Current Treatment of Diabetic Macular Edema: 

A New Paradigm

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Early Treatment Diabetic Retinopathy Study (ETDRS)

Early Treatment Diabetic Retinopathy Study (ETDRS)

- Eyes with clinically significant diabetic macular edema benefited from focal laser treatment.

- Clinically significant diabetic macular edema was defined as retinal thickening that involves or threatens the center of the macula (fovea).
Clinically Significant Diabetic Macular Edema Criteria

- Any retinal thickening within 500μ of the center of the fovea w/wo exudate or hemorrhages.
- Any retinal thickening from 500μ to 1DD from fovea, if greater than 1DA in size.
- Exudate/heme without retinal thickening → NOT criteria
- Retinal thickening >1DD from fovea → NOT criteria
**ETDRS Results at 3 Years**

<table>
<thead>
<tr>
<th>Patients with Clinically Significant Macular Edema</th>
<th>Immediate Focal Laser</th>
<th>Deferred Focal Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of 15 or more letters on the ETDRS eye chart (loss of 3 or more lines)</td>
<td>13%</td>
<td>31%</td>
</tr>
</tbody>
</table>

- Eye with no clinically significant macular edema had low rates of vision loss in both immediate and deferred laser groups.
**ETDRS Results at 3 Years**

<table>
<thead>
<tr>
<th>Patients with Visual Acuity worse than 20/40</th>
<th>Immediate Focal Laser</th>
<th>Deferred Focal Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain of 6 or more letters on the ETDRS eye chart (more than 1 line of gain)</td>
<td>40%</td>
<td>22%</td>
</tr>
</tbody>
</table>

- **Visual improvement uncommon in eyes with good visual acuity (20/40 or better vision) in both groups.**
Early Treatment Diabetic Retinopathy Study (ETDRS)

- As a result of the ETDRS, focal laser treatment has been the standard of care for diabetic macular edema for almost 25 years.
• 2006 – S.G. 55 y/o male
• 20/20 OD & 20/25 OS
• Clinically significant macular edema OS
• Focal laser performed OU
• 2011 – S.G. 60 y/o male
• 20/20 OD & 20/25 OS
• No macular edema OU
- 2009 – A.S. 35 y/o female
- Present with VA 20/30 OS 07/2009
- FA OS shows severe diffuse leakage
- Current VA 20/25 OS
• 76 y/o male B.S.
• s/p multiple focal laser treatments OS 1997-1998
• Current VA 20/400 OS
• Fundus OS – CNV 2° to laser scar
Paradigm Shift in Treatment of Diabetic Macular Edema

- Intravitreal Kenalog (triamcinolone) for DME introduced in 2001.
- 25-30% incidence of glaucoma (1% need glaucoma surgery).
- Increased incidence of cataract.
- Lack of control group for many years.
Paradigm Shift in Treatment of Diabetic Macular Edema

The Diabetic Retinopathy Clinical Research Network

A Randomized Trial Comparing Intravitreal Triamcinolone to Focal/Grid Photocoagulation for Diabetic Macular Edema

Sponsored by the National Eye Institute, National Institutes of Health, U.S. Department of Health and Human Services.
Primary Study Objective

➢ To compare the efficacy and safety of preservative-free IVT (1 mg or 4 mg) with focal/grid laser
DRCR.net Study Design

- Multicenter, randomized clinical trial
- Three treatment groups
  - Focal/grid laser
  - 1 mg IVT
  - 4 mg IVT
- Duration of follow-up: 3 years
- Follow-up visits and re-treatment as often as every 4 months
Mean Visual Acuity Over 3 Years in All Eyes

- Laser (Alleyes)
- 1 mg (Alleyes)
- 4 mg (Alleyes)

Visual Acuity Score
- 20/32
- 20/40
- 20/50
- 20/63
- 20/80

Months
- 0
- 4
- 8
- 12
- 16
- 20
- 24
- 28
- 32
- 36
Median OCT Central Subfield Thickness in Laser and IVT Treated Eyes

Central Subfield Thickness (microns)

