Precision and Practice: Imaging and Injection in Retinal Vascular Disorders

Imaging Biomarkers in Diabetic Macular Edema (DME)

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Diabetic macular edema (DME) remains a leading cause of vision loss in diabetic retinopathy, often showing suboptimal responses to anti-VEGF therapy despite central subfield thickness (CST) reductions. This presentation emphasizes advanced retinal imaging—primarily OCT—to uncover subtle biomarkers beyond mere thickness, explaining structural damage to bipolar axons and poor visual acuity (VA) correlation. OCT's non-invasive utility allows detection of fluid types (intraretinal cysts, subretinal fluid [SRF]), lipid deposits, and disruptions in retinal layers, guiding personalized treatment like steroids over anti-VEGF in inflammatory cases.

Key OCT biomarkers include cystoid macular edema (CME) with large cysts (>200µm in outer nuclear layer [ONL]) causing photoreceptor damage, intracystic hyperreflective material signaling severe blood-retinal barrier (BRB) breakdown and poor prognosis, and disorganization of retinal inner layers (DRIL) predicting persistent capillary non-perfusion. Hyperreflective foci (HRF, <30µm, likely microglia/lipoproteins) indicate inflammation and recurrence risk, responding better to steroids; subretinal HRF links to hard exudates. Hard exudates (>30µm, back-shadowing) relate to serum triglycerides, resolving with steroids, while bridging retinal processes between cysts suggest residual neural elements and better VA recovery.

Negative predictors encompass ellipsoid zone (EZ)/external limiting membrane (ELM) disruption, foveal pit inversion (uveitis-like cytokines), taut posterior hyaloid traction distorting retina, and hyperreflective choroidal foci (HCF) in proliferative diabetic retinopathy (PDR). Protective signs include SRF at fovea (elevated IL-6, better dexamethasone response per RISE/RIDE trials) and photoreceptor outer segment length correlating with VA. Adjunctive imaging like fundus fluorescein angiography (FFA) differentiates neovascularization/IRMA for targeted laser, while OCT-angiography (OCTA) reveals flow voids, reduced vascular density, and enlarged foveal avascular zone (FAZ).

Emerging metrics like choroidal vascularity index (CVI), retinal fluid index, and subfoveal choroidal thickness remain investigational, with conflicting views on VEGF-driven thickening versus perfusion benefits. Fundus autofluorescence highlights lipofuscin/microglia activation. Overall, these biomarkers enable prognostication, adjunct therapies (laser/steroids/surgery), and trials like DRCR Protocol I underscore early intervention in thick baselines.

Optimizing Vision: Art and Science of Intravitreal Injections in DME

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(No Financial Interests)

1. Epidemiology of Diabetic Macular Edema (DME)

• Most common cause of vision loss affecting reading vision in diabetic patients.

• WESDR data:

  - Type I DM: 0% (<5 years), 29% (>20 years duration)

  - Type II DM: 3% (<5 years), 28% (>20 years duration)

• ~50% may lose >2 lines BCVA over 2 years without appropriate management.

2. Pathophysiology

• Breakdown of inner and outer blood-retinal barrier.

• VEGF upregulation and inflammatory mediators.

• Capillary leakage leading to retinal thickening and cystoid changes.

3. Goals of Treatment

• Improve and/or maintain best corrected visual acuity (BCVA).

• Reduce central macular thickness (CMT).

• Minimize treatment burden.

• Address systemic risk factors.

4. Evolution of DME Management

• 1980s: Focal/Grid laser (ETDRS) – reduced vision loss risk.

• 2000s onward: Anti-VEGF era (RISE, RIDE, RESTORE, VIVID, VISTA, Protocol I, T).

• Current gold standard: Intravitreal pharmacotherapy.

5. Treatment Modalities

A. Anti-VEGF Agents (First line)

- Ranibizumab, Bevacizumab, Aflibercept, Brolucizumab, Faricimab, Biosimilars.
- Block VEGF-mediated permeability.
- No cataract or IOP risk.
- Caution in recent MI/Stroke.

B. Steroids

- IV Triamcinolone (IVTA), Dexamethasone implant (Ozurdex), Fluocinolone.
- Anti-inflammatory + anti-VEGF effect.
- Preferred in chronic edema, hard exudates, anti-VEGF non-responders.
- Risks: IOP rise, cataract.

C. Laser

- Non-center involving DME.
- Adjunct for focal microaneurysms.

6. Clinical Decision Points

• When to switch therapy: Suboptimal anatomical/functional response after loading.

• Pseudophakic eyes: Steroids may be considered earlier.

