Diabetic Macular Edema: Past Present and Future

Gaurav K. Shah, MD
The Retina Institute
St. Louis, MO
Clinical Approach to Managing Diabetic Retinopathy

1. Recognize and understand disease pathology
Epidemiology of Diabetic Retinopathy

- An estimated 19 million Americans ≥ 20 have either diagnosed or undiagnosed diabetes mellitus.
- About $\frac{1}{3}$ are not aware that they have the disease.
- An additional 26% of adults (54 million persons) have impaired fasting blood glucose levels.
Pathophysiology of DR

Image from NEJM.org

Image from ScienceDirect.com

Hyperglycaemia

Non-proliferative Diabetic Retinopathy
- Pericyte apoptosis, basement membrane thickening, vascular leakage, alterations in blood flow, tissue hypoxia, acellular capillaries, oedema, microaneurysms, soft exudates, venous beading, intraretinal microvascular abnormalities

Proliferative Diabetic Retinopathy
- Angiogenesis, vascular leakage, fibrovascular ridge, retinal detachment, blindness
Clinical Approach to Managing Diabetic Retinopathy

1. Recognize and understand disease pathology
2. Maximize medical management
Medical Management of DR

- Diabetes Control and Complications Trial (DCCT)
  - Type I diabetics (insulin)
- Epidemiology of Diabetes Intervention and Complications Trial (EDIC)
- United Kingdom Prospective Diabetes Study (UKPDS)
  - Type II diabetics
- United Kingdom Prospective Diabetes Study - Hypertension in Diabetes Study (UKPDS-HDS)
- The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR)
- Early Treatment Diabetic Retinopathy Study (ETDRS)
Medical Management for Diabetic Macular Edema
Medical Management

- Diabetes Control and Complications Trial (DCCT)

Conclusion: Intensive Insulin Therapy Delayed the Onset and Slowed the Progression of Retinopathy, Nephropathy, Neuropathy

- Additional factors
  - blood pressure
  - serum lipids
  - diet
  - exercise
## Treatment Targets to Improve Diabetes Outcomes

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<tr>
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<td>Aggressive glucose control</td>
<td>Reduces microvascular events; improves lipids</td>
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<td>Aggressive weight loss</td>
<td>Improves lipids, glucose, BP, other risk factors</td>
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<td>Aggressive lipid-lowering</td>
<td>Reduces CVD event rates; possible effect on retinopathy</td>
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<td>Aggressive blood pressure control</td>
<td>Reduces kidney damage, eye damage, and CVD</td>
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<td>Anti-thrombosis therapy</td>
<td>Reduces macrovascular event rates</td>
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Lower A1C Correlated With Lower Risk of Complications in the DCCT

Clinical Approach to Managing Diabetic Retinopathy

1. Recognize and understand disease pathology
2. Maximize medical therapy
3. Utilize clinical trial results in clinical practice
Bevacizumab or Laser Therapy (BOLT)
The Past
Diabetic Macular Edema: Treatment Options

2. Laser
Photocoagulation for Diabetic Macular Edema

Early Treatment Diabetic Retinopathy Study Report Number 1

Early Treatment Diabetic Retinopathy Study Research Group

This first report deals only with question number 2. Previous studies have suggested that photocoagulation may be beneficial in the treatment of diabetic macular edema. 

The Early Treatment Diabetic Retinopathy Study (ETDRS) is a National Eye Institute-supported multicenter, randomized clinical trial designed to evaluate photocoagulation and to compare it to the management of patients with nonproliferative or early proliferative diabetic retinopathy. The ETDRS was designed to address the following three major questions:

1. When is the course of diabetic retinopathy in man effective? Is there an effective panretinal photocoagulation?  
2. In photocoagulation effective in the treatment of diabetic macular edema?  
3. Is early treatment effective in altering the course of diabetic retinopathy?

Accepted for publication on Sept 22, 1986. A complete listing of the participants in this research study appears at the end of this report.

Fig 7.—Comparison of percentage of eyes that experienced visual gain of six or more letters (equivalent to more than one-line gain) in eyes with macular edema and mild to moderate diabetic retinopathy assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).
Conclusion: Focal Laser Significantly Reduced the Rate of Moderate Visual Loss (> 15 Letter, Doubling of Visual Angle) in Eyes with CSDME
Before Focal Laser Treatment
After Focal Laser Treatment

Immediate

3 months
Before Grid Laser Treatment
After Grid Laser Treatment

3 Months

3 Months
Diabetic Macular Edema: Treatment Options

1. Medical Management
Laser

- Early Treatment Diabetic Retinopathy Study (ETDRS)

Conclusion: Focal Laser Significantly Reduced the Rate of Moderate Visual Loss (≥ 15 Letter, Doubling of Visual Angle) in Eyes with CSDME
Laser

• Wide angle imaging
  • In refractory cases, assess for contributing factors

PRP to nonperfused periphery may reduce DME
Today
3. Anti-VEGF Agents

- Pegaptanib (Macugen)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- VEGF Trap (Eylea)
Medical Management for Diabetic Macular Edema
Medical Management

• Diabetes Control and Complications Trial (DCCT)

Conclusion: Intensive Insulin Therapy Delayed the Onset and Slowed the Progression of Retinopathy, Nephropathy, Neuropathy

• Additional factors
  • blood pressure
  • serum lipids
  • diet
  • exercise
Laser for
Diabetic Macular Edema
Clinical Approach to Managing Diabetic Retinopathy

1. Recognize and understand disease pathology
2. Maximize medical therapy
3. Utilize clinical trial results in clinical practice
   a. Anti VEGF agents are highly efficacious
Increased Vitreous VEGF Levels Correlate With Greater DME Severity

PDR/ Vein Occlusions Mediated by VEGF

VASCULAR ENDOTHELIAL GROWTH FACTOR IN OCULAR FLUID OF PATIENTS WITH DIABETIC RETINOPATHY AND OTHER RETINAL DISORDERS

Lloyd Paul Aiello, M.D., Ph.D., Robert L. Avery, M.D., Paul G. Arrigo, M.D., Bruce A. Keyt, Ph.D., Henry D. Jampel, M.D., Sabera T. Shah, M.D., Louis R. Pasquale, M.D., Hagen Thieme, Mami A. Iwamoto, M.D., John E. Park, Ph.D., Hung V. Nguyen, M.S., Lloyd M. Aiello, M.D., Napoleone Ferrara, M.D., and George L. King, M.D.

