**AGENDA**

1. Common questions in DME Management
2. Perioperative DME Management
3. Refractory DME Management
4. PDR Management in the anti-VEGF Era

**DISCLOSURES**

- No financial conflict of interest
- Will discuss off-label use of intraocular Bevacizumab (Avastin) for Diabetic Retinopathy

**DME MANAGEMENT**

Common questions in DME Management

- Do all anti-VEGF drugs work the same for all patients?
- Immediate Treatment vs. Treatment Deferral?
- Does Prior Treatment with Laser/Steroids affect outcomes?
- Does Baseline HBA1c and Macular Ischemia affect visual gains with Anti-VEGF?
- Is Monthly Treatment Needed to Maintain or Achieve Vision Gains?

**CASE: SEVERE DME**

- 55 year old DM Type II male. Diagnosed with Diabetes 1 year prior to presentation.
- HBA1c: 6.8 now. Was 12 when diagnosed. BP WNL.
- Decreased VA OU x 1 month
- VA OD: 20/400
- OS: 20/100

**CASE: SEVERE DME – VA 20/400**
**CASE: SEVERE DME – VA 20/100**

**CASE: SEVERE DME**

**EARLY FA OD**

**EARLY FA OS**

**CASE: SEVERE DME**

**LATE FA OD**

**LATE FA OS**

**CASE: SEVERE DME**

**LATE FA OD**

**LATE FA OS**

**MANAGEMENT OPTIONS**

Diffuse Central DME /very severe NPDR/peripheral ischemia
- Systemic management – BS, BP, Lipid control, Fluid retention/renal status, anemia
- Focal/Grid laser – not very effective for diffuse edema. ETDRS – <15% with CSME get improvement in VA
- Anti-VEGF – best option
- Steroid – rescue therapy

**MACULAR EDEMA CURRENT PHARMACOLOGIC OPTIONS**

FDA Approved therapy
- Ranibizumab (Lucentis 0.3 mg) – RIDE/RISE ($1150)
- Afibercept (Eylea) – VIVID/VISTA ($2000)
- Dexamethasone implant (Ozurdex) – MEAD ($1400)
- Fluocinolone implant (Iluvien) – FAME ($9300)

Off label therapy
- Bevacizumab (Avastin) – DRCR.net ($70)
- Intravitreal Triamcinolone (Triessence) - $150
**DME MANAGEMENT**

Common questions in DME Management
- Do all anti-VEGF drugs work the same for all patients?
- Treatment Deferral vs. Immediate Treatment?
- Does Prior Treatment with Laser/Steroids affect outcomes?
- Does Baseline HBA1c and Macular Ischemia affect visual gains with Anti-VEGF?
- Is Monthly Treatment Needed to Maintain or Achieve Vision Gains?

**DRCR.net PROTOCOL T (2016)**

- Comparative trial of Avastin, Lucentis and Eylea for center involved DME (n=660). VA worse than 20/32.
- 2 year study
- PRN Rx once achieved 20/20 and CST normal (250 um or less)

**MEAN CHANGE IN VISUAL ACUITY OVER 2 YEARS**

*Full Cohort*

<table>
<thead>
<tr>
<th></th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>+9.7</td>
<td>+10.0</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>+11.2</td>
<td>+12.3</td>
</tr>
<tr>
<td>Afibercept</td>
<td>+13.3</td>
<td>+12.8</td>
</tr>
</tbody>
</table>

**MEAN CHANGE IN OCT CST OVER 2 YEARS**

*Baseline Visual Acuity 20/32 to 20/40 (~50% of Cohort)*

<table>
<thead>
<tr>
<th></th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>-67</td>
<td>-68</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>-110</td>
<td>-126</td>
</tr>
<tr>
<td>Afibercept</td>
<td>-129</td>
<td>-133</td>
</tr>
</tbody>
</table>

Ranibizumab/Afibercept resulted in significant OCT CST improvement vs. Bevacizumab

**MEAN CHANGE IN VISUAL ACUITY OVER 2 YEARS**

*Baseline Visual Acuity 20/32 to 20/40 (~50% of Cohort)*

<table>
<thead>
<tr>
<th></th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>+7.5</td>
<td>+6.8</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>+8.3</td>
<td>+8.6</td>
</tr>
<tr>
<td>Afibercept</td>
<td>+8.0</td>
<td>+7.8</td>
</tr>
</tbody>
</table>

