Targeting Inflammation in Diabetic Macular Edema: From Basic Science to Clinical Trials to Clinical Practice

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Financial Disclosure

- CLINICAL RESEARCH
  - Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, ThromboGenics

- CONSULTANT
  - Aerpio, Alcon, Alimera, Allegro, Allergan, Ampio, Catalyst, Cell Care, Dose, Eyedaptic, Genentech, Glaukos, jCyte, Novartis, Ophthotech, Regeneron, Revana, SciFluor
INFLAMMATION, A KEY COMPONENT OF DME

- Hyperglycemia - Oxidative stress
- Local Inflammation
  - Activation of microglial cells
  - Dysfunction of Mueller cells
- Inflammatory mediators - Cytokines and Chemokines
- Chronic Inflammation
- Neurodegeneration
- Retinal capillary damage
- Disruption of blood-retinal barrier
- Vascular Leakage - Edema
- Diabetic Macular Edema

## Aqueous Humor Inflammatory Cytokines Are Elevated in Diabetes vs Controls

<table>
<thead>
<tr>
<th>Cytokine,(^a) median (range)</th>
<th>Control (n = 102)</th>
<th>Diabetes (n = 136)</th>
<th>(P) value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1(^\beta)</td>
<td>1.0 (0-38)</td>
<td>8.0 (0-104)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IL-6</td>
<td>13.5 (0-76)</td>
<td>27.5 (0-365)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IL-8</td>
<td>8.0 (0-76)</td>
<td>17.0 (0-198)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IL-10</td>
<td>6.0 (0-55)</td>
<td>5.0 (0-25)</td>
<td>.002</td>
</tr>
<tr>
<td>IL-12</td>
<td>10.0 (0-105)</td>
<td>8.0 (0-46)</td>
<td>.013</td>
</tr>
<tr>
<td>IP-10</td>
<td>1.0 (0-6)</td>
<td>4.0 (0-76)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MCP-1</td>
<td>70.5 (7-811)</td>
<td>385.5 (58-2568)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>VEGF</td>
<td>66.0 (11-676)</td>
<td>982.0 (26-1888)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

\(^a\) No significant difference was seen in IL-1\(\alpha\), IL-2, IL-4, IL-5, IL-7, IL-9, IL-13, IL-15, b-FGF, Eotaxin, GM-CSF, MIP-1\(\beta\), PDGF-BB, or RANTES. 

\(^b\) Mann-Whitney U test.

### Aqueous humor cytokine levels according to severity of DR

<table>
<thead>
<tr>
<th>ETDRS retinopathy severity</th>
<th>N</th>
<th>VEGF</th>
<th>IL-1β</th>
<th>IL-6</th>
<th>IL-8</th>
<th>MCP-1</th>
<th>IP-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>28</td>
<td>967.0</td>
<td>10.0</td>
<td>32.1</td>
<td>22.8</td>
<td>252.2</td>
<td>2.1</td>
</tr>
<tr>
<td>20</td>
<td>23</td>
<td>952.8</td>
<td>11.0</td>
<td>33.5</td>
<td>20.6</td>
<td>303.6</td>
<td>2.5</td>
</tr>
<tr>
<td>35</td>
<td>26</td>
<td>956.4</td>
<td>9.2</td>
<td>33.1</td>
<td>22.7</td>
<td>339.5</td>
<td>5.6</td>
</tr>
<tr>
<td>43</td>
<td>18</td>
<td>1084.7</td>
<td>10.7</td>
<td>33.2</td>
<td>24.4</td>
<td>468.8</td>
<td>5.5</td>
</tr>
<tr>
<td>47</td>
<td>13</td>
<td>1172.6</td>
<td>18.8</td>
<td>56.6</td>
<td>29.2</td>
<td>645.2</td>
<td>9.5</td>
</tr>
<tr>
<td>53</td>
<td>8</td>
<td>1177.3</td>
<td>22.7</td>
<td>106.7</td>
<td>49.4</td>
<td>921.2</td>
<td>22.3</td>
</tr>
<tr>
<td>65</td>
<td>7</td>
<td>1142.7</td>
<td>23.7</td>
<td>116.8</td>
<td>51.0</td>
<td>1215.1</td>
<td>31.3</td>
</tr>
<tr>
<td>75</td>
<td>8</td>
<td>1051.4</td>
<td>27.6</td>
<td>147.0</td>
<td>75.7</td>
<td>1286.6</td>
<td>34.3</td>
</tr>
<tr>
<td>81</td>
<td>5</td>
<td>1165.4</td>
<td>45.8</td>
<td>188.6</td>
<td>74.4</td>
<td>1630.8</td>
<td>29.2</td>
</tr>
</tbody>
</table>

| P-value                    |     | .733  | .003  | <.001 | .001  | <.001 | <.001 |

