Diabetic Macular Edema Achieving Better Early Diagnosis and Control

George Kranias, MD
13/6/16
The prevalence of diabetes among US adults increased from 4.9% in 1990 to 7.3% in 2000, an increase of 49%.

The worldwide prevalence of diabetes will more than double between 2000 and 2030.
Diabetic Retinopathy

The most frequent late complications of diabetes:

* ~ 100% patients with type 1 diabetes.
* ~ 60% of patients with Type 2 diabetes.

Patients ≥ 40 years

* 40.3% diabetic retinopathy
* 8.2% vision-threatening retinopathy
Diabetic Macular Edema

Incidence: 5-10%

DME Risk factors:
- Duration of DM (33% > 20 years)
- Level of HbAIC
- Type II patient age
- Blood pressure (diastolic)
- Blood lipid levels
- Diabetic Nephropathy
- Level of retinopathy (3% NPDR – 71% PDR)
Retina Evaluation: Color photos, OCT, and Fluorescein Angiogram
Treatment of Diabetic Macular Edema (DME)

- Intravitreal VEGF blockade
- Intravitreal corticosteroids
- Focal macular laser photocoagulation
- Pars plana vitrectomy
Prior to treatment evaluate with FANG and OCT to r/o macular ischemia. Correction of systemic factors.
Intravitreal VEGF Blockade
First-line Treatment for Center-involved DME

- Strong evidence of efficacy
  - Phase 3 clinical trials (FDA approved)
    - Ranibizumab
    - Aflibercept
    - Bevacizumab

- Superior to laser and steroids
- Good ocular and systemic safety
Ranibizumab (Lucentis) in DME
RESOLVE (Phase II): anti-VEGF therapy demonstrated superiority to sham

<table>
<thead>
<tr>
<th>Number of injections</th>
<th>RBZ 0.3 mg (N=51)</th>
<th>RBZ 0.5 mg (N=51)</th>
<th>Sham (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>10.2 (2.5)</td>
<td>10.1 (2.6)</td>
<td>8.9 (3.5)</td>
</tr>
</tbody>
</table>

Groups A+B, full analysis set, LOCF, first VA value post-baseline was assessed at Day 8
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; SE, standard error; VEGF, vascular endothelial growth factor


Mean ± SE BCVA change from baseline to Month 1 through Month 12 (ETDRS letters)
RESTORE: anti-VEGF therapy offers an alternative to laser treatment and gains in BCVA are maintained over time.

### Mean change (± SE) in BCVA from baseline (letters)

<table>
<thead>
<tr>
<th>Month</th>
<th>Ranibizumab 0.5 mg (n=83)</th>
<th>Ranibizumab 0.5 mg + laser (n=83)</th>
<th>Laser (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>+8.0</td>
<td>+6.7</td>
<td>+6.0</td>
</tr>
<tr>
<td>Month 11</td>
<td>7.4</td>
<td>7.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Month 23</td>
<td>3.9</td>
<td>3.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Month 36</td>
<td>2.9</td>
<td>2.5</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Mean number of ranibizumab treatments declined over time, while vision gains and retinal thickness remained stable.

**Safety set (LOCF)**

Mitchell P. Data presented at ARVO, Fort Lauderdale, FL, USA, May 2012.
Patients who were initially treated with laser monotherapy and subsequently switched to ranibizumab at 24 months did not achieve equivalent VA gains at 36 months as those treated with ranibizumab from the outset.
Ranibizumab DRCR.net 5 year results/#injections

Wells JA. Data presented at ASRS 2014

**Median number of injections**

<table>
<thead>
<tr>
<th>Year</th>
<th>Ranibizumab + prompt laser</th>
<th>Ranibizumab + deferred laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Year 2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Year 3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Year 4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Year 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Baseline to 5 year visit</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>
Summary of Lucentis in DME

- Sustained VA gains for 5 years with a decreasing injection frequency
- The benefit in VA with the use of differed laser is statistically significant higher than that with prompt laser
- Well-established safety profile supported by extensive clinical trial data and real-world experience
- Restored vision increases independence and improves vision-related functions
Course