Vascular Endothelial Growth Factor Is a Critical Stimulus for Diabetic Macular Edema

QUAN DONG NGUYEN, MD, MSc, SINAN TATLIPINAR, MD, SYED MAHMOOD SHAH, MBBS, JULIA A. HALLER, MD, EDWARD QUINLAN, MD, JENNIFER SUNG, MD, INGRID ZIMMER-GALLER, MD, DIANA V. DO, MD, AND PETER A. CAMPOCHIARO, MD

Anti-VEGF Agents for Diabetic Macular Edema
Anti-VEGF Agents

- Pegaptanib (Macugen)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- VEGF Trap (Eylea)
Pegaptanib (Macugen)

- Phase II, prospective, multicenter, randomized, controlled study
- Inhibits VEGF-165
- 172 patients
- Anti-VEGF proof of concept established
Anti-VEGF Agents

- Pegaptanib (Macugen)
- Ranibizumab (Lucentis)
Ranibizumab (Lucentis)

- Single-center, dose-escalating pilot study
- Inhibits VEGF – all isoforms
  - 10 patients

A Pilot Study of Multiple Intravitreal Injections of Ranibizumab in Patients with Center-Involving Clinically Significant Diabetic Macular Edema

Chun et al, Ophthalmology 113:1706,2006
Results

At month 3

0.3 mg ranibizumab

- 45 microns gain of 12 letters

0.5 mg ranibizumab

- 198 microns gain of 8 letters
• **Ranibizumab for Edema of MAcula in Diabetes**
  - Phase I, prospective, nonrandomized, single-center clinical trial
  - 10 patients

Vascular Endothelial Growth Factor Is a Critical Stimulus for Diabetic Macular Edema

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Nguyen et al, AJO 142:961, 2006
Results

At month 7

0.5 mg ranibizumab

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>7 months</th>
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</thead>
<tbody>
<tr>
<td>Vision</td>
<td>20/80</td>
<td>20/40</td>
</tr>
<tr>
<td>Central Foveal Thickness (microns)</td>
<td>503</td>
<td>257</td>
</tr>
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</table>

P = 0.005
READ – 2 Study

• Ranibizumab for Edema of Macula in Diabetes

Primary End Point (Six Months) Results of the Ranibizumab for Edema of the Macula in Diabetes (READ-2) Study


• Phase II, prospective, randomized, multicenter clinical trial (14 investigators)
  • 120 patients
  • Results: Ranibizumab superior to laser

Ranibizumab equivalent to ranibizumab + laser
READ-2 Safety

• 2-year results
  • no drug ocular adverse events
  • no drug systemic adverse events

Nguyen et al, Ophthalmology
117:2146-2151, 2010

Two-Year Outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study

Quan Dong Nguyen, MD, MSc, Syed Mahmood Shah, MBBS, Afsheen A. Khwaja, MD, Roomasa Channa, MD, Elham Hatem, MD, Diana V. Do, MD, David Boyer, MD, Jeffery S. Heier, MD, Prema Abraham, MD, Allen B. Thach, MD, Eugene S. Lit, MD, Bradley S. Foster, MD, Erik Krüger, MD, Pravin Dugel, MD, Thomas Chang, MD, Arup Das, MD, Thomas A. Ciualla, MD, John S. Pollack, MD, Jennifer I. Lim, MD, Dean Elliot, MD, Peter A. Campochiaro, MD, for the READ-2 Study Group*
Organization: Clinical Sites of the Network

- Overall Network Participation: 227 sites submitted application for Network
  - 797 total Investigators; 2352 additional personnel
- Current Participation
  - 102 active sites
    - 67 community based sites
  - 300 Investigators
  - 801 additional personnel
  - 37 States
## Current DRCR Network Recruitment (as of 7/1/10)

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Study Enrollment and Completion

Eyes Randomized: 
N = 854 (691 Participants)

- Sham + Prompt Laser 
  N = 293
- Ranibizumab + Prompt Laser 
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1 Year Visit Completion: 
94\%*

2 Year Visit Completion: 
87\%**

* Includes deaths
** Includes deaths and excludes pending and dropped who are not yet in window
Mean Change in Visual Acuity* at Follow-up Visits

*Values that were ±30 letters were assigned a value of 30

P-values for difference in mean change in visual acuity from sham+prompt laser at the 52-week visit:
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DRCR Protocol I

Costs of Ranibizumab

- Injections/year: 8
- Total cost of drug: $16,000
- 2 years RX: $32,000
- MD/RN/OCT/staff: $6000

Total = $38,000
DRCR Protocol I

Risks of Ranibizumab

Injections/year: 8
Injections/pt (2 yrs): 16
Endophthalmitis rate: 0.8%/patient (2 yrs)
Reality Check

• For which eyes with DME should anti-VEGF therapy be considered?
• What follow-up interval could be considered after initiating therapy?
• What treatment is employed when the DME no longer is improving?
• What follow-up is employed when the DME does not recur or worsen after an injection is not given?
• When should focal/grid laser treatment be added?
• Can we afford anti-VEGF therapy?
Ophthalmology 117:1064-1077, 2010

854 eyes at 1 year

0.5 mg Ranibizumab + laser

50% > 2-line improvement

0.5 mg Ranibizumab + deferred laser

50% > 2-line improvement

4 mg Triamcinolone + laser

30% > 2-line improvement

Sham + laser

30% > 2-line improvement
Ranibizumab

- RESTORE Study
  - Ranibizumab monotherapy vs. Ranibizumab + Laser

The RESTORE Study

Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema

Paul Mitchell, MD, PhD,1 Francesco Bandello, MD, FEBO,2 Ursula Schmidt-Erfurth, MD,3 Gabriele E. Lang, MD,4 Pascale Massin, MD, PhD,5 Reinier O. Schlingemann, MD, PhD,6 Florian Sutter, MD,7 Christian Simader, MD,8 Gabriela Burian, MD, MPH,9 Ortrud Gerstner, MSc,9 Andreas Weichselberger, PhD,9 on behalf of the RESTORE study group*

- Results: Ranibizumab equivalent to ranibizumab + laser
Ranibizumab RIDE & RISE Phase 3 Study Designs

**Diabetic Macular Edema**

**Screening:** BCVA 20/40-20/320, OCT CSF ≥ 275 µm

**1:1:1 Randomization (One Eye per Subject)**

- Sham Injection (n=122)*
- Ranibizumab 0.3 mg (n=122)*
- Ranibizumab 0.5 mg (n=122)*

**24-Month Controlled Treatment Period**
(monthly intravitreal/sham injections; rescue laser per criteria beginning Month 3)

- Month 24: Ranibizumab 0.5 mg
- Month 36: Ranibizumab 0.3 mg

**Primary Endpoint**

Long-term Open-label Extension with 0.5 mg Ranibizumab

* Target enrollment
Mean Change in BCVA Over Time: (ITT Population)

RIDE

BCVA Change from Baseline, ETDRS letters

RISE

Sham /0.5 mg
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg
Gain of $\geq 15$ letters at 2 years (n = 750)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2-Year BV Change</th>
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</thead>
<tbody>
<tr>
<td>Ranibizumab (0.3 mg)</td>
<td>34 – 45 %</td>
</tr>
<tr>
<td>Ranibizumab (0.5 mg)</td>
<td>39 – 46 %</td>
</tr>
<tr>
<td>Focal Laser</td>
<td>12 – 18 %</td>
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Ranibizumab for Diabetic Macular Edema