IL, interleukin; IP, interferon-inducible protein; MCP, monocyte chemotactic protein; VEGF, vascular endothelial growth factor; ETDRS, early treatment of diabetic retinopathy score

Dong, Molecular Vision 2013
# Steroids Address the Multifactorial Nature of DME

<table>
<thead>
<tr>
<th>Cytokine Conc., pg/mL</th>
<th>IVTA (n = 11)</th>
<th>Bevacizumab (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preinjection</td>
<td>Postinjection</td>
</tr>
<tr>
<td>IL-6</td>
<td>29.9</td>
<td>13.8</td>
</tr>
<tr>
<td>IL-8</td>
<td>28.2</td>
<td>25.3</td>
</tr>
<tr>
<td>IP-10</td>
<td>366</td>
<td>249</td>
</tr>
<tr>
<td>MCP-1</td>
<td>3850</td>
<td>1090</td>
</tr>
<tr>
<td>PDGF-AA</td>
<td>68.7</td>
<td>37.1</td>
</tr>
<tr>
<td>VEGF</td>
<td>55.0</td>
<td>10.5</td>
</tr>
</tbody>
</table>

- Bilateral injection of patients with DME (1 eye IVTA, 1 eye bevacizumab)

*Wilcoxon signed rank test.

IL, interleukin; IP, interferon-inducible protein; IVBe, intravitreal bevacizumab; IVTA, intravitreal triamcinolone acetonide; MCP, monocyte chemotactic protein; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

VEGF & NON-VEGF MEDIATORS IN DME

- **Patients unresponsive to anti-VEGF**
  - Low level of VEGF but high levels of non-VEGF mediators

- **Patients responsive to anti-VEGF**
  - High level of VEGF but low levels of non-VEGF mediators

**Steroids Are Effective in Treating Both Types of Patients**

Phipps and Feener, Kidney Int, 2008  
Kita, Aiello, Feener, Unpublished Information
DRCR Protocol I Sub-analysis

- Sub-analysis to determine if factors may predict anti-VEGF treatment success or failure
- Study eyes were differentiated into 1 of 4 categories based on whether they had at least a 20% reduction from baseline CSF thickness at the 16-week visit

<table>
<thead>
<tr>
<th>CATEGORIZATION OF OCT THICKNESS IMPROVEMENT OF AT LEAST 20% (1-STEP REDUCTION OF LOG) FROM BASELINE (N=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early and Consistent</td>
</tr>
<tr>
<td>Improved at the 16-week study visit and was sustained at the 32-week and 1-year study visits</td>
</tr>
<tr>
<td>n=143 (49.7%)</td>
</tr>
</tbody>
</table>

DRCR.net Protocol I Study
Population (Non-Protocol Post Hoc Analysis)

<table>
<thead>
<tr>
<th></th>
<th>RAN + Deferred or Prompt Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size at baseline</td>
<td>375</td>
</tr>
<tr>
<td>BCVA observed at 12 weeks</td>
<td>340</td>
</tr>
<tr>
<td>CRT observed at 12 weeks</td>
<td>335</td>
</tr>
</tbody>
</table>

Stratification into 3 cohorts at 12w

- < 5 Letters Improvement: 39.7%
- 5-9 Letters Improvement: 23.2%
- ≥ 10 Letters Improvement: 37.1%

BCVA = Best Corrected Visual Acuity. CRT = Central Retinal Thickness
**Eyes with <5 Letter Gain after 3 Injections Showed Limited Additional Improvement for the Study Duration (3 Years)**

- **<5 letters at 12w (N=135)**
- **5-9 letters at 12w (N=79)**
- **≥10 letters at 12w (N=126)**

**Graph Details:**
- BCVA Change from Baseline
- Weeks range from 0 to 156
- p<0.001
Early Analysis of % Eyes with Poor Initial Response Subsequently Responding