104-Week Treatment Group Comparison
- Afibercept vs. Bevacizumab P = 0.02
- Afibercept vs. Ranibizumab P = 0.47
- Ranibizumab vs. Bevacizumab P = 0.11

**MEAN CHANGE IN VISUAL ACUITY OVER 2 YEARS**

*Baseline Visual Acuity 20/50 or Worse (~50% of Cohort)*

<table>
<thead>
<tr>
<th></th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>+11.8</td>
<td>+13.3</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>+14.2</td>
<td>+16.1</td>
</tr>
<tr>
<td>Afibercept</td>
<td>+18.9</td>
<td>+18.3</td>
</tr>
</tbody>
</table>

104-Week Treatment Group Comparison
- Afibercept vs. Bevacizumab P = 0.02
- Afibercept vs. Ranibizumab P = 0.18
- Ranibizumab vs. Bevacizumab P = 0.18
**MEAN CHANGE IN OCT CST OVER 2 YEARS**

Baseline Visual Acuity 20/50 or Worse

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>-135</td>
<td>-185</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>-176</td>
<td>-174</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>-210</td>
<td>-211</td>
</tr>
</tbody>
</table>

2-Year Treatment Group Comparison:
- Aflibercept vs. Bevacizumab P = 0.01
- Aflibercept vs. Ranibizumab P = 0.18
- Ranibizumab vs. Bevacizumab P = 0.18

**DRCR.net PROTOCOL T: MY TAKE**

- Anti-VEGF clearly best treatment for center involved and diffuse edema
- All agents are effective
- Lucentis/Eylea give better results especially in more severe cases with worse vision (<20/50).
- Eylea results in more rapid improvement in severe cases in year 1, no significant difference from Lucentis by year 2
- Lucentis is cheaper than Eylea ($1150 vs. $2000)
- Case by case basis – cost and insurance a factor
- Avastin may be “good enough”

**DME MANAGEMENT**

Common questions in DME Management
- Do all anti-VEGF drugs work the same for all patients?
- Treatment Deferral vs. Immediate Treatment?
- Does Prior Treatment with Laser/Stereoids affect outcomes?
- Does Baseline HBA1c and Macular Ischemia affect visual gains with Anti-VEGF?
- Is Monthly Treatment Needed to Maintain or Achieve Vision Gains?

**RANIBIZUMAB: RIDE/RISE POOLED DATA**

<table>
<thead>
<tr>
<th>Month</th>
<th>Sham Control</th>
<th>RBZ 0.3 mg</th>
<th>RBZ 0.5 mg</th>
<th>OLE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-255.2</td>
<td>-262.0</td>
<td>-253.4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>-261.5</td>
<td>-267.9</td>
<td>-256.1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>-266.0</td>
<td>-273.0</td>
<td>-266.0</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>-265.5</td>
<td>-273.5</td>
<td>-268.0</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>-266.0</td>
<td>-274.0</td>
<td>-268.0</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>-266.0</td>
<td>-274.0</td>
<td>-268.0</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>-266.0</td>
<td>-274.0</td>
<td>-268.0</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>-266.0</td>
<td>-274.0</td>
<td>-268.0</td>
<td></td>
</tr>
</tbody>
</table>

*Data become unstable after Month 54 due to the low number of patients at that point. †Treatment during core study.

**SECONDARY ENDPOINT: MEAN CHANGE IN OCT CFT OVER TIME**

<table>
<thead>
<tr>
<th>Day T</th>
<th>Sham (n=257)</th>
<th>RBZ 0.3 mg (n=250)</th>
<th>RBZ 0.5 mg (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-300</td>
<td>-255</td>
<td>-250</td>
</tr>
<tr>
<td>7</td>
<td>-255</td>
<td>-250</td>
<td>-250</td>
</tr>
<tr>
<td>14</td>
<td>-250</td>
<td>-250</td>
<td>-250</td>
</tr>
</tbody>
</table>

**MEAN CHANGE IN BCVA**

Primary Analysis (LOCF)

<table>
<thead>
<tr>
<th>DME</th>
<th>VIVID</th>
<th>VISTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETDRS Letters</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary Analysis (LOCF): excludes patients who received rescue treatment; P values are not confirmatory

VIVID FAS: laser, n=132; 2q4, n=136; 2q8, n=135, VISTA FAS laser, m=154; 2q4, n=154, 2q8 n=151

µm

Week

**P < 0.0001** vs laser

TREATMENT DELAY FOR DME

• Patients in the RIDE/RISE trials that switched from sham to Lucentis after 2 years never achieved same vision benefit.
• Patients in the VISTA/VIVID trials that switched from laser to Eylea after 2 years never achieved same vision benefit.
• Further subgroup analysis from these trials suggests that benefit seems to be best within 6 months of diagnosis.
• Treatment delay can still improve vision and anatomy, but less robust than immediate treatment.

