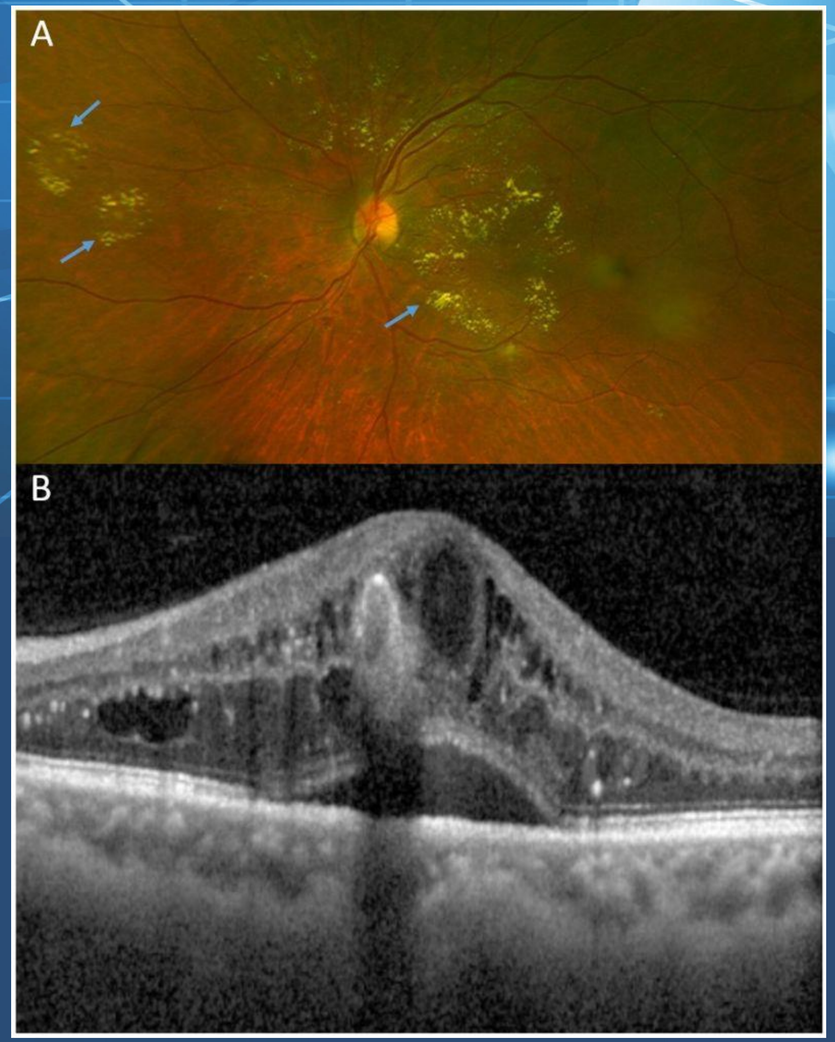
Clinical Implications

•DME often presents bilaterally, although severity may differ between eyes.

•Screening and early detection through regular retinal exams (including optical coherence tomography [OCT] and fluorescein angiography) are critical for preventing vision loss.

•Prompt intervention, including anti-VEGF agents, corticosteroids , and laser photocoagulation, has shown significant improvement in outcomes.

