**My treatment algorithm for diabetic macular edema**

Peter K. Kaiser, MD
Chaney Family Endowed Chair in Ophthalmology Research
Professor of Ophthalmology
Cole Eye Institute
Cleveland, OH USA

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**Epidemiology of DR**

- An estimated 19 million Americans aged 20 years or older have either diagnosed or undiagnosed diabetes mellitus.
- About one-third are not aware that they have the disease.
- An additional 26% of adults (54 million persons) have impaired fasting blood glucose levels.

American Academy of Ophthalmology Preferred Practice Pattern

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**Financial Disclosure**

- Alcon (C, R)
- Alimera (C, R)
- Alcon/Caris (C, S)
- Bayer (C, R)
- Genentech (C, R)
- Ista Therapeutics (C, S)
- Kanghong Biotech (C, R)
- National Eye Institute (R)
- National Institute of Health (R)
- Nexcela (C)
- Ophthalmic (C, S)
- Oraje (C, S)
- Regeneron (C, S)
- Research to Prevent Blindness (R)
- Skis Ocular (S)
- Thromboagene (C)

Reviewed and approved by the Conflict of Interest Committee of the Cleveland Clinic
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)
Treatment Targets to Improve Diabetes Outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive glucose control</td>
<td>Reduces microvascular events; improves lipids</td>
</tr>
<tr>
<td>Aggressive weight loss</td>
<td>Improves lipids, glucose, BP, other risk factors</td>
</tr>
<tr>
<td>Aggressive lipid-lowering</td>
<td>Reduces CVD event rates; possible effect on retinopathy</td>
</tr>
<tr>
<td>Aggressive blood pressure control</td>
<td>Reduces kidney damage, eye damage, and CVD</td>
</tr>
<tr>
<td>Anti-thrombosis therapy</td>
<td>Reduces macrovascular event rates</td>
</tr>
</tbody>
</table>

Aggressive Blood Glucose Control Lowers Risk of Microvascular Complications

- DCCT and UKPDS established intensive glycemic control as current standard of care for diabetes
- DCCT demonstrated protective effect of glycemic control on DMC in type 1 diabetes
  - Intensive therapy reduced risk by 76% in primary cohort group
  - Intensive therapy reduced risk by 54% in the secondary group (but higher progression rates over the first year)

Aggressive Blood Glucose Control Lowers Risk of Microvascular Complications

- DCCT and UKPDS established intensive glycemic control as current standard of care for diabetes
- UKPDS confirmed protective effect of glycemic control on DMC in type 2 diabetes
  - Reduction in microvascular complication rate by 25%
  - For every percentage point decrease in A1C (ie, 8% to 7%), there was a 35% reduction in risk of microvascular complications

Primary interventions

- Early epidemiologic studies have shown showed a consistent relationship between glycated hemoglobin (HbA1c) levels and the incidence of DR. This important observation has been confirmed in large RCTs demonstrating that tight glycemic control reduces both the incidence and progression of DR.
**Lower A1C Correlated With Lower Risk of Complications in the DCCT**

![Graph showing the correlation between Hb A1C and relative risk of complications like retinopathy, nephropathy, neuropathy, and microalbuminuria.](Image)

**Role of BP Control**

- Epidemiologic studies have not found blood pressure to be a consistent risk factor for DR incidence and progression. Evidence from RCTs, however, indicates that tight control of blood pressure is a major modifiable factor for the incidence and progression of DR.

**Reducing Blood Pressure Reduced Risk of Vision Loss in the UKPDS**

- Subjects (n = 1148) were randomized to “less tight” (<180/105 mm Hg) or “tight” blood pressure control (<150/85)
- With a median follow-up of 8.4 years, those assigned to “tight” control had:
  - 34% reduction in progression of retinopathy
  - 47% reduction in risk of deterioration in visual acuity of 3 lines in association with a 10/5 mm Hg reduction in BP

**ABCD Trial**

- Appropriate Blood Pressure Control in Diabetes (ABCD) trial randomized 470 people with type 2 diabetes and hypertension to receive intensive or moderate blood pressure control.
**ABCD Trial**

- Over 5 years, there was no difference in DR progression between the groups.
- The lack of efficacy in this study may be related to poorer glycemic control, shorter follow-up, and lower blood pressure levels at baseline as compared with the UKPDS.

**Renin-Angiotensin System Blockade May Offer Additional Benefits Beyond Blood Pressure Control**

- EUCLID, MICROHOPE studies
- Clinical trials of ACE inhibitors

**EUCLID Trial**

- The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) evaluated the effects of the angiotensin-converting enzyme (ACE) inhibitor lisinopril on DR progression in normotensive, normo-albuminuric patients with type 1 diabetes
  - Over 2 years,
    - Lisinopril reduced the progression of DR by 50% (95% CI 29%-89%)
    - Progression to proliferative DR by 80%

**MICROHOPE study**

- Patients with diabetes and one other risk factor for cardiovascular disease were randomly treated with the angiotensin converting enzyme inhibitor ramipril 10 mg daily or placebo
- 3577 diabetic patients (98% with type 2 diabetes) over 4 years

**MICROHOPE study**

- Systolic blood pressure decreased by 2-3 mm Hg and reduced combined myocardial infarction, strokes, and deaths from cardiovascular diseases by 25%. The relative risk of myocardial infarction was reduced by 22%, the relative risk of stroke by 33%, and relative risk of cardiovascular death by 37%.
- Slight reduction in need for laser surgery

**MICROHOPE study**

- The investigators concluded that angiotensin converting enzyme inhibitors were the first line treatment for blood pressure control in diabetes.

**Euclid and MICROHOPE**

- Retinopathy not primary endpoint
- Reduced incidence of diabetic retinopathy; but may have been an effect of BP lowering

**Blood Pressure and DR Trials**

- Two large RCTs are currently ongoing:
  - Action in Diabetes and Vascular Disease (ADVANCE) study will evaluate the effect of a perindopril-indapamide combination on the incidence of DR
  - Diabetic Retinopathy Candesartan Trial (DIRECT) will evaluate the angiotensin II receptor blocker candesartan.
DIRECT (Diabetic Retinopathy Candesartan Trials):

• Prospective trial with angiotensin receptor blockers (ARBs):
  • Renin-angiotensin system blockade has been shown to be superior to other antihypertensive therapy in slowing progression of renal disease in diabetic patients, but questions remain regarding diabetic retinopathy.

DIRECT (Diabetic Retinopathy Candesartan Trials):

• The primary objective of the Diabetic Retinopathy Candesartan Trials (DIRECT) is to examine primary (incidence) and secondary (progression) prevention of diabetic retinopathy when blocking angiotensin II type 1-receptors.

DIRECT (Diabetic Retinopathy Candesartan Trials):

with candesartan in normoalbuminuric, normotensive Type 1 diabetic patients, and secondary prevention only in normoalbuminuric, normotensive or treated hypertensive Type 2 diabetic patients.