• History of MI/Stroke (<6 months): Avoid anti-VEGF.

• Chronic DME: Consider steroid-first approach.

7. OCT Biomarkers in DME

• Hyperreflective Foci (HRF): 20–40 µm punctiform lesions; may predict inflammation.

• Intracystic Hyperreflective Material (ICHRM): Associated with poorer outcomes.

• Subretinal Fluid (SRF): Not always DME-related; consider CSR or systemic associations.

• ELM/EZ disruption: Correlates with visual prognosis.

8. Special Situations

• Post-vitrectomy eyes: Reduced anti-VEGF half-life; Ozurdex maintains efficacy.

• Brolucizumab: Risk of IOI and vasculitis (low but significant).

• PEVAC/TelCaps: Consider focal laser.

• Vitreomacular traction: Surgical management in tractional edema.

9. Systemic Considerations

• Glycemic control (HbA1c).

• Lipid profile management.

• Cardiovascular risk assessment.

• Unusual associations: Hypergammaglobulinemia in SRF.

10. Practical Algorithm

1. Confirm CI-DME on OCT.
2. Initiate Anti-VEGF (3 loading doses).
3. Assess response (VA + OCT biomarkers).
4. Poor response → Switch Anti-VEGF or consider Steroids.
5. Non-CI DME → Focal/Grid Laser.
6. Evaluate for traction, ischemia, systemic causes.

Key Take-Home Messages

• Individualize therapy based on OCT biomarkers and systemic profile.

• Anti-VEGF remains first-line for most CI-DME.

• Steroids play a crucial role in chronic and inflammatory phenotypes.

• Not all SRF is DME—consider differential diagnoses.

• Holistic diabetic management is essential for optimal outcomes.

Imaging in Age Related Macular Degeneration (AMD)

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Introduction & Role of Biomarkers

- A biomarker is a measurable biological parameter indicating disease activity or treatment response.
- In AMD, structural imaging changes precede functional visual loss.
- OCT biomarkers help predict prognosis, guide treatment intervals, and personalize anti VEGF therapy.

Intraretinal Fluid (IRF)

- Most important biomarker negatively affecting visual acuity.
- Eyes without IRF demonstrate superior BCVA outcomes.
- Foveal and INL IRF independently predict poor long term vision.
- Exudative IRF represents active disease and requires treatment.
- Degenerative IRF over atrophy or scar may not require treatment.
- Greater IRF before switching anti VEGF may predict better response after switch.

Subretinal Fluid (SRF)

- Fluid located between neurosensory retina and RPE.
- SRF alone is often associated with neutral or favorable visual outcomes.
- SRF combined with IRF or PED predicts poorer prognosis.
- Persistent SRF alone may be tolerated clinically.
- Presence of SRF associated with lower risk of geographic atrophy.
- Fluctuating SRF levels correlate with poorer visual outcomes.

Pigment Epithelial Detachment (PED)

- Broad elevation of RPE relative to Bruch's membrane.
- PED alone does not predict visual gain.
- PED combined with IRF leads to poorer outcomes.
- PED height >250 µm linked to poorer response to loading injections.
- Resolution of PED correlates with improved vision.

Subretinal Hyperreflective Material (SHRM)

- Strong predictor of poor visual outcome.
- Ill defined SHRM indicates inflammatory and vascular activity and worst prognosis.
- Well defined SHRM represents mature neovascular tissue.
- Greater vascular SHRM correlates with reduced anti VEGF response.

Drusen and Subretinal Drusenoid Deposits

- Drusen are extracellular deposits between RPE and Bruch membrane.
- Increasing drusen volume increases risk of neovascular AMD.

- Reduction in drusen size may precede geographic atrophy.
- Subretinal drusenoid deposits increase risk of late AMD and GA by 4–6 fold.

RPE Atrophy Spectrum

- Progression includes iORA → iRORA → cORA → cRORA.
- Early OCT sign includes RPE porosity.
- Important for predicting development of geographic atrophy.

Outer Retinal Tubulation (ORT)

- Hyporeflective tubular structures with hyperreflective borders in ONL.
- Represents chronic photoreceptor rearrangement.
- Associated with reduced vision but decreased injection requirement.

Hyperreflective Foci (HRF)

- Possible origins include migrating RPE cells, lipid exudates, or inflammation.
- Increase in HRF volume predicts progression to neovascular AMD.
- May herald geographic atrophy within two years.

Retinal Thickness & Choroidal Parameters

- Extreme retinal thickness associated with poor BCVA.
- Thin choroid (<124 µm) increases risk of geographic atrophy.
- Thicker choroid associated with higher injection burden.