Eyes With Limited (<5-Letter) Gains at Week 12 that Gained \( \geq 10 \) or \( \geq 15 \) Letters From Baseline Through Year 3

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DRCR Protocol I
≥15 Letter Improvement in Visual Acuity at Follow-up Visits

DRCR Protocol I Mean Change in Visual Acuity at Follow-up Visits Among Eyes That Were Pseudophakic at Baseline*

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

FAc Steroid Implant: Percentage of Patients With 15-Letter Improvement Over Baseline

Treatment Effect Seen by Duration of DME at Baseline (Pooled data)

Percentage of patients with ≥15-letter response above and below median DME duration (1.73 years)

DME < 1.73 years

- Sham control (n = 81)
- 0.2 µg/d FAc (n = 192)

Percentage of patients with DME < 1.73 years above and below median DME duration (1.73 years):

- 28.4%
- 25.0%

NS at month 36

DME > 1.73 years

- Sham control (n = 103)
- 0.2 µg/d FAc (n = 183)

Percentage of patients with DME > 1.73 years above and below median DME duration (1.73 years):

- 32.8%
- 11.7%

P < .001 at month 36

DME, diabetic macular edema; FAc, fluocinolone acetonide; NS, not significant.

Ranibizumab in DME: RISE and RIDE Data

RESTORE Study: Mean change in BCVA from baseline over time

- In patients treated with ranibizumab in the core phase, mean BCVA gain at Month 12 was maintained from Month 12 to Month 36
- In patients treated with laser alone in the core phase, mean BCVA progressively improved from Month 12 to Month 36 with ranibizumab treatment

Categorized BCVA change from Day 1 at Month 36

- In patients treated with ranibizumab in the core phase, similar proportion of patients gained ≥ 10 and ≥ 15 letters, and this improvement was maintained from Month 12 through Month 36.
- In patients treated with laser alone in the core phase, a numerically greater proportion of patients lost ≥ 10 and ≥ 15 letters at Month 36.

Ranibizumab in a real-world clinical setting: 2014 interim analysis of the 5-year observational multicenter LUMINOUS study *Eric H. Souied et al. ARVO-2015*

<table>
<thead>
<tr>
<th>Year 1*</th>
<th>Year 2++</th>
</tr>
</thead>
<tbody>
<tr>
<td>nAMD</td>
<td>DME</td>
</tr>
<tr>
<td>Treatment Naive* (N=1628, n=706)</td>
<td>Prior Treated (RBZ) (N=7454, n=3559)</td>
</tr>
<tr>
<td>Mean VA change (ETDRS letters)</td>
<td>+4.4</td>
</tr>
<tr>
<td>Mean number of injections</td>
<td>4.7</td>
</tr>
<tr>
<td>Mean number of visits</td>
<td>7.5</td>
</tr>
</tbody>
</table>

*Observed data set; Primary treated eye; n= number of patients with evaluable data at both baseline and month 12/24.
The table does not present the time course of the absolute VA value.
*Cumulative data for Year 1 and Year 2.
#The observed visual acuity values are based on n=706 but the number of injections are based on N=1828.
**The observed visual acuity values are based on n=240 but the number of injections are based on N=254.
nAMD, neovascular age-related macular degeneration; DME, diabetic macular edema; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; RBZ, ranibizumab.
Protocol T 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 $P = 0.11$

* $P$-values adjusted for baseline visual acuity and multiple comparisons

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

Dexamethasone Implant DME

Phase 3 MEAD Studies Design

To evaluate the safety and efficacy of 700µg and 350µg dexamethasone long acting implant compared to a Sham (needleless) injection

DME, one eye per patient
(eye with shortest duration of DME selected)

Randomization (1:1:1)
N=1048

DEX 700 µg
N=347

DEX 350 µg
N=343

Sham
N=350

Evaluated for retreatment every 3 months after Month 6 visit
Retreatment was allowed every 6 months
(if central retinal thickness > 175 µm or any evidence of residual retinal edema)

Primary Endpoint at 3 years up to 7 treatments allowed

Boyer DS et al. Ophthalmology 2014 Jun 4
Dexamethasone Implant DME BCVA improvement ≥15 letters (ITT)

Patients with improved BCVA (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients with Improved BCVA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEX 700 (n=351)</td>
<td>22.2*</td>
</tr>
<tr>
<td>DEX 350 (n=347)</td>
<td>18.4*</td>
</tr>
<tr>
<td>Sham (n=350)</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*P<0.05, statistically significant versus sham at the final visit.