DIRECT (Diabetic Retinopathy Candesartan Trials):

• 5,231 patients were randomized in 30 countries
• Type 1:
  • 1,421 patients in primary prevention study
  • 1,905 patients in secondary prevention study
• Type 2:
  • 1,905 patients in the secondary prevention study
Role of lipid lowering

- Lipid-Lowering Therapy. Observational studies suggest that dyslipidemia increases the risk of DR, particularly DME.

Accumulating Evidence Supports Aggressive Lipid Control to Treat Exudates

- Multiple observational studies supporting relationship of elevated TG and/or LDL-C with presence or number of hard exudates
- Small studies and case reports support aggressive lipid control

Baseline
- TG 1272 mg/dL
- LDL-C 201 mg/dL

3 mos later
- TG 527 mg/dL
- LDL-C 80 mg/dL

Role of lipid lowering

- A small RCT found a nonsignificant trend in visual acuity improvement in patients receiving simvastatin treatment, while another study reported a reduction in hard exudates but no improvement in visual acuity in those with clinically significant DME treated with clofibrate.

FIELD Study

- Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study
  - 9795 participants with type 2 diabetes,
  - Fenofibrate treated patients were less likely than controls to need laser treatment (5.2% vs 3.6%, $P=0.001$)
CARDS Study

- Collaborative Atorvastatin Diabetes Study (CARDS)
- 2830 patients with type 2 diabetes
- Did not find atorvastatin to be effective in reducing DR progression but the study did not use photographs and there were important missing data.

ASPEN Study

- Atorvastatin Study for Prevention of Coronary Endpoints in NIDDM (ASPEN) will evaluate the effects of atorvastatin on DR

Systemic Treatments for Diabetic Retinopathy in Phase II or III Clinical Trials—New Indications of Approved Drugs*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Current Indication</th>
<th>Potential Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Statin</td>
<td>Hypercholesterolemia</td>
<td>DME, PDR</td>
</tr>
<tr>
<td>Candesartan cilexetil</td>
<td>ARB</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Celecoxib plus laser</td>
<td>COX-2 inhibitor plus laser</td>
<td>Arthritis (coxibs only)</td>
<td>DME</td>
</tr>
<tr>
<td>Osteodide acetate</td>
<td>Somatostatin analog, depot injection</td>
<td>Acromegaly, certain cancers</td>
<td>PDR</td>
</tr>
<tr>
<td>Perindopril-indapamid</td>
<td>ACE inhibitor and calcium channel blocker combination, sulfonylureas</td>
<td>Hypertension; type 2 diabetes</td>
<td>DME, PDR</td>
</tr>
</tbody>
</table>

DME = Diabetic Macular Edema
PDR = Proliferative Diabetic Retinopathy
ARB = Angiotensin Receptor Blocker

*The US FDA has not approved these agents for the treatment of diabetic retinopathy.

Growth Hormone/Insulin like Growth Factor Inhibitors

- The recent JAMA review points out that observations of improvements in DR following surgical hypophysectomy and of increased serum and ocular levels of insulin like growth factor in patients with severe DR led to studies investigating the use of agents inhibiting the growth hormone/insulin like growth factor pathway for prevention of DR.
**Growth Hormone/Insulin like Growth Factor Inhibitors**

- A small RCT conducted over 15 months among 23 patients reported reduction in retinopathy severity with octreotide, a synthetic analogue of somatostatin that blocks growth hormone, but another RCT conducted over 1 year among 20 patients evaluating continuous subcutaneous infusion of octreotide found no significant benefits.

- Two larger RCTs currently evaluating a long-acting–release octreotide injection have reported inconclusive preliminary results, with significant adverse effects (e.g., diarrhea, cholelithiasis, hypoglycemic episodes).

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**Octreotide Prevents Progression to High-Risk PDR**

- OCT=octreotide, m=22 eyes; 1/22 required PRP
- Control, n=24 eyes; 9/24 required PRP
- No adverse events reported

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**Medical Management**

- CSME → Medical Management
- Poor Foveal Capillary Perfusion → No Rx?
  - OCT
  - Focal edema → Laser
  - Diffuse edema → Combination
  - Posterior hyaloidal traction → Vitrectomy
- Good Foveal Capillary Perfusion
- Persistent DME
- Resolution of DME
Intravitreal Steroid

Recurrence of DME

Resolution of DME

Persistent DME

Anti-VEGF

Recurrence of DME

Resolution of DME

Persistent DME

Intravitreal Steroid

Recurrence of DME

Resolution of DME

Persistent DME

Vitrectomy

Resolution of DME

Persistent DME

No Rx

CSME

Medical Management

MAE

Good Foveal Capillary Perfusion

Poor Foveal Capillary Perfusion

Rx?

OCT

No Traction

Posterior hyaloidal traction

Surgical Management of DME
Possible mechanisms responsible for diabetic traction

VEGF
- Renal vasopermeability
- Production of growth factors
- Cellular migration to posterior hyaloid
- Diabetic macular edema
- Cellular contraction
- Traction macular detachment
- Abnormal collagen structure
- Enzyme-mediated vitreous cross-linking

Surgery for posterior hyaloidal traction

Vitrectomy for DME and Traction Associated with PHT

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year (No.)</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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<tr>
<td>Lewis et al.</td>
<td>1992</td>
<td>10</td>
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<td>Van Effenterre et al.</td>
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<td>Gandorfer et al.</td>
<td>2000</td>
<td>12 *</td>
<td>50</td>
<td>50</td>
<td>92</td>
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</table>

* 2 eyes without posterior hyaloidal traction
**Focal vs. Diffuse DME**

- **Focal areas of macular thickening**
- **Diffuse macular thickening**
**ETDRS**

- 23 clinical centers
- 3928 subjects with early PDR, moderate to severe NPDR and or DME in each eye
- 848 page manual of operations (on line at NTIS)
- 1985 Report No. 1 limited to eyes with mild to moderate NPDR and DME; 1490 eyes of which 754 assigned to initial focal Rx

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**Laser Surgery for DR**

*Early Treatment Diabetic Retinopathy Study (ETDRS)*

- Focal laser stops fluid leakage in macular edema
- Focal laser reduced rate of moderate visual loss by 50%

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**ETDRS**

- Overall, decreased moderate visual loss by 50%
  - Treated group 13%
  - Control group 22%

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**“Treatable lesions”**

- Discrete points of hyperfluorescence on FA
  - Most are MAs
- Areas of diffuse leakage
  - MAs, IRMA, diffusely leaking capillary bed
- Retinal avascular zones
  - Retreat Q 4 months if CSME persists

---
**Improvement in vision with laser?**

- Depends where you start. Hard to improve if you start at 20/25, 20/20, or better …

*Numbers of Eyes in Acuity Subgroups*  
85% of patients better than 20/40!

