Diabetic Retinopathy Update 2017

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Basis for DR management standards for past 40 years

Diabetic Retinopathy Study (DRS) 1971-1989
Early Treatment of Diabetic Retinopathy Study (ETDRS) 1979-1990

- Defined CSDME – clinically significant diabetic macular edema – stereoscopic exam, no OCT
- Defined HRPDR – high risk proliferative DR
- Staging system for DR – modern wide field peripheral imaging not available
- Established clear benefit for laser treatment for CSDME and HRPDR – no pharmacologic options then

ETDRS: CSDME

Clinically Significant Macular Edema – Focal/Grid Laser

- Retinal thickening <500 μm from fovea
- Hard exudates <500 μm from fovea with edema
- Retinal thickening ≥1 disc area within 1 disc diameter of fovea

ETDRS/DRS: HRPDR

- High Risk PDR – PRP laser
- NVD > 1/3 Disc area
- Any NVD with Vitreous hemorrhage
- NVE > 1/2 disc area with VH

Laser Photocoagulation: Efficacy

In CSDME and Less Severe DR

- 50% reduction in moderate visual loss
- 15% increased chance of mod visual gain
- Reduced retinal thickening

Outcomes in CSDME:

- 50% reduction in severe visual loss
- Indicated only for high risk PDR

In PDR

- 50% reduction in severe visual loss
- Need to redefine with presence of OCT imaging and intravitreal pharmacologic therapies

Newer terminology:

- Center involving vs non-center involving
- Focal vs Diffuse – definitions vary, but based on:
  - Source of fluorescein leakage
  - Extent and location of macular thickening on OCT
  - Pattern of lipid exudates

ETDRS

Clinically Significant Edema (CSDME) –

- Need to redefine with presence of OCT imaging and intravitreal pharmacologic therapies
Are prior clinical trials still applicable today - PDR?

ETDRS/DRS studies
- HR PDR – required significant NV or NV with presence of Vitreous blood
- Widefield FA to assess ischemia unavailable
- PRP was only Rx and given discomfort and side effects, higher risk threshold to use
- Better laser technology now
- Pharmacologic therapy did not exist
- **Prior thresholds likely too high today**

Macular Edema
Current Pharmacologic options

- **FDA Approved therapy**
  - Ranibizumab (Lucentis 0.3 mg) – RIDE/RISE ($1150)
  - Aflibercept (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

Ranibizumab (Lucentis) for DME

- 1st drug to be approved for DME
- RIDE/RISE trials: 759 patients
- Evaluated 0.3 mg vs. 0.5 mg (AMD dose) vs. sham/laser
- FDA approved 0.3 mg dose for DME 8/2012
- Results equivalent to 0.5 mg and so 0.3 mg felt to be a safer dose in higher cardiovascular risk diabetic patients

Summary of RIDE/RISE Study
Ranibizumab for DME

- Patients in the RIDE/RISE trials that switched from sham to Lucentis after 2 years never achieved same vision benefit
- Benefit seems to be best within 12 months of diagnosis

Ranibizumab for DME – longer term

- RISE/RIDE – extension beyond month 36
  - Patients maintained vision and anatomic benefit with FRN dosing and fewer injections (mean 4.5 injections over next 14.1 months)\(^1\)
  - 25% didn’t require further injections