Results from 2 Phase III Randomized Trials: RISE and RIDE
Mean Change in OCT CFT Over Time: (ITT Population)

Mean Change in CFT (µm) over time for different groups:
- **RIDE**:
  - Sham: -200.1 µm at M36
  - Sham /0.5 mg: -261.2 µm at M36
  - Ranibizumab 0.3 mg: -269.1 µm at M36
  - Ranibizumab 0.5 mg: -256.7 µm at M36

- **RISE**:
  - Sham: -133.4 µm at M36
  - Sham /0.5 mg: -250.6 µm at M36
  - Ranibizumab 0.3 mg: -253.1 µm at M36
  - Ranibizumab 0.5 mg: -259.8 µm at M36
Time to Development of PDR: (Composite Measurement of Disease Worsening)

Rationale for 0.3 mg Ranibizumab in DME

- Both doses demonstrated similar rapid, sustained efficacy in DME through Month 36
- Fewer SAEs potentially related to systemic VEGF inhibition with 0.3 mg in DME
- DME patients often more medically complex
- Bilateral treatment rates higher in DME patients
- 0.3 mg dose provides best balance of efficacy with lower potential systemic exposure

Figure 29. Kaplan-Meier Estimated Rate of Patient Deaths during the 36-Month Study Period

Study Enrollment and Completion

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Mean Change Visual Acuity* at Follow-up Visits

Mean Change in BCVA

**RIDE**

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<th>Sham</th>
<th>Ranibizumab 0.3 mg</th>
<th>Ranibizumab 0.5 mg</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>2.3</td>
<td>12.5</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>9.3</td>
<td>11.9</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>10.7</td>
<td>0.0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
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**RISE**

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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>2.6</td>
<td>12.0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>9.1</td>
<td>10.5</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
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Mean Change in OCT

RIDE

RISE

Mean Change in CFT (µm)

-258.9*
-270.9*
-124.6
-133.6
-250.6*
-253.1*

Sham
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg
Ranibizumab

- DRCR.net, RESTORE, RISE, RIDE
  - consistent efficacy results
  - 2-yr ocular and systemic safety

- August, 2012: FDA approved Ranibizumab for diabetic macular edema
DME Drug Delivery Approaches: Anti-VEGF Agents

• Pegaptanib (Macugen) Phase II
  • Treated eyes more likely to gain 3 or more lines of vision
  • 18% vs. 7%

• Ranibizumab (Lucentis)
  • READ 2, RESOLVE, Phase III RISE and RIDE Trials, DRCR Trial
  • Lucentis 0.3 mg FDA approved for DME, October 2012

• VEGF-Trap (Eylea)
  • Phase II study

• Bevacizumab (Avastin)
  • BOLT Study: 80 patients randomized to IvB or laser for 12 months
    • IVB group gained median 8 letters
    • Laser group lost 0.5 letters (p<0.0002)

Although better side effect profile than steroids, current formulations not designed for sustained delivery and recurrent injections necessary
Anti-VEGF Agents

- Pegaptanib (Macugen)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
Bevacizumab

- Early studies – encouraging results

Haritoglou et al, Retina 26:999, 2006

Primary Intravitreal Bevacizumab (Avastin) for Diabetic Macular Edema

Results from the Pan-American Collaborative Retina Study Group at 6-Month Follow-up

J. Fernando Arevalo, MD, FACS, Juan G. Sanchez, MD, Liheh Wu, MD, Mauricio Maza, MD, Maria H. Berrocal, MD, Adriana Solis-Vivanco, MD, Michel E. Farah, MD, for the Pan-American Collaborative Retina Study Group

Bevacizumab

• BOLT Study
  • Bevacizumab vs. laser

A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema

24-Month Data: Report 3

Ranjan Rajendram, MD, FRCOphth; Samantha Fraser-Bell, PhD, FRANZCO; Andrew Kaines, FRANZCO; Michel Michaelides, MD, FRCOphth; Robin D. Hamilton, DM, FRCOphth; Simona Degli Esposti, MD; Tunde Peto, MD, PhD; Catherine Egan, FRANZCO; Catery Bunce, DSc; Richard David Leslie, MD, FRCP; Philip G. Hykin, MD, FRCOphth

Rajendram et al, Arch Ophthalmol online 2012

• Results: Bevacizumab superior to laser
  Bevacizumab safe at 2 years
Bevacizumab

- **BOLT Study**
  - Bevacizumab vs. laser

  *A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema*

  24-Month Data: Report 3

  Rajendram et al, Arch Ophthalmol online 2012

- Results: bevacizumab superior to laser
  bevacizumab safe at 2 years
Bevacizumab (Avastin)

• Early studies – encouraging results

INTRAVITREAL BEVACIZUMAB (AVASTIN) THERAPY FOR PERSISTENT DIFFUSE DIABETIC MACULAR EDEMA

CHRISTOS HARITOGLOU, MD, DANIEL KOOK, MD, ALIOSCHA NEUBAUER, MD, ARMIR WOLF, MD, SIEGFRIED PRIGLINGER, MD, RUPERT STRAUSS, MD, ARND GANDORFER, MD, MICHAEL ULBIG, MD, ANSELM KAMPIK, MD

Haritoglou et al, Retina 26:999, 2006

Primary Intravitreal Bevacizumab (Avastin) for Diabetic Macular Edema

Results from the Pan-American Collaborative Retina Study Group at 6-Month Follow-up

J. Fernando Arevalo, MD, FACS,¹ Jans Frumow-Guerra, MD,² Hugo Quiroz-Mercado, MD,² Juan G. Sanchez, MD,¹ Lihesh Wu, MD,¹ Mauricio Maia, MD,⁴ Maria H. Berrocal, MD,² Adriana Solis-Vivanco, MD,² Michel E. Farah, MD,¹ for the Pan-American Collaborative Retina Study Group⁵

Bevacizumab

- Crossover effect on fellow eye
  - Bilateral DME
    - OS injected 1.25 mg

Bilateral improvement of persistent diffuse diabetic macular oedema after unilateral intravitreal bevacizumab (Avastin) injection

R Scartozzi, JR Chao, AC Walsh and D Elliott

- OU improved!
Bevacizumab

- Compounding pharmacy not following US Pharmacopoeia chapter 797 guidelines

An Outbreak of *Streptococcus* Endophthalmitis After Intravitreal Injection of Bevacizumab

Roger A. Goldberg, Harry W. Flynn Jr, Ryan F. Isom, Darlene Miller, Serafin Gonzalez

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida
Bevacizumab

- Counterfeit Avastin
  - Must obtain from reputable pharmacy
Anti-VEGF Agents

- Pegaptanib (Macugen)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- VEGF Trap (Eylea)
VEGF Trap