<table>
<thead>
<tr>
<th>VA Score</th>
<th>Baseline</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
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<tbody>
<tr>
<td>-20/15</td>
<td>122</td>
<td>104</td>
<td>128</td>
<td>41</td>
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<tr>
<td></td>
<td>238</td>
<td>187</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>-20/25</td>
<td>356</td>
<td>284</td>
<td>388</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>697</td>
<td>557</td>
<td></td>
<td>258</td>
</tr>
<tr>
<td>-20/30</td>
<td>152</td>
<td>134</td>
<td>161</td>
<td>48</td>
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<tr>
<td></td>
<td>328</td>
<td>252</td>
<td></td>
<td>104</td>
</tr>
<tr>
<td>-20/50</td>
<td>54</td>
<td>44</td>
<td>60</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>94</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>-20/60</td>
<td>80</td>
<td>48</td>
<td>65</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>108</td>
<td>88</td>
<td></td>
<td>44</td>
</tr>
</tbody>
</table>
Outcome based on baseline

- 20/15 or better: No difference
- 20/20 to 20/25: Small benefit
- 20/30 to 20/40: Moderate benefit
- 20/40 to 20/60: Good benefit

Laser Management of DME - ETDRS

Vision Gain

ETDRS

- Excluded patients:
  - Vision worse than 20/200: 7%
  - Age > 70 years: 18%
  - Patients on dialysis: 5%
  - Patients taking coumadin: 3%
  - Simultaneous macular edema and proliferative diabetic retinopathy: 14%
**For persistent or recurrent CSME**

- Consider repeat laser treatment.
- The ETDRS did not test one laser treatment vs observation. The strategy that was tested was treatment Q 3 months if CSME persisted.
- The VA improvement is gradual and a series of treatments are advised.

**How many treatments do you typically recommend?**

- I generally quote a series of three to five treatments over one to two years.
- At some point, it is reasonable to decide that treatment is not working...
- If vision was reduced to 20/40 or worse, anticipate improvement in about 40%

**Role of VEGF in diabetic retinopathy**

- Vasodilation (NO release)
- Angiogenesis
- Vessel permeability
- Diabetic macular edema
- Cell migration
- Cell proliferation
- Proliferative diabetic retinopathy
- Chemotaxis (macrophages, granulocytes)

VEGF-A, vascular endothelial growth factor A
VEGF Levels Are Increased in the Vitreous of Patients With DME

Increased Vitreous VEGF Levels Correlate with Greater DME Severity

Anti-VEGF Agents
- Available now:
  - Pegaptanib
  - Ranibizumab
  - Bevacizumab
- Drugs in clinical trials:
  - VEGF Trap
  - Bevasirinab
  - iCO-007

Study Design
Exploratory, Prospective, Phase 2
- Multicenter, randomized, controlled, double masked, dose-finding study
- Dosing: 0.3, 1.0 and 3.0 mg pegaptanib vs. sham q 6 weeks
- 172 patients; 169 Safety monitoring
**Study Design**
Exploratory, Prospective, Phase 2

- Treatment schedule

<table>
<thead>
<tr>
<th>w0</th>
<th>w6</th>
<th>w12</th>
<th>w18</th>
<th>w24</th>
<th>w30</th>
<th>w36</th>
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<tbody>
<tr>
<td>MAC</td>
<td>MAC</td>
<td>MAC</td>
<td>MAC</td>
<td>MAC</td>
<td>MAC</td>
<td>MAC</td>
</tr>
</tbody>
</table>

At investigator’s discretion

*(60 letters ~ 20/63; 55 letters ~ 20/80)*

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**Results: Lines of Vision Gained**

Proportion of Patients by RX Group

- 0.3 mg N=44
- 1.0 mg N=44
- 3.0 mg N=42
- Sham N=42

*P < 0.05

% of Patients

2> Lines Gained

0 Lines Gained* P < 0.05

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**Results: Mean Change in Retinal Thickness**

OCT – Central Part of the Central Subfield

- 0.3 mg
- 1.0 mg
- 3.0 mg
- Sham

Mean change in retinal thickness (µm)

*P < 0.05

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**Results: Patients Needing Focal/Grid Laser**

Week 12 or Later

- 0.3 mg
- 1.0 mg
- 3.0 mg
- Sham

% Patients needing focal/grid laser

*P < 0.05

25% 30% 40% 48%
**Systemic Safety: Serious Adverse Events Equivalent Across All Subgroups**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Pegaptanib 0.3 mg</th>
<th>Pegaptanib 1 mg</th>
<th>Pegaptanib 0.3 mg</th>
<th>Sham N = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Metabolism and Nutritional Abnormal</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nervous Disorders</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Genitourinary and Admin. Site Conditions</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Infections and Infestations</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Nervous Disorders</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Ocular Safety: Serious Adverse Events**

- Pegaptanib
  - One case of endophthalmitis
  - 1 / 652 injections - 0.15% per injection
  - Did not result in severe vision loss (6 lines)
  - No retinal detachments
  - Vitreous hemorrhage 6/128 - 5%

- Sham
  - Retinal detachment - 1, sham eye
  - Vitreous hemorrhage - 3/41 - 7%

**Retinal Neovascularization Regression with Pegaptanib**

Baseline

Prior Laser only

Week 36

Week 52

NVE response during therapy is transient

---

pegaptanib

Stop Therapy
**Conclusions: Phase 2 DME Study**

- Pegaptanib 0.3 mg
  - Vision Improvement
  - Reduced Thickness
  - Less Laser Needed
  - 0.3 mg is the lowest studied effective dose
  - 1 case of endophthalmitis (0.15% / inj)

**Ranibizumab restores VEGF165-induced delocalization of tight junction proteins in iBREC**

- Claudin-1
- Claudin-5
- Occludin
- ZO-1

- Strong tight junction protein expression
- 3-day VEGF165 treatment (claudin-1 and occludin are no longer expressed)
- 3-day VEGF165 treatment
  - 1-day 100 µg/ml ranibizumab

**Ranibizumab restores endothelial cell barrier by reverting VEGF165-elevated permeability of iBREC**

**Graph:**

- TER, transepithelial electrical resistance
- W, with; wo, without
- Addition of 100 µg/ml ranibizumab

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)

Ranibizumab 0.5 mg

Month 24
Month 36

Primary Endpoint: Long-term Open-label Extension with 0.5mg Ranibizumab

* Target enrollment

Mean Change in BCVA From Baseline Over Time

RISE

Sham (n=130) Ranibizumab 0.3 mg (n=125) Ranibizumab 0.5 mg (n=127)

Mean Change in BCVA From Baseline Over Time

RIDE

Sham (n=130) Ranibizumab 0.3 mg (n=125) Ranibizumab 0.5 mg (n=127)

* p<0.0001 vs. sham (ANOVA t-test [stratified]). Differences were statistically significant starting at Day 7 and at each point thereafter.
† Unadjusted differences in means.
Vertical bars are ±1 standard error of the mean. Last observation carried forward imputation method was used.
BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.
Laser Treatments at 24 Months