TREATMENT DELAY FOR DME: GOOD VISION

• DRCR Protocol V (JAMA 2019)
• Background: Today, OCT allows detection of minimal fluid. Prior anti-VEGF studies did not include patients with VA 20/25 or better.
• Should patients with central DME be started on anti-VEGF as soon as edema is detected on OCT regardless of VA? Or can treatment be delayed until VA drops without affecting long term outcomes?
• Patients were randomized to initial observation (n=208), initiation of monthly Aflibercept (n=205), or focal laser with deferred Aflibercept (n=212).

DRCR.net PROTOCOL V (2019): RESULTS

• At 2 years, all 3 groups had similar outcomes with no statistically significant difference in VA loss.
• Mean VA was 20/20 in all 3 groups.
• 25% of laser group and 34% of observation group needed Aflibercept during the 2 year trial.
• Therefore, about 2/3 of patients required no treatment.
• Can initially observe patients with good VA with DME with the confidence that it will not harm long term VA outcomes and anti-VEGF can be initiated when vision declines.
• Close follow-up needed. Consider individualized approach.

DME MANAGEMENT

Common questions in DME Management
• Do all anti-VEGF drugs work the same for all patients?
• Treatment Deferral vs. Immediate Treatment?
• Does Prior Treatment with Laser/Steroids affect outcomes?
• Does Baseline HBA1c and Macular Ischemia affect visual gains with Anti-VEGF?
• Is Monthly Treatment Needed to Maintain or Achieve Vision Gains?

PRIOR TREATMENT

• RISE/RISE – subgroup analysis. 76% of patients received prior laser or laser plus steroid.
  – Visual acuity and Retinal thickness reduction results were similar across all subgroups receiving Ranibizumab over 24 months*
• VISTA/VIVID – subgroup analysis showed no difference in outcome in those treated previously with another anti-VEGF agent either.

* Sara J. et al. IOVS 2015;56(7):1759-1759.
DME MANAGEMENT

Common questions in DME Management

• Do all anti-VEGF drugs work the same for all patients?
• Treatment Deferral vs. Immediate Treatment?
• Does Prior Treatment with Laser/Steroids affect outcomes?
• Does Baseline HBA1c and Macular Ischemia affect visual gains with Anti-VEGF?
• Is Monthly Treatment Needed to Maintain or Achieve Vision Gains?

Singh RP (Ophthalmology 2016): separated patients treated with Ranibizumab in RIDE/RISE into subgroups based on baseline A1c
  – All subgroups found to have similar VA improvements from baseline
  – HBA1c levels not found to be predictive of PDR when treated with Ranibizumab

Ip MS (Ophthalmology 2015): Baseline macular nonperfusion was also not found to affect extent of visual acuity improvement in RIDE/RISE.

OCT – PREDICTING VISUAL ACUITY

• Disruption of ellipsoid zone (IS/OS junction) correlates with poorer visual outcomes
• Increased Disorganization of retinal inner layers length (DRIL) - poorer visual outcomes


DME MANAGEMENT

20/125 rapidly improved to 20/40 in 3 injections

ELLIPSOID LAYER DISRUPTION AND DRIL

20/400 to 20/150 with 5 injections

DME MANAGEMENT

Common questions in DME Management

• Do all anti-VEGF drugs work the same for all patients?
• Treatment Deferral vs. Immediate Treatment?
• Does Prior Treatment with Laser/Steroids affect outcomes?
• Does Baseline HBA1c and Macular Ischemia affect visual gains with Anti-VEGF?
• Is Monthly Treatment Needed to Maintain or Achieve Vision Gains?
RANIBIZUMAB FOR DME

- DRCR Protocol I – 5 year results of Lucentis for DME with prompt or deferred laser
- Most eyes treated with Lucentis and either prompt or deferred laser maintain vision gains obtained in first year through 5 years with little additional Rx over last 3 years
  - 9 injections year 1
  - 3-4 injections year 2
  - 2-3 injections year 3
  - Almost zero by year 5

