Update on Management of Diabetic Retinopathy and Diabetic Macular Edema

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Diabetic Retinopathy

- Leading cause of acquired blindness among young and working age adults
- Will rise to 336 million in 2030
- Macular edema most common cause of vision loss
  - Affects up to 30% of pts with DM > 20 years
9. VEGF Inhibitors
- Intravitreal Aflibercept Injection
  - VISTA/VIVID Studies
  - FDA Approval
- Intravitreal Ranibizumab Injection
  - RISE/RIDE Studies
  - FDA Approval

10. Intravitreal Bevacizumab Injection
- Bevacizumab BOLT Study

11. Intravitreal Triamcinolone Acetonide
- Intravitreal Steroids

Protocol S - 5 year results

• Randomized, multi-center clinical trial
• **Primary Objective:** Compare the efficacy and safety of PRP with that of intravitreous ranibizumab (0.5-mg in 0.05 mL) in eyes with proliferative diabetic retinopathy (PDR) with or without DME
394 Eyes Randomized (305 Participants)

**Baseline**
- Ranibizumab Group N = 191
- PRP Group N = 203

**2-Years Excluding Deaths**
- Ranibizumab: 88%
- PRP: 86%

**5-Years Excluding Deaths**
- Ranibizumab: 69%
- PRP: 65%

**5-Years Overall**
- Ranibizumab: 61%
- PRP: 61%
## Mean Number of Injections

### 5-Year Completers Only

<table>
<thead>
<tr>
<th>Year</th>
<th>Ranibizumab Group (N = 117)</th>
<th>PRP Group (N = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>7.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Year 2</td>
<td>3.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Year 3</td>
<td>3.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Year 4</td>
<td>2.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Year 5</td>
<td>2.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Cumulative Through 5 Years</td>
<td>19.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Event Description</td>
<td>Ranibizumab Group (N = 191)</td>
<td>PRP Group (N = 203)</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Received PRP During Follow-up, N (%)</td>
<td>26 (14%)</td>
<td>103 (51%)</td>
</tr>
<tr>
<td>Received PRP prior to 104 Weeks, N</td>
<td>6%</td>
<td>45%</td>
</tr>
<tr>
<td>Received PRP after 104 Weeks, N</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>Received PRP during Vitrectomy, N</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Received PRP outside of Vitrectomy, N</td>
<td>5%</td>
<td>44%</td>
</tr>
</tbody>
</table>
Mean Changes in VA From Baseline Over Time - Overall Cohort

Adjusted Mean Difference at 5 Years: +0.6 letters
95% Confidence Interval: (-2.3, +3.5), $P = .68$

Mean Change in VA Letter Score

Outlying values were truncated to 3 SD from the mean
Mean Changes in VA From Baseline Over Time for 5-Year Completers Only

5-Year AUC Difference: +1.6 letters
95% Confidence Interval: (0, 3.2), $P = .05$

Ranibizumab
PRP

Outlying values were truncated to 3 SD from the mean

$N = 117$ of $191$

$N = 123$ of $203$
Mean Change in Cumulative Visual Field Total Point Score (30-2 + 60-4) - Overall Cohort

5-Year Adjusted Mean Difference: 208 dB
95% Confidence Interval (-9, 408), P = .04

Outlying values were truncated to 3 SD from the mean
## Diabetic Retinopathy on Fundus Photographs at 5 Years*

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab</th>
<th>PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 90)</td>
<td>(N = 93)</td>
</tr>
<tr>
<td>Without PDR (≤ level 60), %</td>
<td>43%</td>
<td>37%</td>
</tr>
<tr>
<td>With Regressed NV (level 61A), %</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td>With Active NV (≥ level 61B), %</td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td>Improved from PDR (≥ level 61) to NPDR (≤ level 53)**, %</td>
<td>33%</td>
<td>N/A</td>
</tr>
<tr>
<td>Without DR (≤ level 20)*, %</td>
<td>10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Improved ≥2 steps in DR severity on fundus photos at 5 years**, %</td>
<td>46%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Observed data only, only include eyes with active NV at baseline as graded by reading center. **Not applicable or cannot determine for PRP group.
### DR Adverse Events: Over 5 Years

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ranibizumab (N = 117)</th>
<th>PRP (N = 123)</th>
<th>Adjusted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Retinal detachment, %</td>
<td>6%</td>
<td>15%</td>
<td>-9% (-14%, -4%)</td>
</tr>
<tr>
<td>Retinal Detachment involving Center of the Macula, %</td>
<td>1%</td>
<td>4%</td>
<td>-3% (-7%, 0%)</td>
</tr>
<tr>
<td>Neovascular Glaucoma, %</td>
<td>3%</td>
<td>4%</td>
<td>-2% (-6%, 2%)</td>
</tr>
<tr>
<td>Neovascularization of the Iris, %</td>
<td>3%</td>
<td>1%</td>
<td>1% (-1%, 3%)</td>
</tr>
<tr>
<td>Vitreous Hemorrhage, %</td>
<td>48%</td>
<td>46%</td>
<td>2% (-6%, 11%)</td>
</tr>
<tr>
<td>Vitrectomy, %</td>
<td>11%</td>
<td>19%</td>
<td>-7% (-14%, -1%)</td>
</tr>
</tbody>
</table>
Summary: Protocol S 5-Year Results