- Starting at month 3, patients were evaluated monthly for macular laser
- Laser treatment criteria:
  - CFT ≥250 μm on OCT with <50 μm change from the prior month
  - No laser in the prior 3 months
- Panretinal photocoagulation available for all patients when clinically indicated

<table>
<thead>
<tr>
<th>RIDE</th>
<th>Ranibizumab</th>
<th></th>
<th>RISE</th>
<th>Ranibizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=130)</td>
<td>0.3 mg (n=125)</td>
<td>0.5 mg (n=127)</td>
<td>Sham (n=127)</td>
<td>0.3 mg (n=125)</td>
</tr>
</tbody>
</table>

- Macular focal/grid rescue laser treatment
- Received macular laser, n (%):
  - RIDE: 91 (70.0) 45 (36.0) 25 (19.7)
  - RISE: 94 (74.0) 49 (39.2) 44 (35.2)

- Panretinal photocoagulation (PRP) laser treatment
- Received PRP, n (%):
  - RIDE: 16 (12.3) 2 (1.6) 2 (1.6)
  - RISE: 14 (11.0) 0 1 (0.8)

* Exploratory endpoint. Adjusted differences vs. sham were: -32.8% for the 0.3 mg group and -49.8% for the 0.5 mg group in RIDE; -35.0% for the 0.3 mg group and -39.3% for the 0.5 mg group in RISE; p < 0.0001 for all ranibizumab groups vs. sham (Cochran-Mantel-Haenzel chi-squared test [stratified]). SD = standard deviation. CFT = central foveal thickness. OCT = optical coherence tomography.

ETDRS Retinopathy Severity Scale

- Standardized photographic grading scale for evaluating longitudinal changes in DR
- Evaluated at central reading center by masked graders
- Severity on (simplified) scale has clinical utility

Worsening of Diabetic Retinopathy
Adverse Events and Progression to PDR by Month 24*

<table>
<thead>
<tr>
<th>RIDE</th>
<th>Ranibizumab</th>
<th></th>
<th>RISE</th>
<th>Ranibizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=130)</td>
<td>0.3 mg (n=125)</td>
<td>0.5 mg (n=127)</td>
<td>Sham (n=127)</td>
<td>0.3 mg (n=125)</td>
</tr>
</tbody>
</table>

- RIDE
  - Δ = -7.8 (p=0.0026)
  - Δ = -8.3 (p=0.0069)
- RISE
  - Δ = -13.4 (p=0.0014)

Retinopathy Severity Scale
Changes at Month 24

- % improved
  - RIDE
    - % worsened
      - 0.0 mg 17.6 36.5
      - 0.3 mg 17.6 36.5
      - Sham 2.4 4

- % worsened
  - RIDE
    - % improved
      - 0.0 mg
      - 0.3 mg
      - Sham

* As stated, was considered to have improvement in ETDRS retinopathy severity scale (RS) by Month 24. For any of these conditions, baseline characteristics were unbalanced at baseline and presented as an appendix. Baseline characteristics are described in the appendix.
Mean Change in OCT CFT Over Time

Sham (n=127)
Ranibizumab 0.3 mg (n=125)
Ranibizumab 0.5 mg (n=125)

Mean Change in CFT (µm)
-250.6* -253.1* -133.6

Month
*p<0.0001 vs. sham (ANCOVA t-test [stratified]). Earliest statistically significant difference at Month 1.
†Unadjusted differences in means. Vertical bars are ±1 standard error of the mean. Central foveal thickness (CFT) is defined as center point thickness. Independent review of optical coherence tomography performed at University of Wisconsin Fundus Photograph Reading Center.
ETDRS = Early Treatment Diabetic Retinopathy Study.

Mean Change in Visual Acuity* at Follow-up Visits

Sham+prompt laser
Ranibizumab+prompt laser
Ranibizumab+deferred laser
Triamcinolone+prompt laser

* 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:
ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; and triamcinolone+prompt laser =0.31.

DRCR.net Protocol I

Eyes Randomized:
N = 854 (691 Participants)

Sham + Prompt Laser N = 293
Ranibizumab + Prompt Laser N = 187
Ranibizumab + Deferred Laser N = 188
Triamcinolone + Prompt Laser N = 186

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

1 Year Visit Completion: 94%
2 Year Visit Completion: 87%
**Anti-VEGF works well in DME**

- In ranibizumab and deferred laser group:
  - 70% had no laser at year 1
  - 50% had no laser at year 2
- There was no ranibizumab alone subgroup
- Entire treatment effect could have been anti-VEGF effect with no additive benefit of laser

**Phase 3: RESTORE study design**

- Phase III, randomized, double-blind, multicenter, laser-controlled, efficacy and safety study of intravitreal ranibizumab 0.5 mg as adjunctive therapy and monotherapy in patients with visual impairment due to DME; results due early 2010

**RESTORE treatment schedule**

- Primary endpoint: Mean BCVA change from baseline

**RESTORE Mean BCVA change from baseline**

- Treatment initiation phase: Month 0
- Continuous/resumed treatment phase: Months 1 through 12

- Ranibizumab 0.5 mg
- Sham laser
- Laser
- Sham injection

- Mean change (±SE) in BCVA (letters):
  - Ranibizumab 0.5 mg (n=115)
  - Ranibizumab 0.5 mg + laser (n=118)
  - Laser (n=110)

- Mean change (±SE) in BCVA (letters) at 12 months:
  - Ranibizumab 0.5 mg: +0.1 (±0.1)
  - Ranibizumab 0.5 mg + laser: +0.0 (±0.0)
  - Laser: +0.8 (±0.8)

*According to pre-defined retreatment criteria
†According to the judgment of the investigator in accordance with ETDRS guidelines

---

**Visual impairment due to DME**

- Randomized 1:1:1
- Active laser
- Active laser
- Sham laser
- Sham injection
- Ranibizumab 0.5 mg
- Ranibizumab 0.5 mg

---

**RESTORE**

Mean BCVA change from baseline over time according to baseline CRT

- <300 μm n=60 (18%)
- 300–400 μm n=103 (31%)
- >400 μm n=174 (52%)

Efficacy numbers represent mean BCVA over time from Month 1 to Month 12 according to baseline characteristics.

Data on file, Novartis

---

Mean BCVA change from baseline over time according to type of DME

- Focal n=183 (56%)
- Diffuse n=143 (44%)

Efficacy numbers represent mean BCVA over time from Month 1 to Month 12 according to baseline characteristics.

Data on file, Novartis

---

Mean BCVA change from baseline over time according to prior laser treatment

- Prior laser n=162 (47%)
- No prior laser n=181 (53%)

Efficacy numbers represent mean BCVA over time from Month 1 to Month 12 according to baseline characteristics.

Data on file, Novartis
Ranibizumab efficacy vs # of injections


Significant systemic VEGF inhibition with bevacizumab

- Patients with diabetic retinopathy treated with 1.25 mg intravitreal bevacizumab resulted in significantly decreased systemic VEGF plasma levels.