Fundus Autofluorescence (FAF)

- Used for monitoring geographic atrophy progression.

- Increased autofluorescence at lesion margins predicts faster enlargement.
- Patterns include focal, banded, and diffuse trickling.

OCT Angiography (OCTA)

- Non invasive detection of neovascular flow.
- Useful for identifying non exudative MNV.
- Limitations include motion artefacts and inability to detect leakage.

Fluorescein Angiography & ICGA

- FFA differentiates classic and occult CNVM.
- ICGA is gold standard for PCV and RAP lesions.
- Infrared wavelength allows deeper choroidal visualization.

Special Entities: RAP & PCV

- RAP progresses from intraretinal neovascularization to retinochoroidal anastomosis.
- Fellow eye risk approaches 100% at 5 years.
- PCV OCT signs include sharp PED notch, dome shaped PED, and double layer sign.

Clinical Take Home Messages

- IRF indicates active disease and should be treated aggressively.
- SRF alone may be tolerated in selected cases.
- SHRM and HRF predict poorer prognosis.
- ORT indicates chronic stabilized disease.
- Multimodal imaging enables personalized AMD management.

The Injection Equation in Neovascular AMD

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Nil financial interest declared.

1. Introduction

Neovascular age-related macular degeneration (nAMD) is a chronic, complex disease driven by multiple pathogenic mechanisms. Although anti-VEGF therapy revolutionized management, a significant proportion of patients demonstrate persistent fluid or suboptimal response.

- Key clinical trial observations:
  - CATT: Persistent fluid in 51.5% (ranibizumab) and 67.4% (bevacizumab) at 2 years.
  - VIEW: 19.7–36.6% active exudation at 1 year despite aflibercept.
  - HAWK & HARRIER: Data on durability and fluid resolution.

2. Defining Response to Anti-VEGF Therapy

- Response categories include:
  - Good response – >75% CRT reduction, fluid resolution, VA gain >5 letters.
  - Partial response – 25–75% CRT reduction, persistent fluid.
  - Poor response – <25% CRT reduction, minimal VA gain.
  - Non-response – persistent/increasing fluid and VA decline after loading.

Terminology such as refractory, recalcitrant, tachyphylaxis, and treatment-resistant lacks universal standardization.

3. Mechanisms of Resistance

- Possible mechanisms include:

- Pharmacodynamic tolerance or tachyphylaxis.
- Misdiagnosis (e.g., PCV, RAP).
- Undertreatment or inadequate loading.
- Alternative angiogenic pathways.

4. Does Switching Anti-VEGF Agents Help?

Multiple retrospective studies and meta-analyses have evaluated switching strategies.

- Key Evidence:
  - Ehlken et al. (2014): Benefit seen when switching between bevacizumab and ranibizumab.
  - Greenstein et al. (2016): Small but significant BCVA and CRT improvement after switch to aflibercept.
  - Barthelmes et al. (2016): No significant BCVA change at 12 months post-switch.
  - Despreaux et al. (2015): Some benefit in switchback to ranibizumab.

Overall, switching may improve anatomical outcomes more consistently than functional outcomes.

5. Brolucizumab and Newer Molecules

Brolucizumab is a single-chain antibody fragment allowing higher molar dose delivery per injection.

- Advantages:
  - Greater VEGF binding capacity per injection volume.
  - Superior CST reduction in HAWK & HARRIER.
  - Higher proportion of fluid-free eyes at Weeks 16, 48, 96.

Safety: Rare events of intraocular inflammation and retinal vasculitis have been reported.

6. All Retinal Fluid is Pathological

Evidence suggests IRF, SRF, and PED volumes correlate with visual outcomes. Early fluid-free status is associated with better long-term BCVA and adherence.

7. Real-World Considerations

- Challenges include:
    - High injection burden.
    - Undertreatment in real-world settings.
    - Non-adherence leading to vision loss.

8. Practical Management Algorithm

1. Suggested approach:
    1. Confirm diagnosis and ensure adequate loading.
    2. Assess OCT morphology and functional response.
    3. Optimize dosing (consider Treat-and-Extend).
    4. Consider switching if persistent fluid after adequate therapy.
    5. Individualize based on response and safety profile.

9. Key Take-Home Messages

- nAMD is chronic and multifactorial.
- Response definitions are inconsistent across studies.
- Switching may overcome resistance in selected cases.
- Fluid resolution is critical for optimal outcomes.
- Treatment intensity determines long-term vision maintenance.