ITT, intent-to-treat.

Boyer DS et al. Ophthalmology 2014 Jun 4
Dex Implant in Patients with Naïve or Refractory Diffuse DME

- 76 patients with diffuse DME (40 refractory and 36 naïve)
- Average gain in VA from baseline at month 6
  - Naïve: 12 letters, median re-injection time 5 months
  - Refractory: 8 letters, median re-injection time 4 months

Real-life Studies: Efficacy of Dex Implant
2-3 Injections/6-9 Letters Gained over 12 months

Udaondo¹
Escobar²
Guigou⁴
Medeiros*³

Mean BCVA
0 2 4 6 8 10 12
Mean number of injections
0 2 4 6 8 10 12

2–3 INJECTIONS
6–9 LETTER GAINS

*Data extrapolated from 6 months.
Mean time to re-injection: 5.3 months
Disclaimer: not comparable head-to-head studies; different patient types, study designs and study assessments

2. Fernández Bonet M et al. Poster presented at COPHy 2014 Lisbon, Portugal;
Effect of DEX on ME During Cataract Surgery

Vision improvement observed pre-cataract AE and post-cataract surgery was similar with that observed in the pseudophakic group

*P<0.05, statistically significant versus sham

Boyer DS et al. Ophthalmology 2014 Jun 4
IOP Increase at scheduled visits after study treatment

% of pts with an increase in IOP of >10 mmHg

Maturi, Retina 2016
Dex Implant Shows Improved Safety vs. IVTA

No statistically significant differences in visual outcomes

Number of injections through two years

Bevacizumab = 13.9
Ozurdex = 5

Lipid exudates cleared more readily with Dex Implant

*Ophthalmology* Jan-2016
24-month data: Mean CMT by treatment type

- Although a significantly greater reduction in CMT in the dexamethasone implant group compared to the bevacizumab group was observed at 12 months, no significant difference was found at 24 months.

Meta analysis of Real life studies Dex Implant vs Anti-VEGF

3,859 patients treated for recalcitrant DME with $\geq 6$ prior treatments of intravitreal anti-VEGF: Favors Dex Implant

Adapted from Khan, Ophthalmic Surg Lasers Imaging Retina 2017
DRCRnet Protocol U Study Overview

Enrollment

Run-In (3 months)

Randomization (6 months)

 Eligible for Randomization

Week 0

RA

DEX

RA

RA

RA

RA

RA

RA

RA

SHAM

Week 0

4

8

12

Week 0

4

8

1

1

2

2

2

2

4

4

1

6

4

8

1

2

6

2

4
DRCRnet Protocol U VA Mean Change

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

Pseudophakic

VA Mean Change (Letter Score)

Visit Week

Ranibizumab

Combination

N = 26
N = 32

N = 25
N = 32

+5.1

+2.0

Phakic

N = 39
N = 32

N = 38
N = 32

+4.1

+1.

* P-value for interaction = 0.08
DRCRnet Protocol U
OCT CST Mean Change

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

*Outlying values were truncated to 3 SD from the mean. One image was nongradable due to low resolution.
Time to First PDR Event: RIDE/RISE

- Sham (n = 257)
- Ranibizumab 0.3 mg (n = 250)
- Ranibizumab 0.5 mg (n = 252)

Patients, %

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

Month of First Progression

≈ 34%
≈ 11%
≈ 11%

PDR, proliferative diabetic retinopathy.

3 patients had their final visit after month 36.

$P$ value for 0.2 and 0.5 $\mu$g/day FAc vs sham control based on log-rank test.

