Diabetic Macular Edema: Which Drug? Why?

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Disclosure

- Consultant: Alimera Science, Genentech, Notal Vision
- Research Support: Notal Vision, Optos
- Diabetic Retinopathy Clinical Research Network
  - Served as a vice-chair and currently an investigator
  - Opinions are mine and not on behalf of the network
- Off-label use of bevacizumab and triamcinolone will be mentioned
Diabetic Retinopathy Clinical Research Network (DRCR.net)

Dedicated to facilitating multicenter clinical research of diabetic retinopathy, age-related macular degeneration, hereditary retinal degenerations, and other retinal diseases

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY018817
## DRCR.net Status
**(as of 3/15/18)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Active</th>
<th>Total</th>
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<tbody>
<tr>
<td>Sites (Community &amp; Academic Centers)</td>
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<td>347</td>
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<td>Community Sites</td>
<td>105 (70%)</td>
<td>214 (62%)</td>
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<td>Investigators</td>
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<td>1279</td>
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<td>Other Personnel</td>
<td>1169</td>
<td>4502</td>
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<tr>
<td>Provinces in Canada</td>
<td>5</td>
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</table>
DRCR.net Protocols
Enrolling or in Follow-up


- Tx - Protocol T Extension
- V - Very Good Vision
- W - PDR/DME Prevention
- AA - Ultra-widefield Imaging
- AB - Vx for VH from PDR
- AC - Initial A vs B
- AD - PROMINENT
- Genetics

Recruitment
Followup
Mean Change in Visual Acuity At Follow Up Visits

- Ranibizumab+Deferred Laser (p<0.001)
- Ranibizumab+Prompt Laser (p=0.03)
- Triamcinolone+Prompt Laser (p=0.35)
- Sham+Prompt Laser

N = 626 (52 weeks)
N = 600 (68 weeks)
N = 600 (84 weeks)
N = 628 (104 weeks)
Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment: 5-Year Randomized Trial Results

Michael J. Elman, MD,1 Allison Ayala, MS,2 Neil M. Bressler, MD,3 David Browning, MD,4 Christina J. Flaxel, MD,5 Adam R. Glassman, MS,2 Lee M. Jampol, MD,6 Thomas W. Stone, MD,7 for the Diabetic Retinopathy Clinical Research Network

Ophthalmology 2015;122:375-381
Mean Change in Visual Acuity at Follow-up Visits

- +9.8
- +7.2
### Ranibizumab, Afiblercept and Bevacizumab

<table>
<thead>
<tr>
<th>VEGF inhibitor</th>
<th>Structure</th>
<th>Molecular weight</th>
<th>Molecular characteristics</th>
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<tbody>
<tr>
<td>Ranibizumab</td>
<td><img src="image" alt="Fab" /></td>
<td>48 kDa</td>
<td>Fab fragment (no Fc portion*)</td>
</tr>
<tr>
<td>Afiblercept</td>
<td><img src="image" alt="Fc portion" /></td>
<td>115 kDa</td>
<td>Fusion protein (Fc-containing)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td><img src="image" alt="Fc portion" /></td>
<td>149 kDa</td>
<td>Full length monoclonal antibody (Fc-containing)</td>
</tr>
</tbody>
</table>

* Responsible for recycling via the FcRn receptor

**Fab**, antigen binding fragment; **Fc**, fragment crystallizable region; **FcRn**, the neonatal Fc receptor for IgG; **kDa**, kilodalton.
On-label vs. Off-label
- Aflibercept and ranibizumab: FDA approved for DME
- Bevacizumab: not FDA approved for intraocular use

Cost: Medicare allowable charges
- Aflibercept (2.0 mg): $1961
- Ranibizumab (0.3 mg): $1189
- Bevacizumab (repackaged 1.25mg): $67

Ease of use
- Pre-filled syringes: Bevacizumab, Ranibizumab (0.3 mg, 0.5mg)
Which drug for DME?
Protocol T: Comparative Effectiveness Study of Aflibercept, Bevacizumab, or Ranibizumab for Center Involved DME with Vision Loss