Pretreatment Baseline: Ranibizumab # 1

Month 1: Ranibizumab # 2

Month 2 Ranibizumab # 3

Month 3 Ranibizumab # 4

20/100

20/80

20/80

20/70
Course

Month 4
Ranibizumab # 5
20/70

Month 5:
Ranibizumab # 6
20/60

Month 6
Ranibizumab # 7
20/50

Month 7
?
20/40
Afiblercept in DME (Eylea)
Afiblercept
≥ 2 Step Improvement in DRSS

VIVID
- Laser: 7.5%
- 2q4: 33.3%
- 2q8: 27.7%

VISTA
- Laser: 14.3%
- 2q4: 33.8%
- 2q8: 29.1%

Proportion of Patients

n=80  n=81  n=83

P < 0.0001 2q4 vs. laser
P = 0.0006 2q8 vs. laser

n=154  n=151  n=154

P < 0.0001 2q4 vs. laser
P = 0.0017 2q8 vs. laser

DRSS: Diabetic Retinopathy Severity Score
Compared to baseline: LOCF

Kornblink JF et al. Ophthalmology, 2013; 120(10); 2013-22
Bevacizumab in DME
BOLD Study: Bevacizumab for DME

- 42 patients
- Mean change in BCVA (letters) : + 8
- Mean change in retinal thickness : 130
The BEVORDEX Study: A Randomized Clinical Trial of INT Bevacizumab versus IVT Dexamethasone for DME.

- Bevacizumab: 42 patients / DEX 46
- INT inj. q 4 weeks (mean 8.6) DEX q 6 mo (m 2.7)
- BCVA of 10 or more letters: Avastin 40% / DEX 41%
- CMT decreased: Avastin 122, DEX 187 μm
- Conclusions: both achieved similar rates of visual improvement.

Ophthalmology: December 2014
Aflibercept, Bevacizumab and Ranibizumab for Diabetic Macular Edema

The Diabetic Retinopathy Clinical Research Network

February 18, 2015
Multicenter, randomized clinical trial at 89 clinical sites in the USA

660 participants at least 18 y/o with type I (10%) and type II (90%)
Data, August 22, 2012 – August 28, 2013 (Follow-up 2 years)

Baseline injection followed by monthly injections
Laser at 24 weeks for persisted DME
Average number of injections: 10
VA gain: no clinically meaningful difference observed between the three arms.
VA gains: statistically significant difference in VA for patients with worse baseline VA

Baseline VA < 69 letters (20/50 or worse)

<table>
<thead>
<tr>
<th></th>
<th>Mean baseline BCVA (letters)</th>
</tr>
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<tbody>
<tr>
<td>Aflibercept</td>
<td>56.2</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>56.6</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>56.5</td>
</tr>
</tbody>
</table>

Aflibercept 18.9 (n = 102)
Ranibizumab 14.2 (n = 101)
Bevacizumab 11.8 (n = 102)

Wells JA, et al. NEJM 2015, epub ahead of print
OCT outcomes: bevacizumab less efficient in reducing macular edema compared with ranibizumab and aflibercept

CSFT, central subfield thickness

Wells JA, et al. NEJM 2015, epub ahead of print
Conclusion

Eylea, Avastin and Lucentis were effective and relatively safe treatments for DME.

When initial VA loss was mild, there was little difference in VA at 1 year among the 3 agents.

When initial VA loss was worse, Eylea was more effective in improving vision.
Editorial
Daniel F Martin, M.D. and Maureen M Maguire, Ph.D

Medicare Allowance Charges Each Injection

Eylea : $1,950
Lucentis : $1,200
Avastin : $ 50.00

Eylea should be considered as first line therapy patients with significant visual loss, with Avastin as the alternative given the lack of a significant difference in visual outcome between Avastin and Lucentis and the large difference in cost between the two drugs
Differences in overall VA gain between ranibizumab and aflibercept were not clinically significant.