- DME trial (DA VINCI)
  - phase 2, randomized, controlled study
  - fusion protein – decoy receptor
  - primary endpoint: 24 weeks
  - enrollment: 219 patients

The DA VINCI Study: Phase 2 Primary Results of VEGF Trap-Eye in Patients with Diabetic Macular Edema

At 6 months

A: Laser

B: VEGF Trap 0.5 mg monthly x 6

C: VEGF Trap 2.0 mg monthly x 6

D: VEGF Trap 2.0 mg monthly x 3, then every other month

E: VEGF Trap 2.0 mg monthly x 3, then PRN

+ 2.5 letters + 8.6 letters + 11.4 letters + 8.5 letters + 10.3 letters

+ 5.6 injections + 5.5 injections + 3.8 injections + 4.4 injections
Mean Change in Visual Acuity

Primary Endpoint

Week

ETDRS letters

0 4 8 12 16 20 24 28 32 36 40 44 48 52

14 12 10 8 6 4 2 0 -2

Laser 0.5q4 2q4 2q8 2PRN

-1.3 Laser

13.1 2q4*
12.0 2prn*
11.0 0.5q4
9.7 2q8
Mean Change in Central Retinal Thickness

<table>
<thead>
<tr>
<th>Week</th>
<th>Microns</th>
</tr>
</thead>
<tbody>
<tr>
<td>2q4*</td>
<td>227.4</td>
</tr>
<tr>
<td>0.5q4*</td>
<td>165.4</td>
</tr>
<tr>
<td>2q8*</td>
<td>187.8</td>
</tr>
<tr>
<td>Laser</td>
<td>58.4</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>-67.9</td>
</tr>
</tbody>
</table>
Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320

Patients randomized 1:1:1

- Intravitreal Aflibercept 2.0 mg q4 wks
- Intravitreal Aflibercept 2.0 mg q8 wks*
- Laser Photocoagulation

Primary endpoint: Change in BCVA

Primary Endpoint: Week 52†

Continued treatment to Year 3^*

* Following monthly loading doses; † 100 weeks (VISTA DME); ^ Laser patients may receive aflibercept during Year 3
Mean Change in Best-Corrected VA

**VIVID**

- Mean Change in ETDRS letters for VIVID.
- *P < 0.0001 vs. laser.

**VISTA**

- Mean Change in ETDRS letters for VISTA.
- *P < 0.0001 vs. laser.

ETDRS; Compared to baseline; FAS; LOCF;
VISTA – Laser: n=154; 2q4: n=154; 2q8: n=151 VIVID - Laser: n=132; 2q4: n=136; 2q8: n=135
Mean Change in Best-Corrected VA

ETDRS; Compared to baseline; FAS; LOCF;
VISTA – Laser: n=154; 2q4: n=154; 2q8: n=151 VIVID - Laser: n=132; 2q4: n=136; 2q8: n=135

*P < 0.0001 vs. laser
VIVID FAS- Laser: n=132; 2q4: n=136; 2q8: n=135
VISTA FAS- Laser: n=154; 2q4: n=154; 2q8: n=151
Compared to baseline; LOCF
Proportion of Patients Losing > 15 Letters

- **VIVID**
  - Laser: n=132
  - 2q4: n=136
  - 2q8: n=135
  - Proportion of Patients: 10.6%

- **VISTA**
  - Laser: n=154
  - 2q4: n=154
  - 2q8: n=151
  - Proportion of Patients: 9.1%

Compared to baseline; LOCF
Mean Change in Central Retinal Thickness
VEGF Trap

- Awaiting phase 3 results
Steroids for Diabetic Macular Edema
Diabetic Macular Edema: Treatment Options

Steroids

- Fluocinolone
  - Retisert
  - Iluvien
- Dexamethasone
  - Ozurdex
- Triamcinolone
  - Injection(s)
  - Helical
DME-Steroids

Protocol B
- Affirmed laser, but excluded those not expected to improve with laser
- Risks: $\uparrow$ IOP and cataract

Protocol I
- Pseudophakes had favorable effect of steroid/laser over laser alone (similar to ranibizumab groups)
- Fewer injections

Steroids are useful when the risk of cataract is acceptable and there is no IOP issue.
Clinical Approach to Managing Diabetic Retinopathy

1. Recognize and understand disease pathology
2. Maximize medical therapy
3. Utilize clinical trial results in clinical practice
   a. Anti VEGF agents make excellent first-line agents
   b. Steroids may play a role
Steroids and Macular Edema

- Decrease vascular permeability
- Decrease VEGF expression
- Decrease vasomotor response of vessels
- Stabilize lysosomal membranes
- Stabilize blood retinal barrier
Major Eligibility Criteria Assessed:

- ≥18 years old
- Type 1 or type 2 diabetes
- Center-involved DME (with OCT CSF ≥250 μm)
- VA letter score 73 to 24 (20/40 to 20/320)

Eligible eyes randomized
Subjects with 2 study eyes
assigned alternative treatment in 2\textsuperscript{nd} eye

DRCR.net Protocol B Study Design

Median VA in Laser- and Steroid-Treated Eyes

# Intraocular Pressure During 2 Years of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Laser N=330</th>
<th>1 mg N=256</th>
<th>4 mg N=254</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase ≥10 mmHg</strong></td>
<td>4%</td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>IOP &gt;30 mmHg</strong></td>
<td>1%</td>
<td>9%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Initiate IOP-lowering meds</strong></td>
<td>8%</td>
<td>12%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Open angle glaucoma</strong></td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Glaucoma procedure</strong></td>
<td>0</td>
<td>0</td>
<td>2%*</td>
</tr>
<tr>
<td><strong>Met any of the above</strong></td>
<td>10%</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*2 filtering surgeries, 1 laser trabeculoplasty, 1 ciliary body destruction

# Cataract Surgery Prior to 2 Years

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phakic at Baseline</td>
<td>N=262</td>
<td>N=203</td>
<td>N=197</td>
</tr>
<tr>
<td>Cataract Surgery</td>
<td>13%</td>
<td>23%</td>
<td>51%</td>
</tr>
</tbody>
</table>
Treatment Options: Sustained Release Devices

Steroids

- Fluocinolone
  - Retisert
  - Iluvien
- Dexamethasone
  - Ozurdex
- Triamcinolone
  - Injection(s)
  - Helical
Fluocinolone – Retisert

- **Advantage**
  - extended duration 30 months

- **Disadvantages**
  - operating room based procedure, $$$

![Image](image.png)

- Anchoring strut with suture hole
- Semipermeable polyvinyl alcohol
- Sutured to sclera at pars plana
Fluocinolone – Retisert