**Mean BCVA Maintained During OLE**


**Systemic Serious Adverse Events Potentially Related to VEGF Inhibition**

<table>
<thead>
<tr>
<th>SAE Group Term, n (%)</th>
<th>24-Month Pooled RIDE and RISE</th>
<th>36-Month Pooled RIDE and RISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any systemic SAE</td>
<td>Sham (n=250) LUCENTIS 0.3mg (n=250)</td>
<td>Sham/0.5 mg LUCENTIS 0.3mg (n=253)</td>
</tr>
<tr>
<td>Any bleeding/hemorrhage adverse event</td>
<td>329 (14.8%)</td>
<td>325 (13.6%)</td>
</tr>
<tr>
<td>Any cardiovascular event</td>
<td>33 (15.9%)</td>
<td>31 (13.0%)</td>
</tr>
<tr>
<td>Any respiratory event</td>
<td>5 (2.4%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Any infectious event</td>
<td>3 (1.5%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Any dermatologic event</td>
<td>3 (1.5%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Any endocrine event</td>
<td>2 (1.0%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Any metabolic event</td>
<td>3 (1.5%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Any renal event</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Any bone event</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Any vascular event</td>
<td>6 (3.2%)</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td>Any bleeding event</td>
<td>7 (3.6%)</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>Any bleeding event, any site</td>
<td>13 (6.4%)</td>
<td>10 (4.1%)</td>
</tr>
<tr>
<td>Any bleeding event, same site</td>
<td>10 (5.2%)</td>
<td>7 (2.8%)</td>
</tr>
<tr>
<td>Any bleeding event, other site</td>
<td>3 (1.5%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Any bleeding event, same site 1</td>
<td>3 (1.5%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Any bleeding event, other site 1</td>
<td>7 (3.6%)</td>
<td>5 (2.0%)</td>
</tr>
</tbody>
</table>

\(^1\)Only 2% of LUCENTIS treated patients lost 3 or more lines in vision

**Proportion of Subjects Losing ≥15 ETDRS Letters (3 lines) From Baseline at Month 24**

*Secondary Endpoint*

Only 2% of LUCENTIS treated patients lost 3 or more lines in vision

**Mean Change in OCT CFT Over Time**

- **Secondary Endpoint:** Mean Change in OCT CFT Over Time
- Last observation carried forward imputation method was used. Vertical bars are ±1 SE of the mean. CFT is defined as center point thickness. Independent review of OCT performed at the University of Wisconsin Fundus Photograph Reading Center.

**RIDE/RISE**

- **Pooled RIDE and RISE**
- **24-Month Pooled RIDE and RISE**
- **36-Month Pooled RIDE and RISE**

**Mean BCVA Maintained During OLE**

- Data become unstable after Month 54 due to the low number of patients at that point.
- Treatment during core study.
- Observed data. OLE = open-label extension; RBZ = ranibizumab.

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**Ranibizumab for DME**

- Patients in the RIDE/RISE trials that switched from sham to Lucentis after 2 years never achieved same vision benefit
- Benefit seems to be best within 12 months of diagnosis

**Systemic Serious Adverse Events Potentially Related to VEGF Inhibition**

- Any systemic SAE
- Any bleeding/hemorrhage adverse event
- Any cardiovascular event
- Any respiratory event
- Any infectious event
- Any dermatologic event
- Any endocrine event
- Any metabolic event
- Any renal event
- Any vascular event
- Any bleeding event
- Any bleeding event, any site
- Any bleeding event, same site
- Any bleeding event, other site
- Any bleeding event, same site 1
- Any bleeding event, other site 1

**Ranibizumab for DME – longer term**

- RISE/RIDE – extension beyond month 36
  - Patients maintained vision and anatomic benefit with FRN dosing and fewer injections (mean 4.5 injections over next 14.1 months)\(^1\)
  - 25% didn’t require further injections

**Mean BCVA Maintained During OLE**

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- Observed data. OLE = open-label extension; RBZ = ranibizumab.
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


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

1 Ophthalmology 2015;122:375-381

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


Eylea (Aflibercept) for DME

• Two Phase 3 trials of total 862 patients
• VIVID and VISTA-DME – 2 yr then PRN open label extension (OLE) to 3 years
• 2 mg monthly vs. 2 mg monthly for 5 months then q 2 months vs laser
• Recommended dose by FDA 7/29/14: 2 mg dose monthly for 5 months then q 2 months
• Label update 5/2016: some patients will benefit from monthly dosing

Heier JS, Ophthalmol 2016; 123: 2376-2385

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

Diabetic Retinopathy

- 2/2015 – Lucentis approved to treat DR in patients with DME
- 3/25/15 - Eylea approved to treat DR in patients with DME
- Both shown to reduce progression and improve grade of retinopathy

≥ 2-Step Improvements in DR Seen With Ranibizumab as Early as Month 3

Most DR Improvements Maintained During OLE
ANDROID STUDY

- Evaluate change in peripheral perfusion using UWFA after treatment with Aflibercept (Eylea) in patients with PDR and CRVO
- Eylea q mo for 12 months vs. q mo for 6 months then q 2 mo for 6 mo
- Both groups followed to month 18 with PRN
- UWFA - 55% reduction in area of peripheral non-perfusion by 12 months in both groups
- At Month 18 with PRN, 50% maintained benefit without injections, 50% regressed

Heier J, presented at AAO Retina 10/2016

What about Bevacizumab?