Intravitreal Bevacizumab

- 78 eyes of 64 consecutive DME patients with a minimum follow-up of six months
- 63 (80.8%) treated with 2.5 mg bevacizumab
- 15 (19.2%) treated with 1.25 mg bevacizumab

- Mean follow-up: 6.31 ± 0.81 months
- Mean age: 59.7 ± 9.3 years old
- Male: 54.7%
- Hispanic: 79.7%
After 5 initial monthly doses

**Primary Endpoint:**
Week 52

**Primary endpoint:** Mean change in BCVA

**Key Secondary endpoints**
- Change in OCT
- Change in Diabetic Retinopathy Severity Scale (DRSS)

Continued treatment through Year 3

Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320
N=406 (VIVID)  N=466 (VISTA)

**Treatment Schedule**

Starting in Week 24: Additional (rescue) treatment available to all patients
Patients with BCVA below BSL and loss from previous best BCVA score of ≥10 letters at 1 visit or ≥15 letters on 2 consecutive visits

**Study Design**

IVT Aflibercept 2 mg q4 wks
IVT Aflibercept 2 mg q8 wks
Laser Photocoagulation

Primary endpoint: Mean change in BCVA

Continued treatment through Year 3

**Treatment Experience**

VIVID
- Mean # of Active Injections: 12.2
- Mean # of Active Injections*: 11.8

VISTA
- Mean # of Active Injections: 9.7
- Mean # of Active Injections*: 8.4

*Not considering Rescue Treatment; 10 Injections possible; Minimum # of lasers = 1, maximum = 4/5

**Mean Change in Best-Corrected Visual Acuity**

VIVID
- Laser: n=133; 2q4: n=136; 2q8: n=135

VISTA
- Laser: n=154; 2q4: n=155; 2q8: n=152
### Week 100 Outcomes

**DRSS: Diabetic Retinopathy Severity Score**
- Compared to baseline; LOCF

<table>
<thead>
<tr>
<th>Recurrence of DME</th>
<th>Resolution of DME</th>
<th>Persistent DME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF</td>
<td></td>
<td>Persistent DME</td>
</tr>
<tr>
<td></td>
<td>Anti-VEGF</td>
<td>Resolution of DME</td>
</tr>
<tr>
<td>Intravitreal Steroid</td>
<td>Anti-VEGF</td>
<td></td>
</tr>
</tbody>
</table>

### Proportion of Patients with ≥ 2 Step Improvement in DRSS

<table>
<thead>
<tr>
<th>VIVID</th>
<th>VISTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2q4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2q8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- n=80
- n=81
- n=83
- n=114
- n=161
- n=164

**ETDRS Letters**

- Week 0: 7.5%
- Week 100: 77.7%
- Week 100: 154.3%
- Week 100: 23.8%
- Week 100: 25.1%

**Graphs**

- VISTA: Week 0 to Week 100 outcomes.
- Proportion of patients with ≥ 2 step improvement in DRSS.
Pathophysiology of DME

A&P Changes

Biochemical Factors


DAG = diacylglycerol; HIF = hypoxia-induced factor; ICAM = intercellular adhesion molecule; NOS = nitric oxide synthase; PEDF = pigment epithelium-derived factor; PKC = protein kinase C; VEGF = vascular endothelial growth factor.

Biochemical Factors A&P Changes

Steroids and macular edema

- Decrease vascular permeability
- Decreases VEGF expression
- Decrease vasomotor response of vessels
- Stabilize lysosomal membranes
- Stabilizes blood retinal barrier

**Routes of steroid administration**

- Periocular injections
- Intraocular injections
  - Triamcinolone acetonide (Triessence, Alcon)
  - Triamcinolone acetonide (Trivera, Allergan)
- Intraocular implants
  - Biodegradable
    - Dexamethasone implant (Ozurdex, Allergan)
  - Non-erodable
    - Fluocinolone acetonide implant (Retisert, Bausch and Lomb)
    - Fluocinolone acetonide implant (Iluvien, Alimera)

**PST Steroids**

- 73 PST injections in 63 eyes
  - Male: 32/63 (51%) eyes
  - Mean age: 65 years

**Visual Distribution**

<table>
<thead>
<tr>
<th>Change</th>
<th>1 mos</th>
<th>3 mos</th>
<th>6 mos</th>
<th>12 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3 line</td>
<td>50%</td>
<td>46%</td>
<td>57%</td>
<td>35%</td>
</tr>
<tr>
<td>1 or 2</td>
<td>13(46%)</td>
<td>29(49%)</td>
<td>12(28%)</td>
<td>8(29%)</td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>1(4%)</td>
<td>4(7%)</td>
<td>8(17%)</td>
<td>9(32%)</td>
</tr>
<tr>
<td>≥ 3 line</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(4%)</td>
</tr>
<tr>
<td>N</td>
<td>28</td>
<td>59</td>
<td>47</td>
<td>28</td>
</tr>
</tbody>
</table>

DRCR.net Objective

- To evaluate the efficacy and safety of 1-mg and 4-mg doses of preservative-free intravitreal triamcinolone in comparison with focal/grid photocoagulation for the treatment of diabetic macular edema (DME).

Participants

- Eight hundred forty study eyes of 693 subjects with DME involving the fovea and with visual acuity of 20/40 to 20/320.

DRCR.net Methods

- Eyes were randomized to focal/grid photocoagulation (n=330), 1 mg intravitreal triamcinolone (n=256), or 4 mg intravitreal triamcinolone (n=254). Retreatment was given for persistent or new edema at 4-month intervals. The primary outcome was evaluated at 2 years.
  - Apropos safety, about 500 exposed to IVTA
At 4 months, the visual acuity in the steroid-treated subjects was better than the laser group, but with longer follow up, the difference was no longer apparent. From the 16-month point to the 2-year visit, the laser-treated subjects had better vision.

Table 4. Change in Visual Acuity at 2-Year Primary Outcome

<table>
<thead>
<tr>
<th>Change in Visual Acuity (Letters)</th>
<th>Laser (n = 330)</th>
<th>1 mg (n = 256)</th>
<th>4 mg (n = 254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>1±17</td>
<td>-2±18</td>
<td>-3±22</td>
</tr>
<tr>
<td>Median (25th, 75th percentile)</td>
<td>4 (-6, 11)</td>
<td>1 (-11, 0)</td>
<td>2 (-11, 11)</td>
</tr>
<tr>
<td>Distribution of change at 2 yrs (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 letters improvement</td>
<td>19%</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>14-15 letters improvement</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>9-10 letters improvement</td>
<td>10%</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Same ±4 letters</td>
<td>24%</td>
<td>27%</td>
<td>23%</td>
</tr>
<tr>
<td>5-9 letters worse</td>
<td>10%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>10-14 letters worse</td>
<td>5%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>15 letters worse</td>
<td>14%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Why did laser do so well in the DRCR protocol?