Differences in VA gains observed between subgroups of patients treated with ranibizumab or aflibercept with worse baseline BCVA may be due to suboptimal treatment with ranibizumab 0.3 mg PRN.

Unsurpassed efficacy of ranibizumab 0.5 mg PRN has been demonstrated in clinical trials.
Macular Laser Photocoagulation

Focal DME

Diffuse DME?
Early Treatment Diabetic Retinopathy Study (ETDRS)

Reduce chance of visual loss ~ 50%
- Visual improvement only 3%
- Today with Anti-VEGF 30 – 40%

OLD LASER BURNS
Long Delay in Treatment with Anti-VEGF Agents May Result in Less VA Gain
Intravitreal Triamcinolone (IVT)*

* Not FDA approved
Intravitreal Triamcinolone (IVT)

- IVT for Refractory DME.

- Published Case Series Demonstrating Efficacy of IVT Steroids for Eyes in Which Laser Photocoagulation for DME had Failed.
Problems with Triamcinolone

- High incidences of glaucoma and cataract particularly with higher doses (4 mg).
- Inconsistent product available for off-label use.
- Pseudo-endophthalmitis.
Diabetic Macular Edema
Intravitreal Triamcinolone (IVT)

Before IVT 4 mg
20/100

1 Month later
20/50
Dexamethasone Implant
MEAD study design

Condition to treat: DME
One eye per patient (if both eyes are eligible – eye with shortest duration of DME is selected)

Randomization (1:1:1)
(Intent-to-treat population) N=1048

DEX 700 μg n=351
DEX 350 μg n=347
Sham n=350

Evaluated for retreatment every 1.5 months during the first year and then every 3 months during years 2 and 3
Retreatment was allowed every 6 months
Up to 7 treatments allowed during the 3-year study duration

Boyer SB et al. Ophthalmology 2014 Jun 4.[Epub ahead of print]
BCVA improvement ≥15 letters (ITT)

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

Mean average change in central subfield retinal thickness (ITT)

Mean average decrease from baseline in central subfield retinal thickness was significantly greater with DEX compared with sham.

*P<0.001 versus sham

Boyer SB et al. Ophthalmology 2014 Jun 4.[Epub ahead of print]
Dexamethasone for DME

- **Safety through year 3:**
  - Cataract: 67% in DEX vs 20% in sham
  - IOP elevation: 33% in DEX
  - Glaucoma surgery: 0.6% in DEX

- FDA first approved for DME in pseudophakic eyes or phakic eyes that are scheduled for cataract surgery

- Updated Sept 2014 to include all patients
Why Anti-VEGF Rx does not always work?

- Predominantly VEGF-mediated
- Not predominantly VEGF-mediated
- Both VEGF and inflammatory-mediated
The Role of Vitrectomy in the Management of Diabetic Macular Edema

Catherine Bene, M.D.
George Kranias, M.D.
Mathew Lipman, M.D.

Presented at the AAO, Atlanta 1992
Prior to cataract surgery

9 months S/P cataract sx
DIFFUSED MACULAR EDEMA WITH ATTACHED POSTERIOR HYALOID
Why Should Vitrectomy Works?

- Eliminates the vitreous traction which induces vascular permeability
- Increases oxygenation of the retina
7 ενέσεις anti-VEGF !
Video.
9/3/2011  OD: 1,5/10  OS: 8/10
12/5/2016 OD: 3/10 OS: 10/10
Stepwise Approach to DME

* Correct systemic factors
* Focal DME – Grid laser.
* Defused DME
  - AVASTIN 3-6 injections.
  - EYLEA or LUCENTIS 3 or more. For suboptimal response.
  - IVTA for insufficient response
  - OZURTEX every 4-6 months.
  - Iluvien every 2-3 years
  - Vitrectomy
  - Poor compliance: consider Ozurtext.

GOOD LUCK

ΕΥΧΑΡΙΣΤΩ