•Several new therapies in development


A
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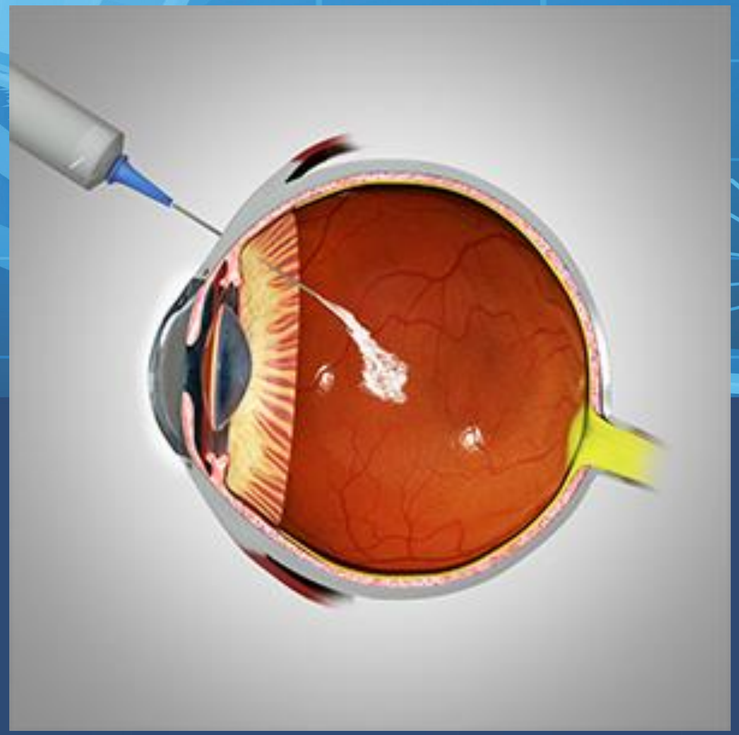
Avastin (Bevacizumab) 2005

- Mechanism: VEGF-A binding to reduce vascular leakage.
- RCR Protocol T: Effective for visual improvement- Similar to Lucentis, slightly inferior to Eylea in patients with Va worse than 20/40
- Limitations: Off-label use; requires frequent dosing.
- Advantages: Cost-effective alternative.
- Most used medication for DME



Lucentis (Ranibizumab) 2006

- Mechanism: High-affinity VEGF-A inhibition for reducing edema.
- RISE and RIDE (Phase III): Effective in restoring visual function.
- Advantages: FDA-approved; lower systemic exposure.

Eylea (Aflibercept) 2011

- Mechanism: VEGF-A and PlGF inhibition for prolonged suppression.
- VIVID and VISTA (Phase III): Prolonged suppression of edema and neovascularization
- Advantages: Prolonged dosing intervals; reduced injection burden.
- Currently most preferred intravitreal VEGF inhibitor in ophthalmology

Vabysmo (Faricimab) 2022

- Mechanism: Dual inhibition of VEGF-A and Ang2, 2 different molecules.
- YOSEMITE and RHINE (Phase III): Effective in reducing edema.
- Benefits: Effective dual-target approach and longer-lasting outcomes.

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Eylea HD 8mg

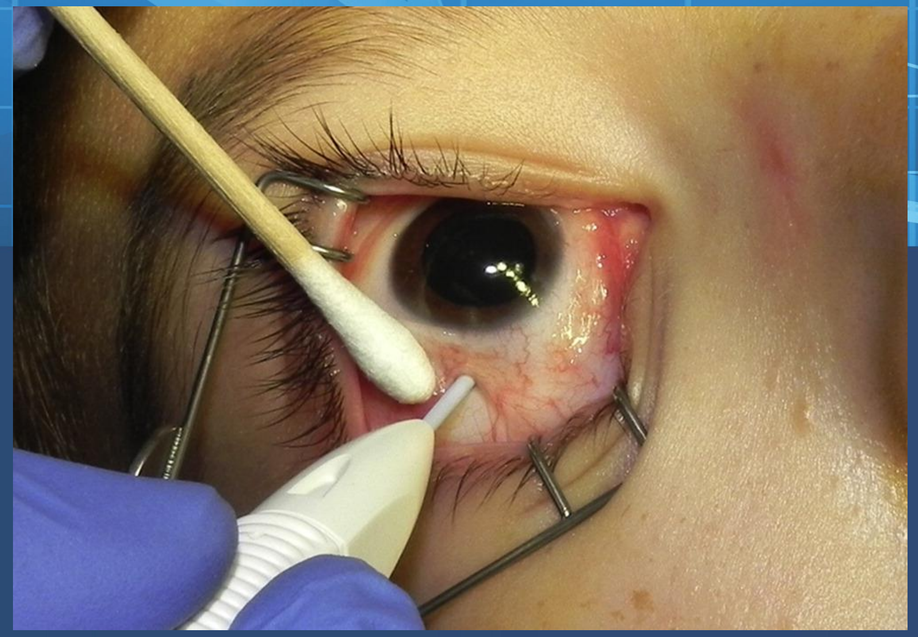
- Higher concentration and higher injected volume than Eylea.
- Extended Dosing Intervals: Up to 16 weeks after three initial monthly doses, potentially reducing the frequency of injections for patients.
- PHOTON Trial: This pivotal study evaluated EYLEA HD in patients with DME. Results showed that 89% and 84% of patients maintained 12- and 16-week dosing intervals, respectively, through 48 weeks, with vision gains comparable to the standard EYLEA regimen.