* Ophthalmology 2015;122:375-381

DRCR PROTOCOL T: DME TREATMENT # ANTI-VEGF INJECTIONS

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Global P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>9 (8, 11)</td>
<td>10 (8, 12)</td>
<td>10 (8, 11)</td>
<td>0.045</td>
</tr>
<tr>
<td>Year 2</td>
<td>5 (1, 7)</td>
<td>6 (1, 9)</td>
<td>6 (1, 9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Over 2 Years</td>
<td>15 (11, 17)</td>
<td>16 (12, 20)</td>
<td>15 (11, 19)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Note: 98% of protocol required re-injections were given over 2 years.

RANIBIZUMAB FOR DME – PRN DOSING

- RESTORE - 12 month randomized trial and open label 24 month extension
- 3 monthly loading doses and then PRN treatment showed efficacy in maintaining visual and anatomic benefit

* Ophthalmology 2013;120:2004-12

RANIBIZUMAB FOR DME – TREX

TREX-DME study:
- Treat and extend dosing of Ranibizumab 0.3 mg resulted in similar visual and anatomic outcomes as monthly dosing at 1 year
- TREX cohort had mean of 10 injections in 1st year
- Adding FA guided laser to this algorithm did not further improve outcomes


RANIBIZUMAB FOR DME – LONGER TERM

- RISE/RIDE – extension beyond month 36
  - Patients maintained vision and anatomic benefit with PRN dosing and fewer injections (mean 4.5 injections over next 14.1 months)*
  - 25% didn’t require further injections

* Ophthalmology 2015;122:2504-13

EYLEA FOR DME

- ENDURANCE STUDY – 12 month extension study following 36 month VISTA trial
- Vision gains maintained with a reduced frequency of injections (mean of 4.5 injections) in year 4 with a PRN approach
- 30% needed no injections
- No reduction in injection burden was observed after macular laser application

CASE: VA 20/400 & 20/100 BASELINE

AFTER EYLEA OU x 5

VA OD: 20/25  VA OS: 20/50-2  PH: 20/40

AT 18 MONTHS ON PRN Rx

VA OD: 20/25  VA OS: 20/20

PERIOPERATIVE ANTI-VEGF THERAPY IN DR

• Anti-VEGF may prevent worsening DME when CE needed
• Leaking MA’s without edema – high risk with CE – Anti-VEGF often can prevent worsening
  – Increased risk of central DME after CE shown in DRCR Protocol Q in these cases
  – Feng [Retina 2019]: Meta Analysis – cataract surgery combined with Bevacizumab showed improved VA and CMT at 1, 3 and 6 months. Less retinopathy progression as well.
• Very helpful to quiet neovascularization pre-Vitrectomy and pre-cataract surgery

WHEN TO USE STEROIDS

Steroids are known to decrease inflammation, reduce breakdown of the blood-retinal barrier, and have anti-angiogenic properties.
1. Diffuse DME with no anatomic response to anti-VEGF – suspect inflammatory role (rule out renal disease as well)
2. Vitrectomized eye requiring very frequent anti-VEGF therapy – steroid implants work best
3. Post cataract surgery CME/DME – usually cystoid in pattern to suggest inflammatory cause

OZURDEX FOR DME- APPROVED 6/2014

• Dexamethasone implant – office injection
• 3 year study for DME (MEAD study)
• Mean 4 treatments in 3 years
• Study 1: 21% vs sham 12% gain > 3 lines
• Study 2: 18% vs sham 10% gain > 3 lines
• 42% needed IOP lowering therapy. Surgery not usually needed, resolves by 6 months
• 68% cataract formation
• Anterior migration if torn posterior capsule
ILUVIEN FOR DME- APPROVED 2/2015

- 3 year study for DME
- 1 injection of implant lasting 3 years
- Steroid challenge prior recommended
- Combined results of 2 trials: 28.7% treated vs. 16.2% control had a >3 line improvement 36 mo.
- Improvement seen at 3 weeks and sustained through month 36
- 18.4% sustained IOP rise, 5% needed glaucoma surgery

DRCR.NET PROTOCOL U (2017)

- 6 month Evaluation of Combination Dexamethasone + Ranibizumab vs. Ranibizumab Alone for Persistent Central-Involved DME Following Anti-VEGF Therapy
- Studied patients with persistent DME with reduced Visual acuity despite Ranibizumab x 3 monthly injections
- Randomized Continued Ranibizumab vs. combination Ranibizumab with Dexamethasone (same visit q 3 mo)