- Bevacizumab (Avastin) - off label, compounded at pharmacy – commonly used due to huge cost savings.

DRCR.net Protocol T

- Comparative trial of Avastin, Lucentis and Eylea for center involved DME (n=660)
- Year 1: q 4 week exam and retreatment if improvement or worsened by ≥5 letters or OCT CST by ≥ 10%.
- PRN once achieved 20/20 and CST normal (250 um or less)
- Laser at 6 mo if vision/OCT stable for 2 consecutive injections and persistent edema
- Year 2: visits could be extended to 16 wks. ReRx if vision or OCT worsened

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>+13.2</td>
<td>+13.3</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>+13.3</td>
<td>+13.8</td>
</tr>
</tbody>
</table>

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

Mean Change in OCT CST Over 2 Years

Baseline Visual Acuity 20/32 to 20/40

<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>Aflibercept</td>
<td>-129</td>
<td>-133</td>
</tr>
</tbody>
</table>

Ranibizumab/Aflibercept resulted in significant OCT CST improvement vs. Bevacizumab
### Mean Change in Visual Acuity

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

<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>Aflibercept</td>
<td>+18.9</td>
<td>+18.3</td>
</tr>
</tbody>
</table>

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 OCT CST Over 2 Years

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

<table>
<thead>
<tr>
<th></th>
<th>Week 52</th>
<th>Week 104</th>
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</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

### Results: 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># of injections: Median (25th, 75th percentile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 (2, 7)</td>
<td>6 (2, 9)</td>
<td>6 (2, 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.

### DME Treatment: Adjunctive Laser

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Global P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one focal/grid laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>37%</td>
<td>56%</td>
<td>46%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year 2</td>
<td>20%</td>
<td>31%</td>
<td>27%</td>
<td>0.046</td>
</tr>
<tr>
<td>Over 2 Years</td>
<td>41%</td>
<td>64%</td>
<td>52%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Pre-Specified Ocular Adverse Events through 2 Years (Study Eyes)

<table>
<thead>
<tr>
<th>% of pts with at least one event</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of pts with at least one event</td>
</tr>
<tr>
<td>No. of injections 2998</td>
</tr>
<tr>
<td>Endophthalmitis*</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Retinal detachment/tear</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
</tr>
<tr>
<td>Injection-related cataract</td>
</tr>
<tr>
<td>IOP elevation</td>
</tr>
</tbody>
</table>

### Pre-specified APTC* Adverse Events through 2 years

<table>
<thead>
<tr>
<th>% of pts with at least one event</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of pts with at least one event</td>
</tr>
<tr>
<td>Non-fatal MI</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
</tr>
<tr>
<td>Vascular Death</td>
</tr>
<tr>
<td>Any APTC Event</td>
</tr>
</tbody>
</table>
Conclusions

- Vision gains (from baseline) at 2 years were seen in all 3 groups — half the number of injections, slightly decreased frequency of visits, and decreased amounts of laser in the 2nd year.
- Among eyes with better VA, no difference in 2-year vision outcomes were identified.
- Among eyes with worse baseline VA:
  - Aflibercept, on average, had superior 2-year VA outcomes compared with bevacizumab, although the difference was diminished.
  - The VA difference between aflibercept and ranibizumab that was noted at 1 year had decreased at 2 years and was no longer statistically significant.

(The source of the data is from the DRCR.net, but the analyses, content and conclusions presented have not been reviewed or approved by DRCR.net.)