Triescence (Kenalog)

- Used for DME, CME, MEFRVO and ocular inflammation
- Commonly used due to relative affordability
- On backorder until recently

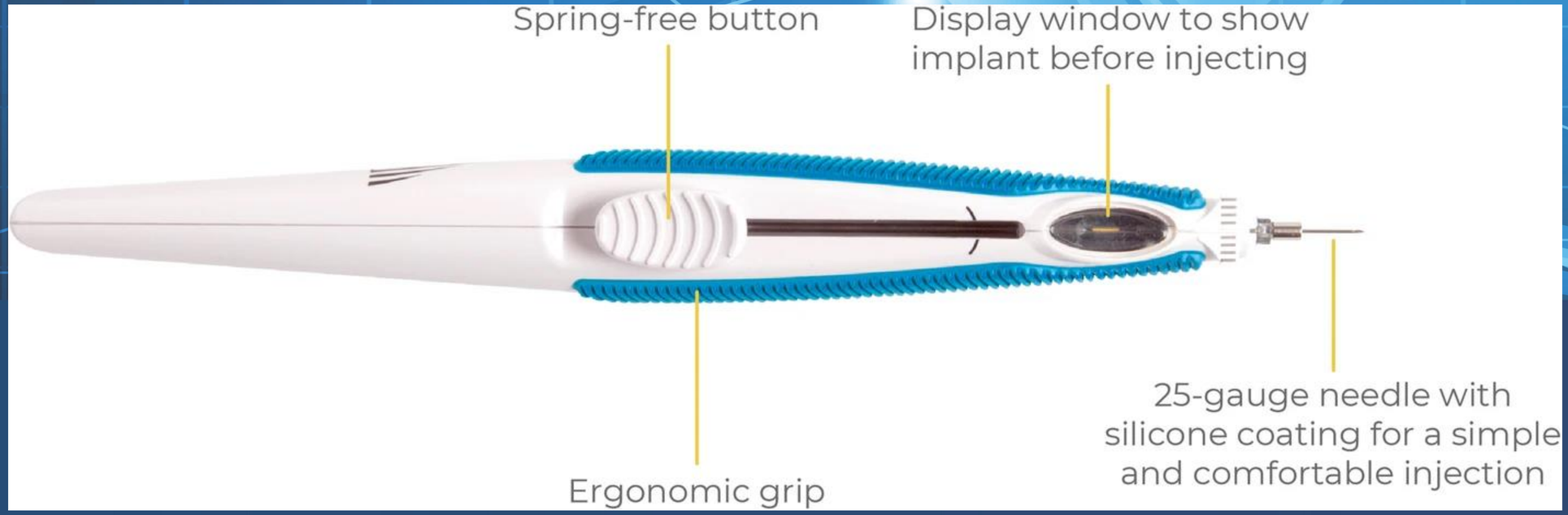
Ozurdex (Dexamethasone Implant)

- Mechanism: Gradual corticosteroid release to suppress inflammation and edema.
- MEAD (Phase III): Significant reduction in edema.
- Challenges: Risk of cataracts and intraocular pressure increase.



Iluvien (Fluocinolone Implant)

- Mechanism: Continuous low-dose corticosteroid release.
- FAME (Phase III): Effective reduction in edema for up to 36 months.
- Advantages: Long-term solution but requires careful monitoring.
- Considerations: $$, overall long duration but perceived to not be as strong as other options, commitment to long therapeutic effect.