FAc, fluocinolone acetonide; PDR, proliferative diabetic retinopathy.
DME Patients Require High Utilization of Healthcare Resources

2007-2011 Mean Annual Healthcare Utilization*

DME vs non-DME

<table>
<thead>
<tr>
<th>Visits/Visit Days/Medications</th>
<th>DME diabetics (1y FU)</th>
<th>non-DME diabetics (1y FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Healthcare Visit Days</td>
<td>25.5^a</td>
<td>24.7^a</td>
</tr>
<tr>
<td>Outpatient Visit Days</td>
<td>14.9</td>
<td>14.4</td>
</tr>
<tr>
<td>Inpatient Visit Days</td>
<td>9.1</td>
<td>6.9</td>
</tr>
<tr>
<td>ER Visits</td>
<td>2.1^a</td>
<td>1.7</td>
</tr>
<tr>
<td>Eyecare-related Visit Days</td>
<td>4.4^a</td>
<td>1.4</td>
</tr>
<tr>
<td>Unique Outpatient Medications</td>
<td>12.1^a</td>
<td>9.0</td>
</tr>
</tbody>
</table>

^aP < .001

DME patients had, on average, 25.5 total annual healthcare visit days, 4.4 of which are eye care related*

*In utilizing patients.

This retrospective study focused on approximately 147,000 insured, working-age adults in the United States. Enrollment and healthcare claims data were drawn from the Truven Health MarketScan® Commercial Claims and Encounters Database from 2007 to 2011, which includes over 100 million individuals.

Systemic Safety and Anti-VEGF Injections

### Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Injection Treatment by Study</th>
<th>Mean Age, y</th>
<th>Completion Rate, No. (%)</th>
<th>Exclusion Criteria for Recent Stroke or MI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISE</strong>&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n = 127)</td>
<td>61.8</td>
<td>103 (81.1)</td>
<td>3 mo</td>
</tr>
<tr>
<td>Ranibizumab, 0.3 mg (n = 125)</td>
<td>61.7</td>
<td>105 (84.0)</td>
<td></td>
</tr>
<tr>
<td>Ranibizumab, 0.5 mg (n = 125)</td>
<td>62.8</td>
<td>106 (84.8)</td>
<td></td>
</tr>
<tr>
<td><strong>RIDE</strong>&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n = 130)</td>
<td>63.5</td>
<td>108 (83.1)</td>
<td>3 mo</td>
</tr>
<tr>
<td>Ranibizumab, 0.3 mg (n = 125)</td>
<td>62.7</td>
<td>105 (84.0)</td>
<td></td>
</tr>
<tr>
<td>Ranibizumab, 0.5 mg (n = 125)</td>
<td>61.8</td>
<td>110 (86.6)</td>
<td></td>
</tr>
<tr>
<td><strong>VISTA</strong>&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n = 156)</td>
<td>61.7</td>
<td>133 (85.3)</td>
<td>6 mo</td>
</tr>
<tr>
<td>Afibercept, 2.0 mg (n = 156)</td>
<td>62.0</td>
<td>125 (80.1)</td>
<td></td>
</tr>
<tr>
<td><strong>VIVID</strong>&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n = 135)</td>
<td>63.9</td>
<td>105 (77.8)</td>
<td>6 mo</td>
</tr>
<tr>
<td>Afibercept, 2.0 mg (n = 136)</td>
<td>62.6</td>
<td>115 (84.6)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Summary of the Main Findings<sup>a</sup>

| Outcome                  | Anticipated Absolute Risk per 1000 Study Population, OR (95% CI)<sup>b</sup> | Relative Effect (95% CI) | No. of Participants/RCTs | Quality of Evidence<sup>c</sup> | Overall Heterogeneity, $I^2$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>13 (19-75)</td>
<td>2.98 (1.44-6.14)</td>
<td>1078/4</td>
<td>Moderate</td>
<td>0%</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>13 (14-64)</td>
<td>2.33 (1.04-5.22)</td>
<td>1078/4</td>
<td>Moderate</td>
<td>0%</td>
</tr>
<tr>
<td>Vascular-related death</td>
<td>11 (12-62)</td>
<td>2.51 (1.08-5.82)</td>
<td>1078/4</td>
<td>Moderate</td>
<td>0%</td>
</tr>
<tr>
<td>Arteriothrombotic event</td>
<td>47 (44-113)</td>
<td>1.58 (0.95-2.62)</td>
<td>1078/4</td>
<td>Moderate</td>
<td>0%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32 (18-66)</td>
<td>1.11 (0.57-2.16)</td>
<td>1078/4</td>
<td>Moderate</td>
<td>0%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes only studies with available data. <sup>b</sup> Based on the ratio of absolute risk between the treatment and control groups. <sup>c</sup> Based on the quality assessment criteria of the Cochrane Collaboration.
Retinal Drug Concentrations with OZURDEX 700ug in Vitrectomized vs Nonvitrectomized Rabbit Eyes