Conclusions

- All 3 agents reduce OCT thickness but bevacizumab appears to be less effective than aflibercept and ranibizumab.
- The implication of the increased rate of APTC events with ranibizumab found in the current study is uncertain due to inconsistency with prior trials, warranting continued evaluation.

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 by year 2.
- Lucentis is cheaper than Eylea ($1150 vs. $2000).
- If quiet, PRN ok - recurrence less risky as in AMD.
- Case by case basis – cost and insurance a factor.
- Avastin may be “good enough.”

Ranibizumab for DME: Early and Long Term Responses

- Protocol I: EARLY Analysis
- ~40% of patients had suboptimal early responses (< 5 letter) and 40% had pronounced early responses (>10 letter) at 12 weeks with ranibizumab +/- laser.
- Eyes with suboptimal early visual response by 12 weeks showed poorer long term visual outcomes than eyes with pronounced early response (mean 3.0 vs. 13.8 letters at 156 weeks).


Ranibizumab for DME: Early and Long Term Responses

- Of the 40% with poor responses early, 28% did get some additional improvement over time.
- Need to personalize Rx.
- Consider Steroid use in poor responders.
- Still those in Ranibizumab group with deferred laser had best results compared to Ranibizumab plus prompt laser and Triamcinolone plus laser with deferred Ranibizumab — Protocol I.

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.
- DRIL - the horizontal extent for which boundaries between the ganglion cell –inner plexiform, inner nuclear and outer nuclear layer could not be identified within the central 3 mm.

OCT

20/70 rapidly improved to 20/30 in 2 injections

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

• Ellipsoid layer disruption

20/400 to 20/160 with 5 injections

• Ellipsoid layer disruption and DRIL

20/400 to 20/160 with 8 injections

• Ellipsoid layer disruption and DRIL

20/400 to 20/150 with 5 injections
**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 and reverses ischemia while treating DME
- Low risk of vision loss from DR while on therapy
- Highly effective for NV – compliance more critical
- Long term sustained benefit – injection burden seems to decrease over time
- Very low risk of complications (ATE, endophthalmitis)

**Other treatments for Macular Edema Vitrectomy**
- Diffuse macular edema caused by posterior hyaloid thickening
- Leakage results from direct vitreoretinal traction
- OCT demonstrates elevation of the fovea
- DRCR Protocol D – after vitrectomy for DME/VMT – edema reduced in most eyes. 28-49% Va improvement, 13-31% worse Va
- Several smaller studies have shown variable visual improvement

**Vitreomacular Traction and Macular Edema**

**When to use steroids**

1. Diffuse DME with no anatomic response to anti-VEGF – suspect inflammatory role
2. Vitrectomized eye requiring very frequent anti-VEGF therapy – implants work best
3. Prior to vitrectomy for ERM/VMT with diffuse DME
4. Post cataract surgery CME/DME – usually cystoid in pattern to suggest inflammatory cause

**Intravitreal Triamcinolone for DME**

- DRCR Protocol B1– focal/grid more effective for DME with fewer side effects than 1 mg or 4 mg IVTA
- Short term effect, but can give an inexpensive trial to see if inflammatory mediated DME would improve – would use lower dose 1 mg
Ozurdex for DME

- Dexamethasone implant – office injection
- 3 year study for DME (MEAD study)
- Evaluated q 3 months but could have injections 6 months apart
- Mean 4 treatments in 3 years
- Study 1: 21% vs sham 12% gain ≥ 3 lines
- Study 2: 18% vs sham 10% gain ≥ 3 lines

Ozurdex for DME

- Approved for DME 6/30/2014
- Main risk is 28% incidence of IOP increase ≥ 10 mm Hg and 68% cataract formation
- 42% needed IOP lowering therapy
- Contraindicated in patients with torn or ruptured posterior capsule – anterior chamber migration and corneal edema
- Contraindicated in patients with significant glaucoma (c/d >0.8)
- Glaucoma surgery usually not needed. IOP normalizes by 6 months

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

Is focal laser still of value?