Spring-free button
Display window to show implant before injecting
25-gauge needle with silicone coating for a simple and comfortable injection
Ergonomic grip

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Eyedrops?

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OCS-01 (Oculis):

- OPTIREACH® technology to enhance drug delivery to the retina.
- DIAMOND trial, demonstrated a significant increase in visual acuity and a reduction in macular edema.
- Stage 2, comprising two 52-week parallel Phase 3 clinical trials, DIAMOND-1 and DIAMOND-2, just finished enrolling participants.

Tivozanib Eye Drops

- Small-molecule vascular endothelial growth factor receptor (VEGFR) and tyrosine kinase inhibitor.
- Phase 2 clinical trial has been initiated to evaluate the efficacy and safety of tivozanib eye drops in patients with DME.

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EXN407 (Exonate):

- This eye drop is designed to inhibit serine/threonine-protein kinase SRPK1, reducing pathological vascular leakage.
- Phase Ib/IIa clinical trial assessed the safety, tolerability, and biological response of EXN407 monotherapy in treatment-naïve patients with mild to moderate non-proliferative diabetic retinopathy and mild DME.
- The study met its pre-specified endpoints, indicating potential as a non-invasive therapy option.

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Dexamethasone Nanoparticle Eye Drops:

- Aims to deliver corticosteroids effectively to the retina via a non-invasive route.
- A clinical trial is underway to evaluate the safety and efficacy of dexamethasone nanoparticle eye drops in patients with DME.

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Macular edema following RVO (MEfRVO)

- **Prevalence:**
  - RVO affects ~0.7–1.6% of adults globally.
  - BRVO (~80%) is more common than CRVO (~20%).
- **Risk Factors:**
  - **Systemic:** Hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease.
  - **Ocular:** Glaucoma, hypercoagulable states.
  - **Demographics:** More common in individuals >50 years; slightly higher incidence in males.

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Macular edema following RVO (MEfRVO)

- **Primary Event:** Venous occlusion due to compression by adjacent arterioles at arteriovenous crossings, leading to: **Venous Stasis and Hypertension** → Increased vascular permeability.
- **Capillary Damage** → Ischemia and breakdown of the blood-retinal barrier.
- **Inflammation** → Release of VEGF (vascular endothelial growth factor) and inflammatory cytokines.
- **Macular Edema Formation** → Fluid accumulation in the macula due to leakage from damaged capillaries.

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Macular edema following RVO (MEfRVO)

- **Anti-VEGF Agents** (First-line):
  - **Drugs:** Ranibizumab, Aflibercept, Bevacizumab (off-label), Aflibercept 8mg in clinical trials
  - **Mechanism:** Inhibits VEGF, reducing vascular permeability and edema.
  - **Dosing:** Monthly injections initially, then treat-and-extend approach.

Macular edema following RVO (MEfRVO)

- **Corticosteroids:**
  - **Drugs:** Dexamethasone intravitreal implant (Ozurdex), Triamcinolone.
  - **Mechanism:** Anti-inflammatory; suppress VEGF and cytokines.
  - **Considerations:** Risk of increased IOP and cataract formation.

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Dry AMD (GA)

- Geographic Atrophy (GA) is an advanced form of **dry age-related macular degeneration (AMD)** characterized by progressive, irreversible degeneration of the **retinal pigment epithelium (RPE)** and **photoreceptors** in the macula.
- Central vision loss.
- Unlike wet AMD, GA does not involve choroidal neovascularization (abnormal blood vessel growth).

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GA

Demographics and Epidemiology:

- **Prevalence:**
  - AMD affects approximately **196 million people globally**; this number is expected to rise to **288 million by 2040**.
  - GA accounts for **20% of late-stage AMD cases**.
- **Age:**
  - Primarily affects individuals **60 years and older**, with prevalence increasing with age.
- **Gender:**
  - Slightly more common in **women** due to their longer life expectancy.
- **Race/Ethnicity:**
  - Most common in **Caucasians**, likely due to genetic and environmental factors.