DRCR.NET PROTOCOL U (2017)

- Mean VA improvement by 6 months was no better in the dexamethasone + ranibizumab group than in the sham + ranibizumab group (mean 3 letters)
- On average, there was a greater reduction in retinal thickness in the dexamethasone + ranibizumab group (-110 vs -62 um)
- Trend towards more improvement in pseudophakic eyes vs. phakic eyes
- 29% Any Increase in IOP in combination group vs. 0% Ranibizumab alone. (15% > 30, 20% required drops)

PDR MANAGEMENT IN THE ANTI-VEGF ERA

CASE STUDY: SEVERE PDR WITH MILD DME

- 29 year old Type I diabetic male with complaints of blurry decreased VA OU and floaters OD.
- Blood sugars poorly controlled with HA1c unknown and LBS 350 at initial visit.
- Medical HX: Hypertension; Kidney Disease
- Patient is a daily smoker
1/28/2020

OD: VA 20/40, MILD VH PRESENT

DME NVE/VH/Mild traction

OD: VA 20/100

Large NVE, Mild edema

EARLY FA OD: 20/40 EARLY FA OS: 20/100

LATE FA OD LATE FA OS

MANAGEMENT OPTIONS

Severe PDR, large NVE, significant peripheral and macular non-perfusion with mild DME but diffuse leakage, and mild vitreous hemorrhage with early traction

• Systemic management – BP, BS, Renal status, smoking
• Immediate PRP laser – risk of worsening DME/diffuse leak
• Focal laser followed by PRP laser – diffuse leakage/ischemia
• Anti-VEGF monotherapy – works, quick, compliance critical
• Anti-VEGF followed by PRP Laser
• Vitrectomy / PRP Laser – high risk in young diabetic
PANRETINAL PHOTOCOAGULATION

- Reduces incidence of severe vision loss by 50% (DRS)
- Decades of clinical experience since the DRS
- PRP has been shown to a highly durable and effective method of regressing PDR
- Once regression achieved, PRP induced PDR regression usually lasts indefinitely.
- Visual outcomes good and don’t vary with follow-up (Vander 1991, Dogru 1999, Blankenship 1991)
- Requires complete treatment with well treated anterior retina

PANRETINAL PHOTOCOAGULATION

Complications/Side effects of treatment
- Decreased night vision
- Decreased peripheral vision
- Decreased accommodation
- Worse macular edema/decreased acuity
- Progression of traction
- Pain/Choroidal detachments
- Uncomfortable time consuming procedure


Ranibizumab vs. PRP for PDR:
Study Design: 394 eyes – 55 sites – 5 year follow-up
- Prompt PRP (completed within 8 weeks) vs. RBZ q 4 wks for 3 monthly doses then PRN
- Follow-up – year 1: RBZ patients q 4 weeks, PRP q 16 wks
- Follow-up - years 2-5: q 4-16 weeks depending on disease
- Eyes with PDR with or without DME allowed
- RBZ allowed in PRP patients as needed for DME

PDR: Do patient characteristics favor any Rx?

Ranibizumab vs. PRP for PDR:
- Bressler S, et al (2019) – looked at 25 baseline characteristics in Protocol S to evaluate if PRP or RBZ were better in certain groups:
  - No baseline characteristics favored PRP
  - Found RBZ better in patients with higher baseline BP, no prior focal laser, increased DR grade (at 2 year endpoint)
**DRCR.net PROTOCOL S: PATIENT CENTERED OUTCOMES**

- Work productivity loss (WPAIQ) was 15.6% less (p=.005) with Ranibizumab at 1 year and 2.9% less (p=.54) at 2 years vs. PRP group.
- 97% Ranibizumab patients were 20/40 or better in 1 eye at 2 years compared to 87% PRP group (p=.005).
- No other differences found using NEI-VFQ-25.

Beaulieu WJ, Brecker RM et al. AJO 2016; 170:206-213

**PDR: DRCR.net PROTOCOL S (2018)**

- Ranibizumab vs. PRP for PDR: 5 year outcomes
  - 66% completed 5 year followup – High non compliance rates in PDR.
  - Fewer injections over time: 7 year 1, mean 3 per year in years 2-5.
  - 90% need treatment again when on PRN within 1 year.