Considerations

- Bottom line - It works!
- Non central edema, focal edema
- MA's surrounded by circinate lipid
- Central edema with leaking MA's peripheral
- Good vision and good perfusion, mild-mod NPDR
- Use modified focal/grid treatment
- Micropulse laser studies ongoing - unclear
Future options

- Refillable implantable ocular drug pump (Replenish, Inc, Pasadena, CA)
- Refillable drug port delivery (Genentech and ForSight Vision4)

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

Future options: AKB-9778

- Phase 2 TIME-2 study: 3 month safety/efficacy study of daily subcu injections with and without monthly Intravit Ranibizumab
- % achieving a ≥ 2 step reduction in DRSS
  - 8.8% Ranibizumab alone
  - 10% AKB-9778 alone
  - 11.4% Ranibizumab/AKB-9778 group
  - AKB-9778 had an effect on fellow eye

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 – testing an Ang-2 antibody: BOULEVARD study at VRS
- REGENERON trial forthcoming to compare Eylea alone with Eylea plus an antibody to Ang-2
**DRCR.net Protocol S**

**PRP vs. Ranibizumab for PDR**

- Summary of Ranibizumab results vs. PRP:
  - Ranibizumab had:
    - Change in VA from baseline no worse than PRP (non-inferiority trial)
    - Superior mean VA over the course of 2 yrs
    - Better mean VF outcomes
    - Decreased need for vitrectomies
    - Decreased development of central DME
    - PRP rarely given for failure or futility of ranibizumab

**Potential Impact of DME presence when treating PDR**

- Presence of DME may influence the benefit of Ranibizumab 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
- 6 monthly initial injections, mean number of injections was about 50% less in year 2
- Long term impact: unknown - A hybrid approach is likely the safest

**DRCR.net Protocol S**

**Conclusions**

- PRP has been effective for 40 years and remains an effective therapy today
- Ranibizumab is an effective alternative to PRP for at least 2 years
- Ranibizumab may be first choice when DME is present
- No substantial safety concerns for at least 2 years – need longer term data
- No reason to believe other anti-VEGF drugs wouldn’t also be effective

**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
- 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 WT, Bressler NM, et al. AJO 2016; 170:206-213

**Cost**

- First year drug cost alone:
  - Ranibizumab ~ $13,800 1st year
  - Aflibercept ~ $18000-$24000
  - Bevacizumab ~ $900
- Frequent exams
- Benefit:
  - Excellent drying of macula
  - VA improvement 7-11 letters

**DRCR.net Protocol S: My take**

- Individualize approach: what the patient wants, systemic status, compliance ability, other eye, presence of DME, degree of retinopathy, vision
- Anti-VEGF for DME/PDR
- Also prefer anti-VEGF for aggressive PDR without edema to quiet down first
- Gradually integrate PRP and may require less intense PRP
- Often use at least one injection prior to PRP to try to prevent DME progression even in cases where long term treatment not possible
21 y.o. female IDDM x 16 yrs.

Other helpful uses of anti-VEGF therapy in DR
Leaking MA’s without edema with need for cataract surgery – often can prevent worsening – (increased risk of central DME after CE shown in DRCR Protocol Q)
Pre-Vitrectomy surgery for PDR – reduces intraoperative and postoperative bleeding, shortens surgery
NVI/NVG – highly effective to calm eye down for glaucoma surgery and easier PRP

When is anti-VEGF not appropriate
Poor compliance
Sick patients
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

What is the role of Vitrectomy for DR
- Dense or recurring Vitreous hemorrhage –
  - hemorrhage often due to ongoing vitreous traction
  - Anti-VEGF of limited benefit in dense VH, but useful as an adjunct preoperatively
  - More immediate vision needs
- Macular subhyaloid hemorrhage
- TRD
- ERM/VMT and DME
Avastin (1 day prior) followed with vitrectomy/PRP

Summary

- Management of diabetic retinopathy as it develops
  - Careful screening of patients at risk – systemic control
  - Anti-VEGF therapy first line for central/diffuse edema. Focal laser for focal non-central DME
  - Try steroid implants for refractory cases
  - Anti-VEGF (often followed with gradual PRP for proliferative retinopathy)
  - Vitrectomy (often with preoperative anti-VEGF) for advanced complications

Thanks for attending!!!