Change in Visual Acuity at 1 Yr (primary outcome) and 2 Yrs

Aflibercept vs. Bevacizumab
Aflibercept vs. Ranibizumab
Bevacizumab vs. Ranibizumab

Aflibercept 2 mg; Bevacizumab 1.25 mg; Ranibizumab 0.3 mg
N=660, VA 20/32 to 20/320
Mean Change in Visual Acuity Over 2 Years: **Full Cohort**

104-Week Treatment Group Comparison

- **Aflibercept** vs. **Bevacizumab** $P = 0.02$
- **Aflibercept** vs. **Ranibizumab** $P = 0.47$
- **Ranibizumab** vs. **Bevacizumab** $P = 0.11$

- **Aflibercept**
  - Weeks: 0, 2, 4, 6, 8, 10, 12
  - Change: +13.3

- **Bevacizumab**
  - Weeks: 0, 2, 4, 6, 8, 10, 12
  - Change: +11.2

- **Ranibizumab**
  - Weeks: 0, 2, 4, 6, 8, 10, 12
  - Change: +9.7

- **Aflibercept**
  - Weeks: 0, 2, 4, 6, 8, 10, 12
  - Change: +12.8

- **Bevacizumab**
  - Weeks: 0, 2, 4, 6, 8, 10, 12
  - Change: +12.3

- **Ranibizumab**
  - Weeks: 0, 2, 4, 6, 8, 10, 12
  - Change: +10.0
Mean Change in Visual Acuity Over 2 Years

Baseline Visual Acuity 20/32 to 20/40

~50% of Cohort

104-Week Treatment Group Comparison

Aflibercept vs. Bevacizumab $P = 0.51$
Aflibercept vs. Ranibizumab $P = 0.51$
Ranibizumab vs. Bevacizumab $P = 0.31$
### Mean Change in Visual Acuity Over 2 Years

**Baseline Visual Acuity 20/50 or Worse**

#### 104-Week Treatment Group Comparison*:

- **Aflibercept vs. Bevacizumab** $P = 0.02$
- **Aflibercept vs. Ranibizumab** $P = 0.18$
- **Ranibizumab vs. Bevacizumab** $P = 0.18$

---

~50% of Cohort

Mean Change in Visual Acuity Letter Score:

- **Aflibercept**: +18.9
- **Bevacizumab**: +14.2
- **Ranibizumab**: +11.8

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**Mean Change in Visual Acuity Over 2 Years**

- **Baseline Visual Acuity**: 20/50 or Worse
- **Cohort Percentage**: ~50%
Mean Change in Visual Acuity Over 2 Years
By Baseline Visual Acuity Subgroup

Mean Change in Visual Acuity Letter Score

Weeks

20/32 to 20/40

20/50 or Worse

Mean Change in Visual Acuity Over 2 Years
By Baseline Visual Acuity Subgroup

Mean Change in Visual Acuity Letter Score

Weeks

20/32 to 20/40

20/50 or Worse

+8.6

+7.8

+6.8

+18.3

+16.1

+13.3
Mean Change in OCT CST Over 2 Years

Full Cohort

2-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P<0.001$
- Aflibercept vs. Ranibizumab $P = 0.08$
- Ranibizumab vs. Bevacizumab $P = 0.001$

Mean Improvement in OCT CSF Thickness from Baseline (µm)

Weeks

Aflibercept Bevacizumab Ranibizumab

-169 -147 -101

-171 -149 -126
Mean Change in OCT CST Over 2 Years

Baseline Visual Acuity 20/32 to 20/40

2-Year Treatment Group Comparison:
- Afiblercept vs. Bevacizumab $P<0.001$
- Afiblercept vs. Ranibizumab $P=0.26$
- Ranibizumab vs. Bevacizumab $P<0.001$
Mean Improvement in OCT CSF Thickness from Baseline (µm)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Aflibercept</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-210</td>
<td>-176</td>
<td>-135</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean Change in OCT CST Over 2 Years

Baseline Visual Acuity 20/50 or Worse

2-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab \(P = 0.01\)
- Aflibercept vs. Ranibizumab \(P = 0.18\)
- Ranibizumab vs. Bevacizumab \(P = 0.18\)
Which Anti-VEGF for DME?