Months

Laser
1 mg
4 mg
Conclusion

- By 2 years, there was a greater VA benefit and fewer side effects (IOP and cataract) in laser group compared with the IVT groups
- 3 year results similar to the 2 year results
- OCT results mirrored VA results
- Focal/grid currently still most effective treatment for patients with DME and is the benchmark against which other new treatments for DME should be compared in clinical trials for DME
- 58 y/o male D.P.
- OS – Focal Laser 4/16/08
- 12/29/10 – OS 20/200
• D.P.
• OS – Intravitreal Kenalog Injection 1/12/11
• 2/16/11 – OS 20/100
• Minimal macular edema OS
• D.P.
• OS – Intravitreal Kenalog Injection 1/12/11
• 3/9/11 – OS 20/100
• Increasing macular edema OS
Paradigm Shift in Treatment of Diabetic Macular Edema

- Intravitreal Avastin (bevacizumab) for DME introduced in 2006.
- Clinical studies showed Avastin may decrease macular edema, but no good control group.
Paradigm Shift in Treatment of Diabetic Macular Edema

The Diabetic Retinopathy Clinical Research Network

Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817
Primary Study Objective

To compare the efficacy of the following four treatment modalities:

- Sham + prompt (within 1 week) focal/grid laser
- Intravitreal ranibizumab + prompt (within 1 week) focal/grid laser
- Intravitreal ranibizumab + focal/grid laser deferred (for at least 24 weeks or more)
- Intravitreal triamcinolone + prompt (within 1 week) focal/grid laser
DRCR.net Study Design

- Multicenter, randomized clinical trial
- Definite retinal thickening due to diabetic macular edema involving the center of the macula
- Four treatment groups:
  - Sham + prompt laser
  - Ranibizumab + prompt laser
  - Ranibizumab + deferred laser
  - Triamcinolone + prompt laser
- Ranibizumab given monthly until stabilization or lack of further improvement is noted
- Duration of follow-up: 2 years
Results

- N = 854 eyes randomized (691 Participants)

- In the Ranibizumab + deferred laser group, 70% of patients did not have any laser treatment during year one of the study.
Mean Change in Visual Acuity* at Follow-up Visits

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

$P$-values for difference in mean change in visual acuity from sham+prompt laser at the 52-week visit: ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; and triamcinolone+prompt laser=0.31.
≥15 Letter Improvement in Visual Acuity at Follow-up Visits

Visit Week

P values for the difference in proportion of 15 letter improvement in visual acuity from sham+prompt laser at the 52-week visit: ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; triamcinolone+prompt laser = 0.07

N = 799 (52 weeks)
N = 484 (104 weeks)
Mean Change in Central Subfield Thickening at Follow-up Visits

P values are for the difference in mean change in OCT CSF retinal thickness from sham+prompt laser at the 52-week visit:
- ranibizumab+prompt laser <0.001,
- ranibizumab+deferred laser <0.001,
- triamcinolone+prompt laser <0.001.
# Major Ocular Adverse Events During 2-Years of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Sham + Prompt Laser N = 293</th>
<th>Ranibizumab + Prompt Laser N = 187</th>
<th>Ranibizumab + Deferred Laser N = 188</th>
<th>Triamcinolone + Prompt Laser N = 186</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of injections</strong></td>
<td></td>
<td>1833</td>
<td>2140</td>
<td>685</td>
</tr>
<tr>
<td><strong>Endophthalmitis</strong></td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Pseudoendophthalmitis†</strong></td>
<td>1(&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Ocular vascular event‡</strong></td>
<td>1 (&lt;1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td><strong>Retinal detachment§</strong></td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vitrectomy</strong></td>
<td>15 (5%)</td>
<td>4 (2%)</td>
<td>7 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><strong>Vitreous Hemorrhage</strong></td>
<td>27 (9%)</td>
<td>6 (3%)</td>
<td>8 (4%)</td>
<td>7 (4%)</td>
</tr>
</tbody>
</table>

*One case unrelated to study drug injection (following cataract extraction) in the sham+prompt laser group; 1 case related to study drug injection and 1 case unrelated to injection (following cataract surgery) in the ranibizumab+prompt laser group; 2 cases related to study drug injection in the ranibizumab+deferred laser group. The 3 cases related to study drug injection in the ranibizumab groups are 0.08% of ranibizumab study drug injections given.

† One case unrelated to the study drug injection (vitreous opacity with hypopyon) and one case related to study drug injection in the triamcinolone group.

‡ Includes 2 central retinal vein occlusions and 4 branch retinal vein occlusions.