- Should not have been a surprise. It did just about the same as laser in the ETDRS.
- The DRCR investigators considered more of an “all-comer” group of patients with a wider range of baseline visions. In fact, subjects had to be worse than about 20/40 to enroll and ranged from 24 to 73 ETDRS letters (about 20/320 to about 20/40) at baseline.
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 2nd eye

Focal/Grid Laser
1 mg IVT
4 mg IVT

Focal/Grid Photocoagulation Treatment
 Modified-ETDRS technique:
- Burn Size: 50 microns
- Burn Duration: 0.05 - 0.1 seconds
- Wavelength: Green to yellow
- Intensity: Barely visible (light gray)
- Grid Treatment: Cover areas of diffuse retinal thickening or nonperfusion 2 burn widths apart
- Direct treatment of microaneurysms: All microaneurysms are treated directly, but only in areas of retinal thickening
- Placement of laser treatment: Retina thickening 500 - 3000 microns from center of fovea
**DRCR.net**  
*Study Enrollment and Completion*

- 840 eyes (693 subjects) enrolled at 88 clinical sites  
  - Treatment Groups  
    - Laser: N = 330  
    - 1 mg: N = 256  
    - 4 mg: N = 254  
  - 2-year visit completion rate  
    - 83% including deaths  
    - 88% excluding deaths

**Baseline Characteristics**

- Mean age: 63 years  
- Diabetes type: 5% type 1, 95% type 2  
- Visual acuity (Snellen equivalent)  
  - 20/40 to 20/63: 58%  
  - Worse than 20/63 to better than 20/200: 38%  
  - 20/200 to 20/320: 5%  
- OCT central subfield thickness  
  - Mean: 424 microns  
  - Range: 133 to 1164 microns

**DRCR vision change at 2 years with laser**

- ≥15 letter improvement 18%  
- 14 to 10 letter improvement 13%  
- 9 to 5 letter improvement 16%  
- Same +/- 4 letters 24%  
- 5 to 9 letter worse 10%  
- 10 to 14 letters worse 5%  
- > letters worse 14%  

\[ \text{47\% improve} + \text{71\% stable} \]

**Treatment 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>Mean number of treatments*</td>
<td>N=272</td>
<td>N=220</td>
<td>N=205</td>
</tr>
<tr>
<td></td>
<td>2.9</td>
<td>3.5</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* Includes only subjects with a 2 year visit
**Primary Outcome:**
*Mean Change in Visual Acuity at 2 Years*

<table>
<thead>
<tr>
<th>Mean Change in VA (letter score)</th>
<th>Laser N=330</th>
<th>1 mg N=256</th>
<th>4 mg N=254</th>
</tr>
</thead>
<tbody>
<tr>
<td>+1</td>
<td>-2</td>
<td>-3</td>
<td></td>
</tr>
</tbody>
</table>

**Pairwise Comparisons**

<table>
<thead>
<tr>
<th></th>
<th>Mean Difference*</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser vs. 1 mg</td>
<td>+3.5 letters</td>
<td>0.02</td>
</tr>
<tr>
<td>Laser vs. 4 mg</td>
<td>+4.6 letters</td>
<td>0.002</td>
</tr>
<tr>
<td>1 mg vs. 4 mg</td>
<td>+1.1 letters</td>
<td>0.49</td>
</tr>
</tbody>
</table>

* Adjusted for baseline VA and prior focal/grid laser

---

**Median VA in laser and steroid treated eyes**

- Laser vs. 1 mg: P < 0.005
- Laser vs. 4 mg: P < 0.005
- 1 mg vs. 4 mg: P < 0.005

---

DRCR Ophthalmology 2008;115:1447–1459
**Patients with increase in VA ≥ 10 letters**

- **Laser**: 40%
- **1 mg**: 34%
- **4 mg**: 0%

**% Decreased ≥10 Letters in Laser and IVT Treated Eyes**

- **Laser**: 40%
- **1 mg**: 30%
- **4 mg**: 20%

**Visual Acuity at 2 Years According to Lens Status**

<table>
<thead>
<tr>
<th>Lens Status</th>
<th>Laser</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>N=272</td>
<td>N=220</td>
<td>N=204</td>
</tr>
<tr>
<td>Mean Change in VA (letter score)</td>
<td>+2</td>
<td>-2</td>
<td>-4</td>
</tr>
<tr>
<td>Pseudophakic at 2 Yrs or Minimal or No Cataract at 2 Yrs</td>
<td>N=178</td>
<td>N=136</td>
<td>N=159</td>
</tr>
<tr>
<td>Mean Change in VA (letter score)</td>
<td>+3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pseudophakic at Baseline</td>
<td>N=54</td>
<td>N=48</td>
<td>N=43</td>
</tr>
<tr>
<td>Mean Change in VA (letter score)</td>
<td>+2</td>
<td>+2</td>
<td>-1</td>
</tr>
</tbody>
</table>

Includes only subjects with a 2 year visit.

**OCT Central Subfield (CSF) Thickening at 2 Years**

<table>
<thead>
<tr>
<th>Change in OCT CSF</th>
<th>Laser</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean*</td>
<td>N=220</td>
<td>N=178</td>
<td>N=162</td>
</tr>
<tr>
<td>Mean*</td>
<td>-139</td>
<td>-86</td>
<td>-77</td>
</tr>
<tr>
<td>Thickness Decreased ≥50%</td>
<td>67%</td>
<td>46%</td>
<td>48%</td>
</tr>
<tr>
<td>Thickness &lt;250 microns</td>
<td>53%</td>
<td>34%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Pairwise Comparisons
- Laser v 1 mg <0.001
- Laser v 4 mg <0.001
- 1 mg v 4 mg 0.91
Median Center Subfield Thickness in laser and steroid treated eyes

Median Center Subfield Thickness in laser and steroid treated eyes

Major Ocular Adverse Events During 2 Years of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endophthalmitis*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pseudophthalmitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment†</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Retinal vein occlusion†</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Retinal artery occlusion†</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anterior ischemic optic neuropathy†</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vitrectomy‡</td>
<td>31</td>
<td>26</td>
<td>19</td>
</tr>
</tbody>
</table>

* 1 case of endophthalmitis occurred after vitrectomy, not related to study drug injection
† Judged not necessarily related to treatment
‡ Includes vitrectomy for diabetic macular edema, vitreous hemorrhage or other cause
**Intraocular Pressure During 2 Years of Follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=330</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase ≥10 mmHg</td>
<td>4%</td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td>IOP &gt;30 mmHg</td>
<td>1%</td>
<td>9%</td>
<td>21%</td>
</tr>
<tr>
<td>Initiate IOP-lowering meds</td>
<td>8%</td>
<td>12%</td>
<td>30%</td>
</tr>
<tr>
<td>Open angle glaucoma</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Glaucoma procedure</td>
<td>0%</td>
<td>0%</td>
<td>2%*</td>
</tr>
<tr>
<td>Met any of the above</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>N=262</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phakic at Baseline N=203 N=197</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract Surgery</td>
<td>13%</td>
<td>23%</td>
<td>51%</td>
</tr>
</tbody>
</table>