Conclusion: No Significant Differences in Retinal Drug Levels following Vitrectomy

Case Study: Patient F.N.
Courtesy of Anat Loewenstein and Michaella Goldstein

- 65 yo F
- RE Regressed PDR (s/p PRP)
- LE Severe NPDR
- BE DME (R>>L)
- s/p RE Focal Laser
- s/p RE Intravitreal Bevacizumab Inj. X 3
For RE Intravitreal Bevacizumab Inj. X3

BCVA – 6/20
CMT - 840µ

BCVA – 6/8.5
CMT - 349µ

5 weeks post monthly Bevacizumab X 3

BCVA – 6/30
CMT - 846µ

BCVA – 6/12
CMT - 512µ

For RE Dex Implant Injection
1 week post Dex Implant Injection

BCVA 20/100  
RE  
CMT - 432µ

BCVA - 20/60  
LE  
CMT - 668µ

For LE Dex Implant Injection

4 weeks post Dex Implant Injection

BCVA - 20/60  
CMT - 227µ

BCVA 20/50  
CMT - 365µ

8 weeks post Dex Implant Injection

BCVA 20/50  
CMT - 209µ

BCVA - 20/40  
CMT - 244µ

11 weeks post Dex Implant Injection

For LE Dex Implant Injection
Key Points: Inflammation in DME

• Retinopathy progresses with time, and is associated with changes in the amounts of multiple cytokines relative to VEGF
  • Steroids are effective at quenching many cytokines
  • Anti-VEGF effective at lowering VEGF only
• Data from sham control groups of RISE/RIDE and RESTORE ranibizumab DME studies and FAME fluocinolone implant DME study are consistent with a shift, or transition, in the distribution of cytokines such that in chronic DME, VEGF expression may be less important than in less chronic DME
• Steroid therapy as shown in dexamethasone implant and fluocinolone implant studies are effective throughout course of DME
• Patients with DME treated with sham for 2 years did not seem to benefit from anti-VEGF
Management of DME 2018: Summary--Anti-VEGF Agents

- Anti-VEGF agents have been shown to be effective for most but not all patients
  - Up to approximately 40% show “sub optimal” response
  - Prolonged delay in initiation of therapy (i.e., in chronic DME) can limit anti-VEGF response

- Systemic side effects of intravitreal anti-VEGF agents may be “real” with increased risk of stroke and death in DME
  - Increased risk with ranibizumab seen in Protocol T—anomalous?

- Real world trials generally achieve similar efficacy results: approximately 28-30% 3 line gainers and approximate mean BCVA gain of 7-8—seen with both anti-VEGF and steroid real world use
Both steroids and anti-VEGF agents are effective for DME

- In real world trials results are comparable with fewer steroid injections
- Both steroids and anti-VEGF alter course of DR

Dex and fluocinolone implant works both early and late

- Steroid implants equally effective in vitrectomized vs non-vitrectomized eyes
- Steroid related ocular side effects seen with all steroids, but easiest to manage in Dex implant treated eyes (particularly IOP)

Most patients benefit from steroid therapy but almost 40% non-responder or sub-optimal responder to anti-VEGF

EARLY study from Protocol I shows that long term outcomes predictable after 3 injections of Anti-VEGF
Management of DME 2018: Conclusions

- Typically initiate therapy with anti-VEGF injections
  - Discuss with patient need for regular visits, particularly in 1st year
  - Systemic management of A1C, BP, and lipid levels important
  - Systemic safety concerns exist
    - consider deferral of anti-VEGF therapy or initiate steroid therapy if recent cardiovascular or cerebrovascular event
  - Chronic DME may show limited response to anti-VEGF
    - Difficult to identify these cases a priori
    - Trial with anti-VEGF therapy may identify these cases
  - When response is “sub-optimal” after three anti-VEGF injections, reasonable to consider alternatives
    - If bevacizumab therapy was initial therapy, many would consider switching to aflibercept or ranibizumab
    - If aflibercept was initial therapy, consider switching to steroid therapy (typically dex implant)

- Steroid implant therapy to be considered early if recent MI/stroke or vitrectomized eye or pseudophake or unable to come in monthly
Thank you!