- Approved in U.S. for chronic noninfectious posterior segment uveitis


Fluocinolone Acetonide Implant (Retisert) for Noninfectious Posterior Uveitis

Thirty-Four-Week Results of a Multicenter Randomized Clinical Study

Glenn J. Jaffe, MD,1 Daniel Martin, MD,2 David Callanan, MD,3 P. Andrew Pearson, MD,4 Brian Levy, OD, MS,5,6 Timothy Comstock, OD, MS,5 Fluocinolone Acetonide Uveitis Study Group*

Fluocinolone – Retisert
Diabetic Macular Edema Clinical Trial

• Phase III, 4-year, prospective, multicenter, randomized, controlled study
  • 196 eyes
  • Persistent / recurrent DME
  • Prior laser treatment

Fluocinolone Acetonide Intravitreal Implant for Diabetic Macular Edema: A 3-Year Multicenter, Randomized, Controlled Clinical Trial

P. Andrew Pearson, MD,1 Timothy L. Comstock, OD,2 Michael Ip, MD,3 David Callanan, MD,4 Lawrence S. Morse, MD, PhD,5 Paul Ashton, PhD,6 Brian Levy, OD,2 Eric S. Mann, MD, PhD,7 Dean Elliott, MD8

Fluocinolone – Retisert: Results

- Statistically significant improvement through 2 years
  - Visual acuity
  - Resolution of macular edema
  - Retinal thickness
  - Diabetic retinopathy severity score

- Reduction in efficacy beginning ~ 30 months
  - Drug depletion
Fluocinolone – Retisert: Visual Acuity > 3 Line Improvement
Cataracts requiring extraction at 4 years

**Implant**
- 91% of phakic eyes
- between 6 and 18 mos

**Standard of Care**
- 20% of phakic eyes
Fluocinolone – Retisert: Adverse Events

Elevated IOP (> 30 mm Hg) at any time over 4 years

**Implant**
- 61%
- 32% trabeculectomy
- 2% explantation

**Standard of Care**
- 6%
Fluocinolone – Iluvien

- **Advantages**
  - smaller device
  - clinic-based transconjunctival implantation (25 g)
  - extended duration
    - low release rate - 3 years
    - high release rate – 1.5 years

- **Disadvantage**
  - not bioerodible
  - hollow polyamide tube remains
Fluocinolone – Iluvien: Studies

- Phase III, prospective, multicenter, randomized, controlled study
  - No phase I or II studies
  - 956 eyes
  - Prior laser

FAME Studies:
Fluocinolone Acetonide for (Diabetic) Macular Edema

Long-term Benefit of Sustained-Delivery Fluocinolone Acetonide Vitreous Inserts for Diabetic Macular Edema

Peter A. Campochiaro, MD,¹ David M. Brown, MD,² Andrew Pearson, MD,³ Thomas Ciulla, MD,⁴ David Boyer, MD,³ Frank G. Holt, MD,⁵ Michael Tolentino, MD,⁵ Amed Gupta, MD,⁶ Lilianne Duarte, MD,⁷ Steven Madreperla, MD,⁸ John Gonder, MD,¹¹ Barry Kopik, BS,¹² Kathleen Billman, BS,¹² Frances E. Kane, PhD,¹² for the FAME Study Group⁹

Campochiaro et al, Ophthalmology 118:626-635, 2011
Fluocinolone – Iluvien: Visual Acuity ≥ 3 Line Improvement

Full Data Set. Trial A & Trial B Combined.
Fluocinolone – Iluvien: Visual Acuity ≥ 3 Line Improvement

Full Data Set. Trial A & Trial B Combined.
Percentage of Patients With ≥ 15-Letter Improvement: DME ≥ 3 Years

- Control (n = 112)
- 0.2 μg/d FAc (n = 209)

Primary Readout

- P < .001
- P < .001
- P < .001

Patients (%)

0 3 6 9 12 15 18 21 24 27 30 33 36

Months

0 5 10 15 20 25 30 35 40
Percentage of Patients With ≥ 15-Letter Improvement: DME < 3 Years

- Control (n = 72)
- 0.2 µg/d FAc (n = 166)

- Patients (%): 22.3% (P = .275), 27.8% (P = .984), 22.3% (P = .958)

Primary Readout:
- P = .984
- P = .958
- P = .275
Fluocinolone – Iluvien: Adverse Events at 24 & 36 Months

<table>
<thead>
<tr>
<th></th>
<th>Trials A &amp; B Combined</th>
<th>Control N=185</th>
<th>ILUVIEN N=375</th>
<th>Control N=185</th>
<th>ILUVIEN N=375</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>As of the Month 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data Base Lock</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>As of Trial Completion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of Subjects Responding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP &gt; 30 mmHg</td>
<td>2.7%</td>
<td>16.3%</td>
<td>4.3%</td>
<td>18.4%</td>
<td></td>
</tr>
<tr>
<td>Trabeculoplasty</td>
<td>0.0%</td>
<td>1.3%</td>
<td>0.0%</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>IOP Lowering Surgeries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trabeculectomy</td>
<td>0.0%</td>
<td>2.1%</td>
<td>0.0%</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>0.0%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>Other Surgery Performed</td>
<td>0.5%</td>
<td>1.6%</td>
<td>0.5%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Patients Requiring One or More IOP Lowering Surgeries</td>
<td>0.5%</td>
<td><strong>3.7%</strong></td>
<td>0.5%</td>
<td><strong>4.8%</strong></td>
<td></td>
</tr>
</tbody>
</table>
Fluocinolone – Iluvien

• Conclusions
  • Efficacious at 24 months
  • No unexpected safety issues
  • June 2010: submitted NDA for low dose implant (24-month data)
  • December 2010: USFDA asked for 36-month data
Fluocinolone – Iluvien

• Conclusions
  • Efficacious at 24 & 36 months
  • IOP surgery < 5% at 36 months

• Nov. 2011: FDA complete response letter
  • Denied approval
  • 2 additional clinical trials required!!
  • Resubmission to FDA with results in 2014
Fluocinolone – Iluvien

- European “FDA” approval granted
  - Awaiting payment approval
- USFDA
  - Recently resubmitted for chronic DME
    - Second line therapy
Dexamethasone – Ozurdex

- **Advantages**
  - Bioerodible 6-8 weeks (PLGA)
  - Clinic-based implantation
  - Short duration (up to 6 months)

- **Disadvantages**
  - Shorter duration
Dexamethasone – Ozurdex

- Phase II, randomized, controlled, multicenter trial
- Persistent macular edema
  - Diabetes, vein occlusion, postoperative, uveitis
- Approved for vein occlusion & uveitis

Dexamethasone – Ozurdex

- Phase II trial: 171 eyes with DME
  - 700 µg implant - efficacy
    - 90 days
      - improvement ≥ 10 letters 33% vs. 12% controls ($p<.05$)
    - 180 days
      - improvement ≥ 10 letters 30% vs. 23% controls ($p>.05$)
Dexamethasone – Ozurdex