Visits, Injections, Safety

– 66% of participants (excluding death) completing 5-year visit
  - Ranibizumab = 117
  - PRP = 123

– Median number of visits*
  - Ranibizumab = 43
  - PRP = 21

– Mean number of injections
  - Ranibizumab = 19  (Mean of 3 per year- Years two through five)
  - PRP = 5

– APTC events appeared similar between groups. No ocular safety concerns were identified.

* Counting participants with one study eye only
Protocol T

• Head to head comparison of efficacy between Aflibercept, bevacizumab, and ranibizumab in patients with center involved DME
• PRN treatment regimen (If improved or worsened by > 5 letters or >10% CST change)
• Focal laser rescue after 24 weeks if persistent DME not improving after at least 2 injections
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
Mean Change in Visual Acuity Over 2 Years

By Baseline Visual Acuity Subgroup

20/32 to 20/40

20/50 or Worse

Mean Change in Visual Acuity Letter Score

0  2  4  6  8  10  12  14  16  18  20

Weeks

0  8  16  24  32  40  48  56  64  72  80  88  96  104

Aflibercept  Bevacizumab  Ranibizumab

+18.1
+16.1
+13.3

+8.6
+7.8
+6.8
Mean Change in OCT CST in 2 years
By baseline visual acuity subgroup

Baseline Visual Acuity 20/32 to 20/40

Baseline Visual Acuity 20/50 or Worse

2-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P = 0.01$
- Aflibercept vs. Ranibizumab $P = 0.19$
- Ranibizumab vs. Bevacizumab $P = 0.19$

2-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P < 0.001$
- Aflibercept vs. Ranibizumab $P = 0.26$
- Ranibizumab vs. Bevacizumab $P < 0.001$
Most patients required focal laser
Conclusions from Protocol T

• All 3 drugs maintained 1-year visual gains (with half the number of injections in year 2)
• At 2 years, advantage of aflibercept over bevacizumab persisted but difference was diminished
  – Posthoc analysis suggests in eyes with <20/50 vision or CST >400, aflibercept may have superior VA outcomes to bevacizumab
  – But remember this is STUDY 20/50 (including refraction)
• Among eyes with PDR at baseline, aflibercept associated with higher rates of DR severity improvement compared to bevacizumab and ranibizumab
Corticosteroids for DME

- Anti-VEGFs are now the gold standard for treatment of DME
- Corticosteroids may be most helpful in:
  - Pseudophakes with DME not responsive to anti-VEGF +/- focal/grid laser
  - Patients desiring less intravitreal injections
  - Possibly pregnant patients
- 3 choices intravitreal
  - Triamcinolone acetonide (Triesence®) – off label
  - Dexamethasone (Ozurdex®)
  - Fluocinolone acetonide (Iluvien®)
- Mechanism of action:
  - Stabilize, reconstitute the inner blood-retinal barrier
  - Downgrade VEGF production
Corticosteroids for DME

• Ocular Risks associated with intravitreal injection of corticosteroids
  – Injection risks:
    • Endophthalmitis – infectious and non-infectious
      – Theoretical greater risk than anti-VEGFs
    • Vitreous hemorrhage – same as anti-VEGF
    • Retinal tear – same as anti-VEGF
  – Intrinsic to Corticosteroids
    • IOP rise
    • Cataract, esp posterior subcapsular
DRCR.net Protocol U

- Eyes with persistent DME and VA impairment despite previous anti-VEGF treatment
- 129 Eyes, 116 participants
- 3 month run-in with monthly ranibizumab, 6 month followup of study
- Monthly ranibizumab + dexamethasone q3mo vs monthly ranibizumab + sham q 3mo

**Combination**

- Dexamethasone + Continued Ranibizumab
- N = 63 (97%)

**Ranibizumab**

- Sham + Continued Ranibizumab
- N = 64 (100%)
VA Mean Change

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

N = 64

Run-In
Randomization

+ 3.0

N = 64
VA Mean Change

Adjusted Mean Difference: -0.5 letters
95% Confidence Interval: (-3.6, +2.5), P = 0.73

Run-In
Randomization

Visit Week

N = 64
N = 65

N = 64
N = 63

Ranibizumab
Combination

VA Mean Change (Letter Score)
VA Mean Change: Baseline Lens Status

**Pseudophakic**

- Ranibizumab
- Combination

<table>
<thead>
<tr>
<th>Visit Week</th>
<th>Ranibizumab</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N = 26</td>
<td>N = 32</td>
</tr>
<tr>
<td>4</td>
<td>N = 25</td>
<td>N = 32</td>
</tr>
<tr>
<td>8</td>
<td>N = 30</td>
<td>N = 32</td>
</tr>
<tr>
<td>12</td>
<td>N = 29</td>
<td>N = 32</td>
</tr>
<tr>
<td>16</td>
<td>N = 28</td>
<td>N = 32</td>
</tr>
<tr>
<td>20</td>
<td>N = 27</td>
<td>N = 32</td>
</tr>
<tr>
<td>24</td>
<td>N = 26</td>
<td>N = 32</td>
</tr>
</tbody>
</table>