- Vision excellent – mean 20/25 in both groups.
  - 6% in each group lost > 3 lines. 52% RBZ vs. 41% PRP gained > 2 lines.

Results non inferior to PRP.

JAMA Ophthalmology July 2018 (Gross JG, et al)

**Lower incidence of TRD and DME in Ranibizumab group**

- 38% DME in PRP group vs. 22% RBZ. 19% TRD in PRP group vs. 7% RBZ.
- 48% PRP eyes vs. 46% RBZ developed any VH in follow-up period.
  - Some may be due to vitreous traction and release on NV.
- 19% of PRP treated eyes required vitrectomy vs. 11% RBZ.
- VF better in Ranibizumab group, but both groups showed worsening VF over time (VF results converged).

JAMA Ophthalmology July 2018 (Gross JG, et al)

**DRCR.net PROTOCOL S (2018)**

- 51% PRP group required additional PRP vs. 14% RBZ needing PRP.
  - Of the 14% in RBZ group, 9% were during Viterectomy only 5% outside.
  - Of the 51% in PRP group, 44% were outside of vitrectomy.

- PRP rarely given for failure or futility of ranibizumab.

JAMA Ophthalmology July 2018 (Gross JG, et al)
**PDR: CLARITY STUDY (2017)**

Aflibercept vs. PRP for PDR: 1 year outcomes
- 232 patients. 1:1 Randomization. No baseline edema.
- Aflibercept given 3 monthly then PRN – mean of 4 injections over 1 year. PRP in multiple sessions
- Aflibercept had:
  - Superior mean VA and VF after 1 year
  - Decreased need for vitrectomies
  - Decreased development of central DME
  - Higher patient satisfaction with Aflibercept vs. PRP

Sivaprasad S. et al, Lancet May 2017

---

**PDR: ANTI-VEGF Rx**

- Anti-VEGF alone performed well in a tightly controlled clinical trial (Protocol S/Clarity studies)
- Durability limited - 5 year Protocol S data showed:
  - Continued need for mean 3 injections for years 2-5 with PRN
  - 84% of RBZ treated eyes needed Rx when treated PRN
  - Tadayoni et al (Macula society 2018) – Despite improvement in clinical features of DR, area of retinal nonperfusion same or continued to worsen on PRN anti-VEGF Rx
  - VF declined over time in Protocol S on anti-VEGF
- At this time, anti-VEGF for PDR must be regarded as requiring indefinite long term Rx

---

**PDR: DRCR.net PROTOCOL S (2018)**

Ranibizumab vs. PRP for PDR: 5 year outcomes
- Likely longest data we have
- Ranibizumab safe and effective alternative to PRP in compliant patients
- PRP fewer treatments and follow-up exams, durable and long lasting
  - 50% need some additional treatment within 5 years
- Anti-VEGF vs. PRP vs. combo? - Decision based on presence of DME, compliance ability, cost, medical stability

---

**PDR: COMPLIANCE**

Compliance is a key concern in this patient population
- Unanticipated events can occur even in the most reliable patients (6 million diabetics hospitalized annually)*
- Protocol S – 33% lost to follow-up in 5 years
- Obeid A et al (2018) – 25.4% lost to follow-up after treatment of PDR in 4 years
  - Rates highest for low income, younger patients, and African American/Hispanic/Native American races
- Johnson M (Retina society 2018): 77% lost > 3 lines from PDR if lost to follow-up if treated only with anti-VEGF


---

**PDR: COMPLIANCE**

- In our practice, a common management approach is utilizing a combination of anti-VEGF with modified, less aggressive PRP in an effort to reduce visual side effects.
- Hypothesized that this strategy balances the effectiveness and preferred side effect profile of anti-VEGF therapy with the durability of PRP in an often high-risk, noncompliant patient population.
PURPOSE
The goal of this study was to review the clinical course and real-world outcomes of patients with PDR managed with combination anti-VEGF and PRP therapy.