---

**DRCR Protocol B**

**DRCR Protocol B**

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/32 to 20/63 N=189 N=149 N=149</td>
<td>23%</td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td>20/63 to 20/200 N=129 N=94 N=92</td>
<td>43%</td>
<td>33%</td>
<td>39%</td>
</tr>
<tr>
<td>20/200 to 20/320 N=12 N=13 N=13</td>
<td>42%</td>
<td>46%</td>
<td>77%</td>
</tr>
</tbody>
</table>
**Steroids not as good as laser...**

- Protocol B conclusion: “focal/grid photocoagulation is more effective and has fewer side effects than intravitreal triamcinolone”

**Steroids caused cataract**

- Protocol B: Dramatic increase in cataract extraction rates in steroid group

![Mean change in vision](image)

**Protocol I**

- Protocol I: Similar downward trend in vision for steroid group after 6 months

**Steroids as effective as anti-VEGF**

- In Protocol I, pseudophakic patients had similar visual gains as ranibizumab...
**IV steroid: Complications**

- **Increased IOP:**
  - 30-50% eyes treated with glaucoma gtts
  - <1% refractory (requiring surgery)
- **Endophthalmitis:**
  - Noninfectious: ~2%
  - Infectious: ~0.5
- **Cataract:**
  - ~2% (6 mo)-Probably underestimated
  - Likely higher w/time & repeat injections

**Ozurdex**

**Scanning EM of Dexamethasone Implant**

- Before Implantation
- After 3 Weeks

**PLGA (poly [lactic-glycolic] acid) Formulation and Metabolism**

- Biodegradable

```
Lactic Acid  Glycolic Acid
Water & Carbon Dioxide
```
**Overall Results:**

**Improvements in Visual Acuity**

<table>
<thead>
<tr>
<th></th>
<th>Observation (n=105)</th>
<th>Dexamethasone-DDS 350 µg (n=103)</th>
<th>Dexamethasone-DDS 700 µg (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong> values</td>
<td><strong>P = .001</strong></td>
<td><strong>P = .001</strong></td>
<td><strong>P &lt; .001</strong></td>
</tr>
<tr>
<td><strong>10 or more letters</strong></td>
<td>13.3</td>
<td>21.0</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>15 or more letters</strong></td>
<td>32.4</td>
<td>7.6</td>
<td>10.5</td>
</tr>
</tbody>
</table>

**P** values are 700 µg vs. Observation. 700 µg dosed patients received no rescue therapy between day 90 and 180.

**DME Sub-group* Patients:**

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>350 µg</th>
<th>700 µg</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>57</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Age (Mean)</td>
<td>63.8 ± 10.2</td>
<td>63.8 ± 11.6</td>
<td>62.9 ± 12.0</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>52.6%</td>
<td>50.9%</td>
<td>54.4%</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>71.9%</td>
<td>75.4%</td>
<td>71.9%</td>
</tr>
<tr>
<td>BCVA (Letters)</td>
<td>54.4 ± 10.0</td>
<td>54.7 ± 11.0</td>
<td>54.4 ± 11.9</td>
</tr>
</tbody>
</table>

*Study not powered to show statistical differences between groups in this subset.

**Primary Endpoint: Day 90 DME subgroup**

**Improvement in Visual Acuity**

<table>
<thead>
<tr>
<th></th>
<th>Observation (n=57)</th>
<th>Dexamethasone-DDS 350 µg (n=57)</th>
<th>Dexamethasone-DDS 700 µg (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong> values</td>
<td><strong>P = .007</strong></td>
<td><strong>P = .007</strong></td>
<td><strong>P = .051</strong></td>
</tr>
<tr>
<td><strong>10 or more letters</strong></td>
<td>12.3</td>
<td>23.3</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>15 or more letters</strong></td>
<td>21.1</td>
<td>5.3</td>
<td>10.5</td>
</tr>
</tbody>
</table>

**Macular Thickness Changes (Day 90)**

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Dex DDS 3µg</th>
<th>Dex DDS 7µg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean change in retinal thickness (µm)</strong></td>
<td>30.21</td>
<td>-42.57</td>
<td>-132.27</td>
</tr>
</tbody>
</table>

This measure not assessed at day 180. **P** value is for the 700 µg group vs observation.
Rescue IVTA/Focal Laser Between Day 90-Day 180

<table>
<thead>
<tr>
<th>Treatment</th>
<th>350 µg (n=57)</th>
<th>700 µg (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

No. of Subjects Receiving Treatment

<table>
<thead>
<tr>
<th>10 or more letters</th>
<th>Day 90</th>
<th>Day 180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>12.3</td>
<td>21.1</td>
</tr>
<tr>
<td>Dexamethasone-DDS 350 µg</td>
<td>22.8</td>
<td>22.8</td>
</tr>
<tr>
<td>Dexamethasone-DDS 700 µg</td>
<td>7.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Efficacy of 700 µg Persists Through Day 180 – Visual Acuity Improvements

DME Sub-group Analysis

- The efficacy and safety of 700 µg dexamethasone DDS that was seen in a mixed population of ME patients was confirmed in the subgroup analysis
- Statistically significant benefit over observation at day 90 for the primary outcome
- 0 patients in the 700 µg-treated group required/received rescue therapy between Day 90 and Day 180
- Clinically significant improvements in visual acuity seen in patients with ME due to diabetic retinopathy Persisted at least through day 180
- Study not powered to detect statistical significance in these subgroups
- Improvements in visual acuity were accompanied by statistically significant improvements in macular thickness and fluorescein leakage

Selected Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>350 µg</th>
<th>700 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased IOP‡</td>
<td>0/57 (0%)</td>
<td>8/55 (15%)*</td>
<td>5/53 (9%)*</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1/57 (2%)‡</td>
<td>1/55 (2%)</td>
<td>0/53 (0%)</td>
</tr>
<tr>
<td>视网膜出血</td>
<td>9/57 (16%)</td>
<td>7/55 (13%)</td>
<td>9/53 (17%)</td>
</tr>
<tr>
<td>视网膜出血</td>
<td>3/57 (5%)</td>
<td>11/55 (20%)*</td>
<td>12/53 (23%)*</td>
</tr>
</tbody>
</table>

‡All patients with elevated IOP were managed with either observation or topical medications, and none required surgery.

