Pathophysiology of Diabetic Retinopathy

Jennifer I. Lim, MD
Professor of Ophthalmology
Marion H. Schenk Esq., Chair in Ophthalmology
University of Illinois Department of Ophthalmology
Director of the Retina Service

Retina Symposium April 11, 2014
In 2010, 25.6 million people ≥20 years old in the US had diabetes¹
  - 11.3% of the population¹

By 2020, prevalence is expected to rise to 15% of adults in the US (39 million)²

Systemic Factors in Diabetic Retinopathy

- Diabetes Control and Complications Trial (DCCT)
  - Type 1 diabetics (insulin)
- Epidemiology of Diabetes Intervention and Complications Trial (EDIC)
- United Kingdom Prospective Diabetes Study (UKPDS)
  - Type 2 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>

Mechanical Factors in Diabetic Retinopathy?

Macular Edema

- OCT
- No Traction
- Posterior hyaloidal traction
# 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>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al.</td>
<td>1992</td>
<td>10</td>
<td>90</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Van Effenterre et al.</td>
<td>1993</td>
<td>22</td>
<td>64</td>
<td>45</td>
<td>86</td>
</tr>
<tr>
<td>Harbour et al.</td>
<td>1996</td>
<td>7</td>
<td>57</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Pendergast et al.</td>
<td>2000</td>
<td>55</td>
<td>85</td>
<td>82</td>
<td>49</td>
</tr>
<tr>
<td>Gandorfer et al.</td>
<td>2000</td>
<td>12 *</td>
<td>50</td>
<td>50</td>
<td>92</td>
</tr>
</tbody>
</table>

* 2 eyes without posterior hyaloidal traction
Pathophysiology of DR

A&P Changes
- Thickened basement membrane
- Tight Junctions
- Antioxidant capacity of RPE
- Taurine transport of RPE
- Pericyte loss
- Capillary nonperfusion
- Chronic inflammation
- Leukostais

Biochemical Factors
- DAG
- HIF-1α
- AGE & RAGE
- PKC
- PEDF
- Endothelin 1
- VEGF
- Stromal-derived factor-1
- Cytokines
- Occludin
- NOS


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.
CSME

Medical Management

FA

Poor Foveal Capillary Perfusion

Good Foveal Capillary Perfusion
Pathophysiology of DR


DAG=dicacylglycerol; 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.
VEGF Levels Are Increased in the Vitreous of Patients with DME

*P<0.0001

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

The DIRECT Programme Study Group, http://www.direct-results.org/Retinal_photography.html
Increased Vitreous VEGF Levels Correlate with Greater DR Severity

DME Is Partially Caused by the Overexpression of Intraocular VEGF

Hyperglycemia triggers a metabolic response, causing inflammation and microvascular damage. Metabolic response and ischemia from microvascular complications can cause VEGF levels to increase in the eye.

Increased VEGF levels lead to both macular edema and neovascularization complications in the eye.

2. Antonetti et al. JBC. 1999;274:23463
VEGF in Diabetic Retinopathy

- VEGF levels elevated in vitreous of eyes with DME and with diabetic retinopathy

- Clinical Trials:
  - Phase 3: DRCR
  - RESTORE
  - RIDE/RISE
  - Phase 2: RESOLVE
  - READ-2
  - BOLT
  - VISTA/VIVID

Increases Vascular Permeability
Science 1983; 219:983

Angiogenic
Science 1989; 246:1306
Science 1989; 246:1309

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
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg

Month 36
Long-term Open-label Extension with 0.5mg Ranibizumab

Primary Endpoint

* Target enrollment

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)

Patients randomized 1:1:1

IVT Aflibercept 2 mg q4 wks

IVT Aflibercept 2 mg q8 wks*

Laser Photocoagulation

Primary endpoint: Mean change in BCVA

Primary Endpoint: Week 52

Continued treatment through Year 3

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

*After 5 initial monthly doses

Anti-VEGF Therapy Affects Overall Diabetic Retinopathy Progression to PDR by Month 24*

<table>
<thead>
<tr>
<th>AEs related to worsening of DR, n (%)</th>
<th>RIDE</th>
<th>RISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=127)</td>
<td>Ranibizumab</td>
<td>Ranibizumab</td>
</tr>
<tr>
<td>Iris Neovascularization</td>
<td>2 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal Neovascularization</td>
<td>7 (5.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Vitreous Hemorrhage</td>
<td>19 (15.0)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Δ = -7.6 (p=0.0206†)  
Δ = -8.3 (p=0.0069†)  
Δ = -9.4 (p=0.0114†)  
Δ = -13.4 (p=0.0001†)

*A subject was considered to have progressed to proliferative diabetic retinopathy (PDR) by Month 24 if for any of these conditions, neovascularization was not present at baseline and present at any post-baseline visit at or prior to Month 24. †Cochran-Mantel-Haenszel chi-squared test (stratified). The differences in the graph are unadjusted. The last observation carried forward (LOCF) imputation method was used. Vertical bars are 95% confidence interval. ETDRS=Early Treatment Diabetic Retinopathy Study. *Medical Dictionary for Regulatory Activities, Version 13.1 (MedDRA) High Level Term or Preferred Term.
Improvement in Retinopathy Severity Scale at month 24 with Anti-VEGF Rx


The size of the circles is proportional to the percentage of subjects.

3-step progression (worsening): secondary endpoint, 2-step progression (worsening) and improvement: exploratory endpoints
3-step improvement: not prespecified endpoint, no statistical testing performed

*p=0.0073 (Cochran–Mantel–Haenszel chi-squared test [stratified]; LOCF imputation used). For the exploratory endpoints p-values are not shown on the slide.
Based on scoring of fundus photographs at UWFPRC.
Pathophysiology of DME

A&P Changes

- Thickened basement membrane
- Tight Junctions
- Antioxidant capacity of RPE
- Taurine transport of RPE
- Chronic inflammation
- Leukostais
- Pericyte loss
- Capillary nonperfusion
- Hypoxia

Biochemical Factors

- NOS
- Occludin
- Cytokines
- Aldose reductase
- DAG
- AGE & RAGE
- HIF-1α
- PKC
- PEDF
- Endothelin 1
- ICAM-1
- VEGF
- Stromal-derived factor-1


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.
Mechanism of Action of Steroids

- Steroids affect the synthesis of > 600 proteins
- Angiostasis
  - ↓ VEGF synthesis but unbound VEGF levels are 100x those with anti-VEGF drugs
- Restoration of blood retinal barrier
- Vasoconstrictor
  - improved Starling’s law: Net Driving Pressure = (Pc – Pi) – (Qc – Qi)
- Anti-inflammatory
  - ↓ synthesis of other growth factors and chemokines
  - ↓ VEGF feedback loop

JI Lim, MD
Routes of Steroid Administration

- Periocular injections
- Intraocular injections
  - Triamcinolone acetonide (Triesence)
  - Triamcinolone acetonide (Trivaris)
- Intraocular implants
  - Biodegradable
    - Dexamethasone implant (Ozurdex)
  - Non-erodible
    - Fluocinolone acetonide implant (Retisert)
    - Fluocinolone acetonide implant (Iluvien)
Pathophysiology of Diabetic Retinopathy

- **Systemic Factors**
  - BP, HgA1C, Renal Status, Lipids
- **Mechanical Factors**
  - Vitreous traction
- **VEGF mediated Pathways**
  - Anti-VEGF
- **Non-VEGF Mediated Pathways**
  - Steroids
  - Novel therapies
Thank you!