- Phase II trial: 171 eyes with DME
  - 700 µg implant – safety
    - 180 days
      - No cataracts
      - IOP > 25 at any time 13% vs. 0 controls, no glaucoma procedures

Randomized Controlled Trial of an Intravitreous Dexamethasone Drug Delivery System in Patients With Diabetic Macular Edema

Julia A. Haller, MD; Baruch D. Kuppermann, MD, PhD; Mark S. Blumenkranz, MD; George A. Williams, MD; David V. Weinberg, MD; Connie Chou, PhD; Scott M. Whitcup, MD; for the Dexamethasone DDS Phase II Study Group

- Phase III trial – Efficacious for DME
Dexamethasone – Ozurdex in Vitrectomized Eyes

- 6-month prospective trial
  - 56 patients with persistent DME

- Retinal thickness decreased

- Visual acuity improved
  - > 10 letters 33%
  - Short duration
    - peaked at week 8

Triamcinolone Helical Implant l-vation

• Advantages
  • Large surface area
  • Extended duration
    • Low release rate - 2 years
    • High release rate – 9 months

• Disadvantages
  • Operating room based
  • Possible conjunctival erosion and cap exposure
I-vation Helical Implant

- Conjunctival peritomy
- 25 g needle penetration
- Cap remains on outer surface of sclera
- Conjunctiva closed over cap
Vision Gain

Early Treatment Diabetic Retinopathy Study

Photocoagulation for Diabetic Macular Edema

Early Treatment Diabetic Retinopathy Study Report Number 1

Early Treatment Diabetic Retinopathy Study Research Group

Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) show that focal photocoagulation of “clinically significant” diabetic macular edema substantially reduces the risk of visual loss. Focal treatment also increases the chance of visual improvement, decreases the frequency of severe macular edema, and causes any minor visual field loss. In this update of the ETDRS report, 754 eyes that had macular edema and satisfied inclusion criteria for focal laser photocoagulation, were randomly assigned to photocoagulation treatment or to monitoring for focal laser photocoagulation. The cumulative effect of treatment demonstrated in this trial supported that all eyes with clinically significant diabetic macular edema should be considered for focal photocoagulation. Clinically significant macular edema, defined as retinal thickening that is at least 1 disc diameter, the center of the macula, and without visual acuity of 20/20 or better, and is associated with macular edema, was investigated. Follow-up of all ETDRS patients continued without further modifications in the study protocols.

For editorial comment use

This first report deals only with question number 2.

Previous studies have suggested that photocoagulation may be beneficial in the treatment of diabetic macular edema. These studies did not provide conclusive evidence because of size or lack of the following reasons: (1) Patients were not randomized. (2) Visual acuity was measured without prior refraction and was not measured by a “masked” observer. (3) There were confounding effects of advanced proliferative diabetic retinopathy and/or panretinal photocoagulation. (4) The number of patients was small. (5) Treatment techniques were incompletely described. (6) Evaluation of possible photocoagulation effects on visual field loss other than visual acuity was not reported. Because of these limitations, clinical guidelines for the treatment of macular edema were difficult to formulate.

In the ETDRS, the effects of focal photocoagulation for macular edema are being evaluated in a prospective, large-scale, randomized clinical trial involving 30 centers (including 28 clinical centers). This first ETDRS report presents the data that support the conclusion that focal photocoagulation for macular edema is beneficial.

Patients and Methods

From April 1983 to August 1984, the ETDRS research group enrolled 1239 diabetic patients with non-proliferative or early proliferative diabetic retinopathy. The ETDRS was designed to address the following three major questions:

1. When in the course of diabetic retinopathy is it most effective to initiate panretinal photocoagulation?
2. Is photocoagulation effective in the treatment of diabetic macular edema?
3. Is angiography treatment effective in altering the course of diabetic retinopathy?

Accepted for publication May 27, 1985.

Supported by grants from the National Eye Institute, Bethesda, Md (EY 05621), and the Research to Prevent Blindness, Inc., New York, N.Y.

EtDRS Research Group

Chloramphenicol Ophthalmic Emulsion—ETDRS Research Group

Fig 7.—Comparison of percentage of eyes that experienced visual gain of six or more letters (equivalent to more than one-line gain) in eyes with macular edema and mild to moderate diabetic retinopathy assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

Conclusion: Focal Laser Significantly Reduced the Rate of Moderate Visual Loss (≥ 15 Letter, Doubling of Visual Angle) in Eyes with CSDME.
Before Focal Laser Treatment
After Focal Laser Treatment

Immediate

3 months
Before Grid Laser Treatment
After Grid Laser Treatment

3 Months

3 Months
Laser & Widefield Imaging

- Wide-field imaging
  - In refractory cases, assess for contributing factors

Benefit of PRP to nonperfused periphery may reduce DME?
Widefield Angiography: More Than You Expect to See
Classification of Diabetic Retinopathy with Ultra-Widefield Angiography

ULTRA-WIDE-FIELD ANGIOGRAPHY IMPROVES THE DETECTION AND CLASSIFICATION OF DIABETIC RETINOPATHY

MATTHEW M. WESSEL, MD, GRANT D. AAKER, BA, GEORGE PARLITIS, MD, MINHIE CHU, MD, DONALD J. D'AMICO, MD, SZILA MATTHEW M. WESSEL, MD, GRANT D. AAKER, BA, GEORGE PARLITIS, MD, MINHIE CHU, MD, DONALD J. D'AMICO, MD, SZILA MATTHEW M. WESSEL, MD, GRANT D. AAKER, BA, GEORGE PARLITIS, MD, MINHIE CHU, MD, DONALD J. D'AMICO, MD

Purpose: To evaluate patients with diabetic retinopathy using ultra-wide-field fluorescein angiography and to compare the visualized retinal pathology with that seen on an overlay of conventional 7-standard-field (7SF) imaging.

Methods: Retinal photographs were taken for 169 diabetic patients who underwent diagnostic fluorescein angiography using the Optos Optomap Panoramic 200A imaging system. The visualized area of the retina, retinal nonperfusion, retinal neovascularization, and retinal photocoagulation were quantified by two independent masked graders. The retinal areas identified on the ultra-wide-field fluorescein angiography image were compared with an overlay of a modified 7SF image as outlined in the Early Treatment Diabetic Retinopathy Study.

Results: Ultra-wide-field fluorescein angiography imaging, on average, demonstrated 3.2 times more total retinal surface area than 7SF. When compared with 7SF, ultra-wide-field fluorescein angiography showed 3.9 times more retinal nonperfusion (P < .001), 1.9 times more neovascularization (P < .001), and 3.8 times more potential photocoagulation (P < .001). In 22 eyes (10%), ultra-wide-field fluorescein angiography demonstrated retinal pathology (threshold nonperfusion and neovascularization) not evident in an 7SF overlay. The image quality of the ultra-wide-field fluorescein angiography makes significantly more retinal vascular pathology in patients with diabetic retinopathy, improved retinal visualization may alter the classification of diabetic retinopathy and may therefore influence follow-up and treatment of these patients.