§Includes 1 traction retinal detachment with proliferative diabetic retinopathy and prior panretinal photocoagulation at baseline.
# Elevated Intraocular Pressure/Glaucoma During 2-Years of Follow-up

<table>
<thead>
<tr>
<th>Elevated Intraocular Pressure/Glaucoma</th>
<th>Sham +Prompt Laser N = 293</th>
<th>Ranibizumab +Prompt Laser N = 187</th>
<th>Ranibizumab +Deferred Laser N = 188</th>
<th>Triamcinolone +Prompt Laser N = 186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase ≥10 mmHg from baseline</td>
<td>8%</td>
<td>9%</td>
<td>6%</td>
<td>42%</td>
</tr>
<tr>
<td>IOP ≥30 mmHg</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
<td>27%</td>
</tr>
<tr>
<td>Initiation of IOP-lowering meds at any visit*</td>
<td>5%</td>
<td>5%</td>
<td>3%</td>
<td>28%</td>
</tr>
<tr>
<td>*Excludes eyes with IOP lowering medications at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of eyes meeting ≥1 of the above</strong></td>
<td>11%</td>
<td>11%</td>
<td>7%</td>
<td>50%</td>
</tr>
<tr>
<td>Glaucoma surgery**</td>
<td>&lt;1%</td>
<td>1%</td>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Includes 2 filter and 2 ciliary body destruction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Cataract Surgery During 2-Years of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Sham +Prompt Laser</th>
<th>Ranibizumab +Prompt Laser</th>
<th>Ranibizumab +Deferred Laser</th>
<th>Triamcinolone +Prompt Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phakic at baseline</strong></td>
<td>N = 192</td>
<td>N = 131</td>
<td>N = 134</td>
<td>N = 124</td>
</tr>
<tr>
<td><strong>Eyes that had cataract surgery</strong></td>
<td>12%</td>
<td>12%</td>
<td>13%</td>
<td>55%</td>
</tr>
</tbody>
</table>
## Cardiovascular or Cerebrovascular Events According to Antiplatelet Trialists’ Collaboration through 2-Years

<table>
<thead>
<tr>
<th>Event</th>
<th>Sham $^\ddagger$ N$^*$ = 130</th>
<th>Ranibizumab N$^*$ = 375</th>
<th>Triamcinolone N$^*$ = 186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-fatal cerebrovascular accident-ischemic or hemorrhagic (or unknown)</td>
<td>6%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Vascular death (from any potential vascular or unknown cause$^\ddagger$)</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Any APTC event</td>
<td>12%</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* N=Number of Study Participants. Study participants with 2 study eyes are assigned to the non-sham group. Multiple events within a study participant are only counted once per event.

$^\ddagger$One participant had a non-fatal myocardial infarction and a non-fatal stroke (only counted once in the any cardiovascular event row)

$^\ddagger$Four of the vascular deaths in the sham group, 1 of the vascular deaths in the ranibizumab group, and 1 of the vascular deaths in the triamcinolone group were from an unknown cause.
Study Summary

- Intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser had superior VA and OCT outcomes compared with triamcinolone + prompt laser and focal/grid laser treatment alone.

- Results were similar whether focal/grid laser was given starting with the first injection or it was deferred >24 weeks.

- In the Ranibizumab + deferred laser group, 70% of patients did not have any laser treatment during year one of the study.
• 87 y/o male A.S.
• OS – Focal Laser 4/23/07, 8/27/07
• 8/31/10 – OS 20/50
• A.S.
• OS – Avastin Injxn 9/10/10, 11/2/10, 12/21/10
• 2/28/11 – OS 20/25
• No macular edema OS
• 47 y/o female E.S.
• 8/27/10 – OD CF 4 ft
• No prior treatment
• E.S.
• OS – Avastin Injxn 9/3/10, 10/11/10, 1/3/11, 2/7/11
• 3/8/11 – OS 20/200
• Minimal macular edema OS
Current Treatment of Diabetic Macular Edema

- Focal laser is still viable and effective treatment for clinically significant macular edema not involving the center of the macula (avoids risk of endophthalmitis and retinal detachment).
- For center involving edema, bevacizumab (Avastin) given monthly until stabilization or lack of further improvement is noted (ranibizumab not yet approved by FDA for DME).
- For patients unresponsive or partially responsive to bevacizumab or ranibizumab, focal laser treatment &/or intravitreal triamcinolone may be helpful.