*P ≤ 0.05 vs observation; ‡Nonstudy eye.
Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>350 µg</th>
<th>700 µg</th>
<th>P* value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein leakage ≥3 levels improvement</td>
<td>1 (1.1%)</td>
<td>14 (15.6%)</td>
<td>24 (25.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OCT change in retinal thickness</td>
<td>+11 µm</td>
<td>-61 µm</td>
<td>-142 µm</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*700 µg vs observation

Iluvien™ (Alimera)

- Intravitreal cylindrical tube 3.5 mm long, 0.37 mm in diameter
- 180 µg fluocinolone acetonide
- Inserted through a self sealing wound via 25-gauge proprietary injector system

Iluvien Drug Delivery System

- Non-bioreodable cylindrical tube 3.5 mm long, 0.37 mm in diameter
- Injected through a self sealing wound via 25-gauge proprietary injector (straight In, angled entry, no beveling required)
- Two doses compared 0.2µg (Low Dose) and 0.5µg (High Dose) of fluocinolone acetonide (FAc) per day

Phase 3 FAME Study Design

Subjects with DME:
- ≥1 previous laser
- BCVA ≥19 and ≤68 letters (20/50 to 20/400) in study eye
- TD-OCT center point thickness ≥250 µm

Laser Allowed After Week 6*
Retreatment any time after Month 12 (if eligible)**

Primary Readout: N=956

Low Dose (0.2 µg/d)
High Dose (0.5 µg/d)
Sham Control
Randomization 2:2:1

Study Ends

Month: 0 6 12 18 24 30 36

* At investigator discretion
** If BCVA loss ≥5 letters or TD-OCT increase ≥50µm from best reading in previous 12 months

Campocharo P. et al Angiogenesis 2011

Camp et al Angiogenesis 2013
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 185)</th>
<th>0.2 µg/d FAc (n = 375)</th>
<th>0.5 µg/d FAc (n = 393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean</td>
<td>61.9</td>
<td>63.0</td>
<td>62.2</td>
</tr>
<tr>
<td>Males, %</td>
<td>58.4%</td>
<td>57.3%</td>
<td>61.8%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71.4%</td>
<td>70.4%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Black</td>
<td>5.9%</td>
<td>5.9%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Asian</td>
<td>21.6%</td>
<td>22.7%</td>
<td>22.1%</td>
</tr>
<tr>
<td>Other</td>
<td>1.1%</td>
<td>1.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Type 2 diabetes, %</td>
<td>51.9%</td>
<td>90.3%</td>
<td>93.1%</td>
</tr>
<tr>
<td>Diagnosis (y), mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>16.4</td>
<td>17.1</td>
<td>16.1</td>
</tr>
<tr>
<td>DME</td>
<td>3.9</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Phakic, %</td>
<td>59.4%</td>
<td>82.7%</td>
<td>87.4%</td>
</tr>
</tbody>
</table>

≥15-Letter Improvement Over Baseline

Adverse Events

<table>
<thead>
<tr>
<th>Subjects, % (Study Eye)</th>
<th>Control (n = 121)</th>
<th>0.2 µg/d FAc (n = 235)</th>
<th>0.5 µg/d FAc (n = 265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract considered an AE*</td>
<td>50.4</td>
<td>81.7</td>
<td>88.7</td>
</tr>
<tr>
<td>Cataract extraction performed*</td>
<td>27.3</td>
<td>80.0</td>
<td>87.2</td>
</tr>
</tbody>
</table>

IOP-Related Events

<table>
<thead>
<tr>
<th>Subjects, % (Study Eye)</th>
<th>Control (n = 185)</th>
<th>0.2 µg/d FAc (n = 375)</th>
<th>0.5 µg/d FAc (n = 393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP &gt; 30 mm Hg</td>
<td>4.3</td>
<td>18.4</td>
<td>22.9</td>
</tr>
<tr>
<td>Any IOP-lowering med*</td>
<td>14.1</td>
<td>38.4</td>
<td>47.5</td>
</tr>
<tr>
<td>Trabeculoplasty</td>
<td>0.0</td>
<td>1.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Incisional IOP-lowering surgery</td>
<td>0.5</td>
<td>4.8</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Time to Cataract AE*
Comparison of implant sizes

![Comparison of implant sizes](image)

Persistent DME Patients (DME ≥3 Years)

![Persistent DME Patients](image)

≥15-Letter Improvement by lens status

![≥15-Letter Improvement by lens status](image)

Retisert Implant

![Retisert Implant](image)
**Fluocinolone Acetonide Implant**

Baseline 12 months

**Visual Acuity 36M Change from Baseline**

<table>
<thead>
<tr>
<th>Change from Baseline</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>〉3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>18.9%</td>
<td>15.9%</td>
<td>27.6%</td>
<td>14.5%</td>
</tr>
</tbody>
</table>

**I-vation™ Sustained Drug Delivery System**

- Intravitreal triamcinolone acetonide implant made by SurModics

**I-vation™ Sustained Drug Delivery System**

- Novel helical design
  - Implant through a 25 gauge needlestick
  - Maximum surface area for drug delivery
  - Self-anchoring within sclera
  - Easily removable
  - SurModics polymer coating technology
  - Adjustable drug elution rates
  - Compatible with range of molecules
**I-vation™ Sustained Drug Delivery System**

- Implant coated with a mixture of a non-biodegradable polymer coating matrix (Bravo™) and 925 μg of TA
- Ratio of polymer to drug creates different elution rates:
  - Slow-release formulation (1 μg / day)
  - Fast-release formulation (3 μg / day)

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**I-vation Implantation**

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**I-vation Removal**

---

**I-vation Removal**

---

**I-vation Implantation**

---

**I-vation Removal**

---

**I-vation Implantation**
**Poor Prognosis DME**

- Significant central retinal capillary nonperfusion
- Severe cystoid macular edema
- Hard exudates in the FAZ
- Visual acuity 20/200 or less

**Vitrectomy for DME without 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 of ≥ 2 lines (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachi et al.</td>
<td>1996</td>
<td>58</td>
<td>19</td>
<td>98</td>
<td>53</td>
</tr>
<tr>
<td>Ikeda et al.</td>
<td>1999</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Otani et al.</td>
<td>2000</td>
<td>13</td>
<td>31</td>
<td>54*</td>
<td>38</td>
</tr>
<tr>
<td>Yang **</td>
<td>2000</td>
<td>13</td>
<td>100</td>
<td>Not stated</td>
<td>85</td>
</tr>
<tr>
<td>Kadonosono et al.</td>
<td>2000</td>
<td>11</td>
<td>Not stated</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Ruby et al.</td>
<td>2001</td>
<td>26</td>
<td>100</td>
<td>50</td>
<td>54</td>
</tr>
</tbody>
</table>

* By optical coherence tomography
** DME with massive hard exudates
Conclusions

• Intensive control of glycemia, blood pressure is current standard of care
• Lipid control and ACE inhibition may confer additional benefit for diabetic retinopathy
• Current standard of care for DME is laser – better than most realize!
• Anti-VEGF drugs
  • Safety? long-term safety?
  • Longer term efficacy?
• Steroids
  • Short term efficacy; Poor safety?
• Combination therapy...

Thank you...