Judy’s Algorithm

20/32-20/40

- OCT CST < 500 um: Aflibercept, Bevacizumab, Ranibizumab
- OCT CST >500 um: Aflibercept

20/50 or Worse

- OCT CST < 500 um: Aflibercept, Ranibizumab
- OCT CST >500 um: Aflibercept, Ranibizumab
After at least 6 monthly injections of anti-VEGF for DME, some eyes still have unresolved DME and reduced VA.
What About Steroids?
Mean Change in Visual Acuity At Follow Up Visits

- Ranibizumab+Deferred Laser
  (p<0.001)
- Ranibizumab+Prompt Laser
  (p=0.03)
- Triamcinolone+Prompt Laser
  (p=0.35)
- Sham+Prompt Laser

N = 626 (52 weeks)
N = 600 (68 weeks)
N = 600 (84 weeks)
N = 628 (104 weeks)
Mean Change in Visual Acuity at Follow-up Visits among Eyes that were Pseudophakic at Baseline*
Corticosteroids have been considered as an alternative treatment for DME
- Decrease inflammation
- Reduce breakdown of the blood-retinal barrier
- Have anti-angiogenic properties
Protocol U

Short-Term Evaluation of Combination

Dexamethasone + Ranibizumab vs. Ranibizumab Alone

in Eyes with persistent DME and VA impairment despite previous anti-VEGF treatment
Persistent Edema

- VA letter score $\leq 78$ and $\geq 24$ (20/32 to 20/320)
- Central-involved DME on clinical exam and OCT
- Despite at least 3 anti-VEGF tx prior to enrollment (in 20 wks)

Run-in Phase*

- 3 injections of study ranibizumab, given every 4 weeks

* 9 additional subjects were either lost to follow-up (2), died (1), requested to withdraw (1), were withdrawn by the site (2), or were believed to no longer need Injections by the investigator (3)
†Dropped = 2 eyes
Study Overview

Enrolled (236 eyes)

Run-In (3 months)

Randomization (6 months)

Eligible for Randomization?

Week 0

RAN

Week 0

RAN

65 eyes

DEX

RAN

DEX

RAN

RAN

RAN

Week 0

RAN

64 eyes

SHAM

SHAM

4

8

12

20

24

4

8

12

16

20

24

12

8

4
Visual Acuity (VA)
VA Mean Change

63 (20/63)
Mean Randomization Letter Score (~Snellen Equivalent)

N = 64

Ranibizumab

VA Mean Change (letter score)

Run-In
Randomization

N = 64
Adjusted Mean Difference: -0.5 letters
95% Confidence Interval: (-3.6, +2.5), P = 0.73
VA Mean Change: Baseline Lens Status

**Pseudophakic**

- Ranibizumab: +5.1
- Combination: +2.0

**Phakic**

- Ranibizumab: +4.1
- Combination: +1.1

*P-value for interaction = 0.08*
Change in VA (Letter Score) from Randomization at 24 Weeks

**Combination N = 63**

- Mean SD: 2.7 (9.8)

**Ranibizumab N = 64**

- Mean SD: 3.0 (7.1)
## Binary VA Outcomes*

<table>
<thead>
<tr>
<th></th>
<th>Combination Group (N = 63)</th>
<th>Ranibizumab Group (N = 64)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VA at 24 Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/20 or better</td>
<td>6%</td>
<td>5%</td>
<td>0.70</td>
</tr>
<tr>
<td>20/40 or better</td>
<td>51%</td>
<td>52%</td>
<td>0.80</td>
</tr>
<tr>
<td>20/200 or worse</td>
<td>6%</td>
<td>5%</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Changes at 24 Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 letters improvement</td>
<td>11%</td>
<td>2%</td>
<td>0.03</td>
</tr>
<tr>
<td>≥10 letters improvement</td>
<td>22%</td>
<td>14%</td>
<td>0.34</td>
</tr>
<tr>
<td>≥15 letters worsening</td>
<td>6%</td>
<td>5%</td>
<td>0.62</td>
</tr>
<tr>
<td>≥10 letters worsening</td>
<td>13%</td>
<td>6%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Pre-planned secondary outcomes
Central Subfield Thickness (CST)
**OCT CST Mean Change**