METHODS
• Retrospective, noncomparative case series
• Inclusion Criteria
  – Review of all consecutive eyes with a NEW diagnosis of Proliferative Diabetic Retinopathy between 2015-2018 by 3 retina specialists in our practice with similar management methodology
  – Treatment with BOTH anti-VEGF injections and PRP
  – Follow-up for at least 1 year

RESULTS: BASELINE CHARACTERISTICS
• 378 patients treated with anti-VEGF and PRP for PDR were identified by EMR
  – 156 eyes from 114 patients satisfied inclusion and exclusion criteria
• Average Age (years): 54.73 (range: 21-82)

RESULTS: BASELINE CHARACTERISTICS
• Male: 60.3%
• Female: 39.7%
• Diabetes Type I: 28.2%
• Diabetes Type II: 71.2%
• Average A1c: 8.86% (range: 5 - 14.1)

RESULTS: OUTCOMES
• Mean follow-up: 1075 days (range: 365 – 2315 days)
• Loss to follow-up >2 months beyond prescribed: 60.0% of eyes
• Average Longest Interval between visits: 216.4 days (range: 35 – 1808)

RESULTS: PRESENTATION
• Presence of the following at the time of PDR diagnosis:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Macular Edema</td>
<td>77.6%</td>
</tr>
<tr>
<td>Epiretinal Membrane</td>
<td>25.0%</td>
</tr>
<tr>
<td>Vitreomacular Traction</td>
<td>5.8%</td>
</tr>
<tr>
<td>Vitreous Hemorrhage</td>
<td>45.5%</td>
</tr>
<tr>
<td>Tractional Retinal Detachment</td>
<td>7.1%</td>
</tr>
<tr>
<td>Neovascularization of the iris</td>
<td>5.8%</td>
</tr>
</tbody>
</table>
RESULTS: INTERVENTIONS

- Average number of injections per eye: 7.63 (range: 1 - 20)
- Average Interval between injections: 84.01 days (range: 21 - 644)
- Distribution of Medications Used (of 1190 total injections):
  - Bevacizumab 75.3%
  - Ranibizumab 19.1%
  - Aflibercept 5.5%

- PRP performed in clinic in 89.8% of eyes (10.3% at time of PPV)
  - Average Power used in a Session: 267 (range: 80 – 500)
  - Average Total Number of Spots: 1087 (range: 336 – 2760)
- Average Number of Sessions: 1.36 (range: 1 – 4)
- 28.0% of eyes underwent a second PRP session
- 5.1% of eyes underwent a third PRP session
- Early Vitrectomy performed in 17.3% of eyes

RESULTS: OUTCOMES

- Average presenting VA: 20/57 (range: 20/20 – LP)
- Average final VA was 20/63 (range: 20/20 – NLP)
- \( p = 0.48234 \)
- 24.3% of eyes gained at least 3 lines of vision
- 55.8% of eyes maintained vision similar to their presenting vision
- 19.9% of eyes lost at least 3 lines of vision

- Worsening of PDR occurred in 54.5% of eyes
  - Increased Neovascularization 31.4%
  - Vitreous Hemorrhage 45.5%
  - Vision-Limiting Ischemia 5.8%
  - Neovascular Glaucoma 2.6%
  - Tractional Retinal Detachment 14.1%

- Worsening of disease required PPV in 21.8% of eyes
  - 4.5% of all eyes required a second PPV
  - 0.6% of all eyes required a third PPV

RESULTS: SUBSET ANALYSIS

Factors Associated with Final Decreased Vision < 20/50 (n=40/156)

- Initial Vision ≤ 20/400 - 15%
- Initial Complex Advanced PDR (NVI or TRD) - 32.5%
- Loss of Follow-up > 2 months beyond prescribed - 67.5%
RESULTS: SUBSET ANALYSIS

Factors Associated with Poor Visual Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Final VA better or equal to 20/50 (n=116)</th>
<th>Final VA worse than 20/50 (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial VA worse than or equal to 20/400</td>
<td>6.03%</td>
<td>15%</td>
</tr>
<tr>
<td>Advanced PDR on presentation (TRD or NVI)</td>
<td>6.03%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Loss to Follow up &gt;2 months beyond prescribed</td>
<td>56.03%</td>
<td>67.5%</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Patients with PDR are known to have high rates of noncompliance and loss to follow-up occurred in >50% of our real-world patients.
- In addition to anti-VEGF therapy, patients in this study received modified PRP to decrease the risk of late vision loss. Still 54% showed some progression of disease and 21% required surgery.
- Mean final vision was not significantly changed over a mean 3 year follow-up. Most maintained or gained vision.
- Final visual outcomes remained excellent with the exception of patients who initially presented with end-stage disease. (TRD or NVI)

POTENTIAL IMPACT OF DME PRESENCE WHEN TREATING PDR

- Presence of DME influences the benefit of anti-VEGF over PRP
- When DME is present and treatment with anti-VEGF agent is planned, PRP may be unnecessary in most cases, if patient can be compliant with follow-up
- Compliance not generally predictable
- Long term impact: A combination approach is likely the safest, but would ultimately complete a full PRP.