**Phakic**

- Ranibizumab
- Combination

<table>
<thead>
<tr>
<th>Visit Week</th>
<th>Ranibizumab</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N = 39</td>
<td>N = 32</td>
</tr>
<tr>
<td>4</td>
<td>N = 38</td>
<td>N = 32</td>
</tr>
<tr>
<td>8</td>
<td>N = 37</td>
<td>N = 32</td>
</tr>
<tr>
<td>12</td>
<td>N = 36</td>
<td>N = 32</td>
</tr>
<tr>
<td>16</td>
<td>N = 35</td>
<td>N = 32</td>
</tr>
<tr>
<td>20</td>
<td>N = 34</td>
<td>N = 32</td>
</tr>
<tr>
<td>24</td>
<td>N = 33</td>
<td>N = 32</td>
</tr>
</tbody>
</table>

+5.1
+2.0
+4.1
+1.1

*P*-value for interaction = 0.08
VA Mean Change: VA Improvement

**VA Improved During Run-In**

- Ranibizumab: +3.6
- Combination: +2.6

**VA Did Not Improve During Run-In**

- Ranibizumab: +2.8
- Combination: +2.3

*P*-value for interaction = 0.65
VA Mean Change: OCT Improvement

Retinal Thickness on OCT
Improved During Run-In

Retinal Thickness on OCT
Did Not Improve During Run-In

N = 38
N = 38

N = 37
N = 38

N = 27
N = 26

N = 26
N = 26

VA Mean Change (Letter Score)

0 4 8 12 16 20 24

Visit Week

* P-value for interaction = 0.27
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.
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.
Conclusions of Protocol U

- 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
Conclusions on Corticosteroids

• Possible additional treatment option for those with persistent DME despite adequate treatment with anti-VEGF and/or focal/grid laser
  – Likely superior CST thinning with combination treatment
  – Overall VA results similar but may differ based on lens status (further studies needed)

• Cataracts and IOP rise are expected side effects
What is the Future of Diabetic Retinopathy/ Diabetic Macular Edema Treatment?
Selected Upcoming DRCR.net protocols

• Protocol V: Treatment of center involved DME in eyes with very good visual acuity
• Protocol W: Intravitreal anti-VEGF treatment for prevention of vision threatening diabetic retinopathy in eyes with high risk
• Protocol AB: Anti-VEGF vs prompt vitrectomy for vitreous hemorrhage in patients with PDR
• Protocol AC: Randomized trial of aflibercept vs bevacizumab + deferred aflibercept for treatment of center-involved DME
Faricimab (RG7716)

- Anti-VEGF/Anti-angiopoietin 2 bispecific antibody
- First bispecific antibody for intravitreal use
- To address both neovascular and inflammatory mechanisms of diabetic macular edema
- Phase 3 studies currently enrolling (YOSEMITE & RHINE)
BOULEVARD Phase 2 Trial

- All 3 arms had similar BCVA outcomes and CST reductions at 24 weeks.
- Higher proportion of patients maintained stability without additional injection through 16 weeks (Defined as VA decrease <5 ETDRS letters AND CST increased <50 um).
Improved VA compared to Ranibizumab

Faricimab Met Its Primary Endpoint, Showing Statistically Significant BCVA Gains vs Ranibizumab in Anti-VEGF Treatment-Naïve Patients

- +13.9
- +11.7
- +10.3

P = 0.03
80% CI 1.53, 5.61
Durability potential

**Durability Potential**

**Time to ≥5 ETDRS Letter Loss**
- Week 30: 82%
- Week 34: 64%
- Week 30: 54%
- Week 34: 47%

**Time to ≥50 µm Increase in CST**
- Week 30: 82%
- Week 34: 70%
- Week 30: 69%
- Week 34: 56%

![Graphs showing durability potential](image)
Suprachoroidal Injection
Triamcinolone

- TYBEE Phase 2 trial: suprachoroidal CLS-TA + Intravitreal Eylea q3 mo vs monthly Eylea
- CLS-TA was noninferior (12.3 letters gained vs 13.5 letters), slightly better CST reduction (208 microns vs 177 microns)
- Elevated IOP 8.3% vs 2.9%
- Cataract 5.6% vs 2.9%
- Possible phase 3 forthcoming
Kodiak Sciences

- KSI-301 is an anti-VEGF antibody biopolymer conjugate (ABC)
- Phase 1a showed rapid response within 1 week, with durable response at 12 weeks
- Phase 1b planned with multiple-doses
Thank you!