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GA

- **Risk Factors:**
  - **Genetics** (e.g., CFH, ARMS2/HTRA1 variants)
  - **Smoking** (2–3 times higher risk)
  - **Hypertension** and cardiovascular disease
  - **Obesity**
  - **Nutritional deficiencies** (low antioxidants and zinc)
  - **UV light exposure**

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GA

- **RPE and Photoreceptor Degeneration:**
  - Begins with dysfunction and apoptosis of the **retinal pigment epithelium (RPE)**, critical for photoreceptor survival and waste removal.
  - Loss of RPE leads to **secondary photoreceptor atrophy** and **choriocapillaris loss**.
- **Drusen Accumulation:**
  - Drusen deposits form between the **RPE** and **Bruch's membrane**, interfering with nutrient and waste exchange.
  - Over time, drusen contribute to **oxidative stress**, **inflammation**, and complement system activation.
- **Complement System Dysregulation:**
  - Genetic mutations, especially in complement factor H (CFH), lead to excessive immune activation and **chronic inflammation**, accelerating RPE damage.

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GA

- **Visual Symptoms:**
  - Gradual **central vision loss** with relative sparing of peripheral vision.
  - **Scotomas** (blind spots) develop in areas of atrophy.
  - Difficulty with **reading, recognizing faces**, and **low-light adaptation**.
- **Progression Rates:**
  - Average growth rate of GA lesions: **1.78–2.64 mm²/year**.
  - Larger baseline lesions and multifocal patterns progress more rapidly.
- **Bilateral Involvement:**
  - **~40–50%** of patients develop GA in both eyes over time.

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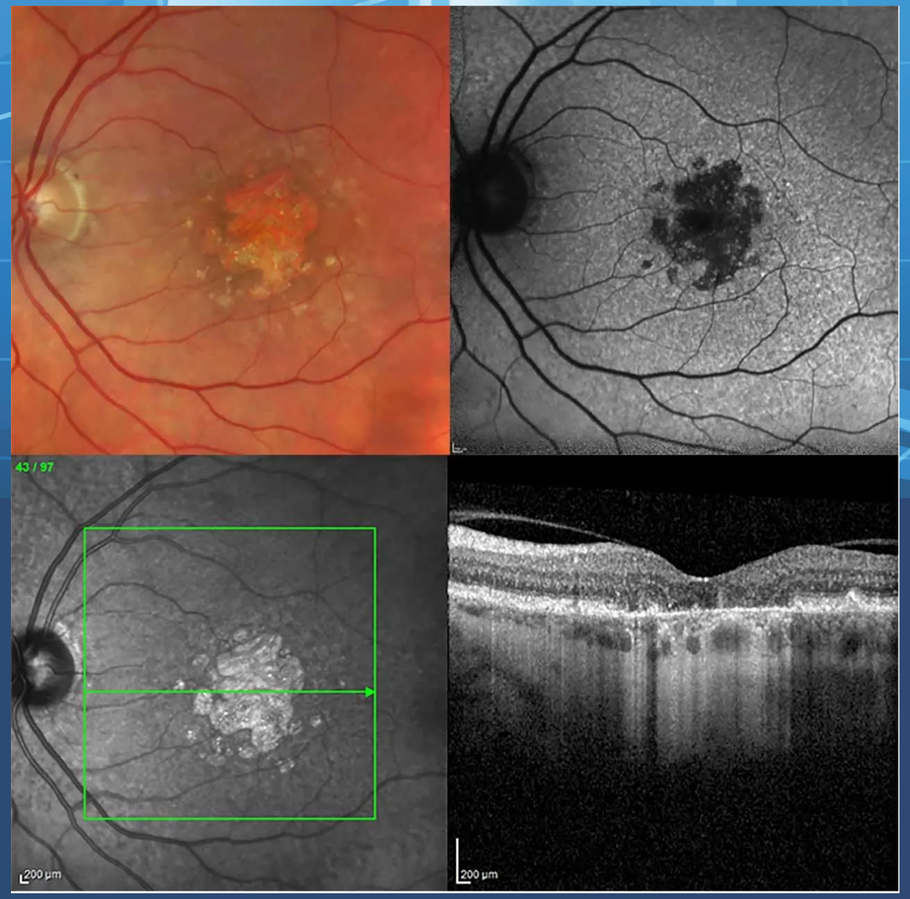
GA

5-Year Risk of Progression:

- Early AMD to GA: **12–20%**.
- Intermediate AMD to GA: **25–30%**.