INSIGHTS FROM THE DIABETIC RETINOPATHY STUDY

Diabetic retinopathy is one of the leading causes of blindness in the United States. As the prevalence of diabetes grows, so too will the morbidity and societal costs of DR, making the treatment of this disease all the more important. Much of our management of diabetic patients is guided by the results of the seminal study on the topic nearly 30 years ago, the Diabetic Retinopathy Study (DRS). Since that time, our knowledge of the disease process has greatly increased. We now understand more about the pathology of retinal ischemia, the release of angiogenic growth factors such as vascular endothelial growth factor, and the mechanisms of vascular proliferation. Retinal imaging technology has also greatly evolved over the last 30 years, with the use of digital image capture and greater visualization of the peripheral retina.

Since its development nearly 50 years ago, fluorescein angiography remains instrumental in the evaluation of DR, allowing for the visualization of areas of retinal nonperfusion, vascular leakage, microvascular abnormalities, and neovascularization (NV). Traditional angiograms use retinal photographic equipment that is able to visual approximately 30° to 40° of the retina at one time. The DRS developed the
Ultra-Widefield Angiography
Widefield Angiography in Recalcitrant Diabetic Macular Edema

Characterization of Ischemic Index Using Ultra-widefield Fluorescein Angiography in Patients With Focal and Diffuse Recalcitrant Diabetic Macular Edema

Ravi D. Patel, Leonard V. Messner, Bruce Trestennan, Kimberly A. Michel, and Mina M. Khaderpur

**ARTICLE IN PRESS**

**FIGURE 2.** An example of the method used in this study for calculating ischemic index. The total fundus area was encircled (solid line) and the area of nonperfusion was delineated (dotted line). Ischemic index was the ratio of the area of nonperfusion over the total fundus area. This eye was in Cohort 4 and had an ischemic index of 59%.
Diabetic Macular Edema: Treatment Options

- Vitrectomy
Vitrectomy for DME

- Posterior vitreous traction (tangential)
  - Attached hyaloid may contribute to DME
    - Eyes with DME less likely to have PVD than those without DME
    - Development of PVD may result in resolution of DME

Nasrallah et al, Ophthalmology 1988
Hikichi et al, Ophthalmology 1997
Vitreoretinal Interface Patterns

• Categories

1. No PVD, + taut hyaloid
2. No PVD, + vitreofoveal traction (+/- ERM)
3. No PVD, no observable traction
4. + PVD, + ERM
5. + PVD, no ERM
Vitrectomy for DME and Traction Associated with PHT

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Eyes (No.)</th>
<th>Previous Macular Laser (%)</th>
<th>Complete Resolution of DME (%)</th>
<th>Improvement in Visual Acuity ≥ 2 lines (%)</th>
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<td>Lewis et al.</td>
<td>1992</td>
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<td>90</td>
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<td>Van Effenterre et al.</td>
<td>1993</td>
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<td>Harbour et al.</td>
<td>1996</td>
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<td>Pendergast et al.</td>
<td>2000</td>
<td>55</td>
<td>85</td>
<td>82</td>
<td>49</td>
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<tr>
<td>Gandorfer et al.</td>
<td>2000</td>
<td>12 *</td>
<td>50</td>
<td>50</td>
<td>92</td>
</tr>
</tbody>
</table>
Rationale: Vitrectomy for DME

- Case series report resolution of DME and improving VA
- Most series not prospective, many in pre-OCT era
- Possible positive impacts:
  - Anatomic resolution of vitreomacular tractional forces
  - Physiologic changes: improved oxygenation or beneficial changes in retinal microenvironment
Overall Study Design

Prospective Cohort Study

At least one eye meeting *all* of the following criteria:

- DME on clinical exam
- BCVA letter score $> 20/400$
- Presence of vitreomacular traction associated with macular edema **OR** judgment that edema will not to respond to focal/grid photocoagulation

Vitrectomy performed by the investigator’s usual routine.
Distribution of Change in Visual Acuity from Baseline in the Primary Cohort

![Diagram showing distribution of change in visual acuity from baseline over 3 and 6 months. The diagram compares improvement and worsening across these time points.]
Primary Cohort Change in OCT CSF and VA from Baseline to 6 Months

Thicker / VA Better (Paradoxical Change)

Correlation: $r = 0.31$, $N = 74$

Thinner / VA Better

Thicker / VA Worse

Thinner / VA Worse (Paradoxical Change)
Visual Results: Vtx for DME

- **Anatomic:** Median decrease in OCT CSF thickening of 153 microns
  42% resolution of central DME (CSF≤250 microns)
  Two-thirds of eyes had 50% reduction or more

- **Functional:** Visual acuity improved ≥ 10 letters (= 2 lines) in 37% at 6 months
  VA decreased ≥ 10 lines in 23% at 6 months
Vitreofoveal Traction

- Posterior hyaloid attached at fovea
- Perifoveal hyaloid detached

with ERM

without ERM
Rationale for Surgery

- Rationale for ERM peeling
  - Removal of traction exerted by ERM
ILM Peeling: Necessary?

Pars plana vitrectomy with internal limiting membranectomy for refractory diabetic macular edema without a taut posterior hyaloid

Long-term Follow-up Results of Pars Plana Vitrectomy for Diabetic Macular Edema

Teiko Yamamoto¹, Shinobu Takeuchi², Yukihiro Sato³, and Hidetoshi Yamashita⁴

Visual acuity comparison of vitrectomy with and without internal limiting membrane removal in the treatment of diabetic macular edema

Mehmet Bahadur - Aylin Urtar - Özgür Mertoğlu

Effects of Internal Limiting Membrane Peeling in Vitrectomy on Diabetic Cystoid Macular Edema Patients

Yumi Kamura¹, Yukihiro Sato², Takao Isomae³, and Hiroyuki Shimada³

Visual outcome of patients with macular edema after pars plana vitrectomy and indocyanine green-assisted peeling of the internal limiting membrane

Pars Plana Vitrectomy With Removal of the Internal Limiting Membrane in the Treatment of Persistent Diabetic Macular Edema

FRANCO M. RECCHIA, MD, ALAN J. RUBY, MD, AND CYNTHIA A. CARVALHO RECCHIA, MD

Modified Grid Laser Photocoagulation Versus Pars Plana Vitrectomy With Internal Limiting Membrane Removal in Diabetic Macular Edema

ATES YANYALI, MD, AHMET F. NOHUTCU, MD, FATIH HOROZOGLU, MD, AND ERKAN CELIK, MD
ILM Peeling: Necessary?