![Graph showing OCT CST Mean Change over visit weeks.](image)

- **Visit Week:** 0, 4, 8, 12, 16, 20, 24

- **Ranibizumab**
  - N = 64

*Outlying values were truncated to 3 SD from the mean. One image was non-gradable due to low resolution.*
OCT CST Mean Change

Adjusted Mean Difference: -52 µm
95% Confidence Interval: (-82, -22), \( P < 0.001 \)

-62
-110

*Outlying values were truncated to 3 SD from the mean. One image was nongradable due to low resolution.*
OCT CST Mean Change: AUC

Adjusted Mean Difference (AUC): -55
95% Confidence Interval: (-78, -31), $P < 0.001$

*Outlying values were truncated to 3 SD from the mean. One image was non-gradable due to low resolution.*
## Ocular Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Combination Group (N = 65)</th>
<th>Ranibizumab Group (N = 64)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes with at least one ocular adverse event</td>
<td>63%</td>
<td>31%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased IOP at any visit</td>
<td>29%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased ≥10 mmHg from randomization</td>
<td>23%</td>
<td>0</td>
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</tr>
<tr>
<td>IOP ≥30 mmHg</td>
<td>15%</td>
<td>0</td>
<td></td>
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<tr>
<td>Received ocular anti-hypertensives</td>
<td>20%</td>
<td>0</td>
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Summary of Findings

- Mean VA improvement by 6 months was no better in the dexamethasone + ranibizumab group than in the sham + ranibizumab group.
- On average, there was a greater reduction in retinal thickness in the dexamethasone + ranibizumab group.
- Study was not sufficiently sized to determine whether treatment response might differ by lens status.
Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema

A DRCR Network Phase 2 Randomized Clinical Trial

Raj K. Maturi, MD; Adam R. Glassman, MS; Danni Liu, MSPH; Roy W. Beck, MD; Abdhish R. Bhavsar, MD; Neil M. Bressler, MD; Lee M. Jampol, MD; Michele Melia, ScM; Omar S. Punjabi, MD; Hani Salehi-Had, MD; Jennifer K. Sun, MD; for the Diabetic Retinopathy Clinical Research Network
What about fluocinolone acetonide implant?
<table>
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<th>PALADIN</th>
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<tbody>
<tr>
<td>Type of Study</td>
<td>Retrospective Chart Review</td>
<td>Phase IV Prospective</td>
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<tr>
<td>DME</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Study Complete</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Study Duration</td>
<td>Final: Mean 403 days</td>
<td>Target: 3 years</td>
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<tr>
<td># Study Subjects/eyes</td>
<td>130 (160 eyes)</td>
<td>51 (60 eyes) 12 month completer</td>
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<td></td>
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<td>Target: 153pts 201 eyes</td>
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<tr>
<td># Study Sites</td>
<td>4</td>
<td>41</td>
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Visual Acuity: USER (N=160)

Before

1 treatment every 2.9 months

After

1 treatment every 14.3 months

P<0.001

* Snellen equivalent
VA Outcomes Based on Baseline VA: USER

- Eyes with worse baseline VA require more frequent tx

P values for difference in frequency of treatments pre- and post-ILUVIEN

1 Treatment every 2.3 mos
1 Treatment every 3.2 mos
1 Treatment every 2.9 mos
1 Treatment every 22 mos
1 Treatment every 15.2 mos
1 Treatment every 7.0 mos
1 Treatment every 6.7 mos

# Letters Visual Acuity

- Baseline ILUVIEN
- 9 Month
- 12 Month
- 15 Month

- 36M Pre
- 12M Pre

- worse than 20/200 (N=12)
- 20/200 to < 20/100 (N=20)
- 20/100 to < 20/40 (N=61)
- 20/40 & Better (N=67)
Consider Steroids

- Non-responders to anti-VEGF
- Recent stroke
- Pregnancy
- Breast feeding
- Pseudophakic
- Non-steroid responder
- Need for longer treatment interval
Thank you!