Vision Impairment:

- GA contributes to **20% of legal blindness** cases in industrialized nations.



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Syfovre (Pegcetacoplan). (2023)

- Mechanism: C3 complement inhibitor to slow GA progression.
- DERBY and OAKS (Phase III): Slowed lesion growth and protected retinal cells.
- Advantages: Preserves vision with regular dosing, q2m(21%) or q1m(31%).
- Recent data shows decreased rate of progression up to 40% at 3 years
- Controversies: Few cases of hemorrhagic retinal vasculitis reported
- Large injected volume 0.1ml, thick substance.

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Izervay (Avacincaptad pegol) 2023

- Mechanism: blocks complement cascade at C5 to block cell death.
- Phase III Trials: Reduced progression of retinal atrophy (35%).
- Advantages: Preserves retinal structure and reduces inflammation, no significant reported cases of severe ocular inflammation.
- Controversies: Q1month dosing, no FDA approval past 1 year of treatment, large injection volume 0.1ml

45 YEARS

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Elamipretide

AMD is associated with mitochondrial dysfunction and oxidative stress in retinal pigment epithelial (RPE) cells and photoreceptors.

Elamipretide's mechanism of action—mitochondrial stabilization and reduction of oxidative stress

- Protect retinal cells from damage.
- Slow the progression of atrophy.
- Improve mitochondrial energy production in RPE cells.

Clinical Studies in AMD (Stealth)

- SQ daily injection
- Improved mitochondrial function in retinal cells.
- Reduced oxidative damage.
- Slower progression of cellular atrophy in the retina.

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AVD-104

- Intravitreal glycan-coated nanoparticle designed to inhibit retinal macrophage activity, as well as inhibiting complement cascade amplification.
- SIGLEC trial, a double-masked, randomized, controlled study
- Currently underway and aims to enroll approximately 300 patients comparing avacincaptad pegol (Izervay)
- Results second half 2015

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Biosimilars

- Biologic drugs that are highly similar, not necessarily the same, as existing FDA-approved biologic therapies, known as reference products.

- **Cost Savings:** Typically, biosimilars are more affordable, increasing access for patients.
- **Comparable Efficacy:** Clinical trials have demonstrated similar effectiveness in reducing fluid accumulation and improving vision.
- **Regulatory Assurance:** FDA and other regulatory bodies ensure strict standards for safety, purity, and potency.

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Biosimilars

- **Byooviz (ranibizumab-nuna):** Approved by the FDA in September 2021 as a biosimilar to Lucentis.
- **Cimerli (ranibizumab-eqrn):** Approved in 2022, another biosimilar to Lucentis with interchangeable status.
- **Pavblu (Aflibercept-ayyh)** Approved in 2024, biosimilar to Eylea

45 YEARS

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Thanks for your attention!

Top Left to Bottom Right: Thalmon R. Campagnoli, MD; Kyle S. Fallgatter, MD; S.K. Steven Houston III, MD, FASRS; Jonathan A. Staman, MD; Abdallah M. Jeroudi, MD; Raul J. Moreno, MD; Jaya B. Kumar, MD, FASRS; Benjamin J. Thomas, MD; Luis G. León-Alvarado, MD; Nisarg P. Joshi, MD; Matthew A. Cunningham, MD, FASRS; James A. Staman, MD; Elias C. Mavrofrides, MD; Tomas A. Moreno, MD; and Thomas A. Barnard, MD.

Thank you for the great opportunity to speak with you this evening!

Florida Retina Institute truly appreciates your time and are grateful for the partnership we share. Looking forward to our continued collaboration.