- No definitive answer
  - Most studies say “likely beneficial”
  - A few studies say “no additional benefit”
  - More likely to restore foveal anatomy

- DRCR.net Vitrectomy Study
  - 54% elected to peel ILM
Taut ILM

- Post-vitrectomy eyes may have edema from taut ILM

Gentile et al, Ophthalmologica 2011
Taut ILM

- Post-vitrectomy eyes may have edema from taut ILM
  - s/p ILM peel

Images show:
- ILM with glial cells
- ILM with smooth muscle actin immunopositivity
Vitrectomy for DME Summary

- Post-vitrectomy eyes may have edema from taut ILM

Gentile et al, Ophthalmologica 2011

Taut Internal Limiting Membrane Causing Diffuse Diabetic Macular Edema after Vitrectomy: Clinicopathological Correlation

Ronald C. Gentile\textsuperscript{a,c}, Tatyana Milman\textsuperscript{a,b}, Dean Elliott\textsuperscript{d}, Juan M. Romero\textsuperscript{a}, Steven A. McCormick\textsuperscript{a,c}

Gentile et al, Ophthalmologica 2011
Vitrectomy for DME Summary

- Post-vitrectomy eyes may have edema from taut ILM
  - s/p ILM peel

ILM with RPE & glial cells

ILM with smooth muscle
actin immunopositivity
ILM Traction

- ILM fine folds exert tangential traction

Noted on segmentation analysis (3D)

Not noted on tomography

Three-dimensional imaging of the inner limiting membrane folding on the vitreomacular interface in diabetic macular edema

Sachi Abe · Teiko Yamamoto · Yoshiko Kashiwagi · Eriko Kirii · Sakiko Goto · Hidetoshi Yamashita

Abe et al, Jpn J Ophthalmol 2013
Other Maneuvers?

- Subretinal lipid irrigation
- Intraretinal cyst coalescence

These maneuvers not typically performed
Prognostic Factors

- IS/OS disruption associated with poor visual acuity in diabetic macular edema

Maheshwary et al, Am J Ophthalmol 2010
Prognostic Factors

• **ELM integrity** correlates with postoperative outcome
  - Favorable prognosis
    - ELM intact
    - IS/OS discontinuous

Prognostic Factors

• Longer axial length associated with better outcome

Axial Length as a Factor Associated With Visual Outcome After Vitrectomy for Diabetic Macular Edema

Yoshihiro Wakabayashi, Keisuke Kimura, Daisuke Muramatsu, Yoshihiko Usui, Kazuhiko Umazume, Jun Suzuki, and Hiroshi Goto

Wakabayashi et al, Invest Ophthalmol Vis Sci 2013
Prognostic Factors

- Glycemic control (systemic factors) associated with favorable outcome

Yamada et al, Current Eye Research 2013
Prognostic Factors

- **Hyperreflective foci** associated with poor outcome

  - HYPERREFLECTIVE FOCI IN OUTER RETINA PREDICTIVE OF PHOTORECEPTOR DAMAGE AND POOR VISION AFTER VITRECTOMY FOR DIABETIC MACULAR EDEMA.

  - Nishijima K, Murakami T, Hirashima T, Uji A, Akagi T, Horii T, Ueda-Arakawa N, Muraoka Y, Yoshimura N.

In press: Nishijima et al, Retina 2013
Vitrectomy for DME Summary

- When performed for select cases
  - Favorable anatomic results
    - Foveal thickness usually decreases
      - 100-250 microns, ≥ 50% reduction of thickening
  - Limited visual results
    - Visual acuity usually improves 5-15 letters, but may worsen
      - Vitrectomy performed for refractory cases
      - Long standing edema
      - Irreversible macular damage
    - Possibly due to delayed intervention
Vitrectomy for DME Summary

1. No PVD, + taut hyaloid – usually performed
2. No PVD, + VMT (+/- ERM) – usually performed
3. No PVD, no observable traction – select cases
4. PVD, + ERM – select cases
5. PVD, no ERM – occasionally performed
Vitrectomy for DME Summary

- Eyes with observable vitreous and/or epiretinal traction are most likely to improve after vitrectomy

- Eyes with refractory edema and no observable traction are less likely to improve
Vitrectomy for DME Summary

- Improvement in retinal thickening is often more impressive than improvement in visual acuity
- A strong correlation exists between preoperative and postoperative visual acuity
  - Early intervention associated with better outcome
  - Foveal thickness, IS/OS integrity, ELM integrity, axial length, glycemic control, hyperreflective foci
Pharmacologic Vitreolysis

- Ocriplasmin injection – tractional DME
courtesy of George Williams
Clinical Approach to Managing Diabetic Retinopathy

1. Recognize and understand disease pathology
2. Maximize medical therapy
3. Utilize clinical trial results in clinical practice
4. Individualize treatments
DME-Conclusion

- Manage Risk Factors
- Control Systemic Issues
- Laser
- Anti-VEGF
- Steroid
- Surgery
Thank You
Clinical Approach to Managing Diabetic Retinopathy

• Recognize and understand disease pathology
• Maximize medical therapy
• Utilize clinical trial results in clinical practice
Clinical Approach to Managing Diabetic Retinopathy

- Anti VEGF agents make excellent first-line agents
- Steroids play an important role
- Don’t forget to consider laser
- Surgical intervention may aid refractory cases
- Individualize treatment and manage patient expectations
Conclusions

- Intensive control of glycemia, blood pressure is current medical standard of care
- Lipid control and ACE inhibition may confer additional benefit for diabetic retinopathy
- Anti-VEGF drugs
  - Good to excellent efficacy; reasonable safety
- Steroids
  - Short-term efficacy; ocular side-effects
- Laser should still be considered as viable treatment option
- Surgery may help refractory cases
Vitrectomy for Diabetic Macular Edema
Vitrectomy for DME

- Posterior vitreous traction (tangential)
  - Attached hyaloid may contribute to DME
    - Eyes with DME less likely to have PVD than those without DME
    - Development of PVD may result in resolution of DME

Nasrallah et al, Ophthalmology 1988
Hikichi et al, Ophthalmology 1997
Vitreofoveal Traction

- Posterior hyaloid attached at fovea
- Perifoveal hyaloid detached

Best seen by OCT

With ERM

Without ERM
Pharmacologic Vitreolysis

• Jetrea injection – tractional DME
courtesy of George Williams
Diabetic Macular Edema: Treatment Options

1. Medical Management
Diabetic Macular Edema: Treatment Options

2. Laser
3. Anti-VEGF Agents

- Pegaptanib (Macugen)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- VEGF Trap (Eylea)
Diabetic Macular Edema: Treatment Options

Steroids

• Fluocinolone
  • Retisert
  • Iluvien
• Dexamethasone
  • Ozurdevex
• Triamcinolone
  • Injection(s)
  • Helical
Diabetic Macular Edema: Treatment Options

5. Vitrectomy
The Past
Today