HOW MUCH PRP IS ENOUGH IN ANT-VEGF ERA?

ANTERIOR PERIPHERY NEEDS BEST TREATMENT

- Studies are ongoing to use Ultra wide field imaging to study benefits for targeted PRP to anterior ischemia.

Mugit et al 2013: Targeted PPP using UWF guidance showed regression of PDR in 70% by 12 weeks, and 35% complete regression at 24 weeks.

DRCR Protocol AA – 4-year prospective study looking at UWF photo/FA in determining whether it improves assessment and prediction of DR worsening compared to standard imaging.

More expensive technology than standard camera

AFTER AVASTIN X 6 OU: PRP PERFORMED OU

VA OD: 20/40

VA OS: 20/60

Edema gone

NVE regressed/PRH resolving

Edema gone

NVE regressed/PRH resolving
FOLLOW-UP THROUGH 8 ADDITIONAL MONTHS: VA IMPROVED, Q 3MO TREAT AND EXTEND
VA OD: 20/25 VA OS: 20/50

DIABETIC RETINOPATHY
• 4/2017 – Ranibizumab (Lucentis) approved to treat DR in patients without DME
  – ≥ 2 step improvements in DR stage seen as early as 3 months
• Was shown to reduce progression and improve grade of retinopathy
• Similar findings for Aflibercept (Eylea) in VIVID/VISTA studies

DIABETIC RETINOPATHY
RISE/RIDE study: Ranibizumab
• Fellow untreated eyes
  – Nearly 30% of eyes with mod-severe to severe NPDR could progress to PDR within 2 years
• With RBZ, nearly 89% of eyes with above level of DR achieved ≥ 2 step improvement in DR severity at 2 yrs
• Early intervention in the management of DR beneficial
Protocol S:
• RBZ Rx resulted in ≥ 2 step improvement in 48% by 2 yrs (PRN Rx)

SUMMARY: WHEN TO USE ANTI-VEGF
Anti-VEGF therapy for Diffuse DME/DR:
• Largest chance of vision improvement
• Prevents worsening DR and actually improves grade of retinopathy
• Potentially reverses some ischemia while treating DME (not sustained with PRN approach)
• Low risk of vision loss from DR while on therapy
• Highly effective for NV – compliance critical and can’t be assured. Adding PRP likely best approach for PDR
• Long term benefit – injection burden seems to decrease over time, but still needed.
• Very low risk of complications (ATE, endophthalmitis)

WHEN IS ANTI-VEGF NOT APPROPRIATE
• Poor compliance
• Sick patients
• Significant active traction

CONSEQUENCES OF FAILING TO RETURN FOR ANTI-VEGF TREATMENT FOR PDR CAN BE DISASTROUS – PERFORM PRP SOON

TRACTION – USE ANTI-VEGF IMMEDIATELY PRIOR TO SURGERY TO AVOID CONTRACTION
FUTURE OPTIONS: LONG TERM DELIVERY DEVICES FOR ANTI-VEGF
- Refillable drug port delivery for RBZ (Roche/Genentech)

FUTURE OPTIONS: TARGET DR
- Aerpio Therapeutics, AKB-9778 - activates TIE-2 transmembrane tyrosine kinase receptor on endothelial cells
- Inhibits permeability, blood retinal barrier breakdown and inflammation
- Subcutaneous self administered injection, high ocular bioavailability, rapid clearance systemically
- Phase 2 positive benefit over RBZ alone

FUTURE OPTIONS
- Angiopoietin-1 (Ang-1) – endogenous protein that can activate TIE-2 to stabilize vascular permeability
- Ang-2 competes with Ang-1 for binding and is high in patients with DME
- ROCHE-GENENTECH – Farcimab – biospecific monoclonal antibody that neutralizes VEGF and Ang-2: BOULEVARD study – 229 patient study of DME: positive benefit over RBZ alone
- REGENERON trial forthcoming to compare Eylea alone with Eylea plus an antibody to Ang-2

Update on Diabetic Retinopathy Management: 2020
Sundeep Dev, MD
VRSF Retina Update Course 2020