Diabetic Macular Edema: Management in the Era of Ever-Increasing Treatment Options

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Diabetic Macular Edema (DME)

Diabetes, DR, and DME

Newer approved treatment modalities

Preferred “first line” treatment and shift in paradigm away from laser photocoagulation

Combination treatment

Surgery
## Incidence of Diabetes in U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage of Adults</th>
<th>Number of Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>11.3%</td>
<td>26 million</td>
</tr>
<tr>
<td>2020</td>
<td>15%</td>
<td>39 million</td>
</tr>
<tr>
<td>2050</td>
<td>33%</td>
<td>???</td>
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Retinal Microvascular Disease

DME results from damage to retinal blood vessels from angiogenesis and inflammation leading to vascular permeability and increase central macular thickening.
**DME** accounts for **75%** of vision loss from diabetic retinopathy
Important for Patients to be Engaged in their Health!

**Better management of blood glucose** diminishes likelihood of blindness (DCCT, UKPDS)

Insulin pumps and modern biphasic insulin units help with **tight control**

**Diet and exercise** to maintain a healthy weight

**No** smoking

**HemoglobinA1c**

Control **blood pressure**

Regular **eye exams**
Major Risk Factors for DME

Hyperglycemia, hypertension, and hyperlipidemia—all common features of poorly controlled diabetes
Other Potential Risk Factors for DME

- Diabetic nephropathy
- Anemia
- Sleep apnea
- Glitazone usage (Actos, Avandia)
- Pregnancy
Treatment of DME

for decades:

Encouraging optimal *metabolic control*

**Focal/grid laser** photocoagulation according to the guidelines established by (ETDRS) in 1985 – Laser reduced moderate vision loss by 50% in patients with CSME

ETDRS- only 15% gained 3 lines of vision with Laser.
ETDRS definition of CSME no longer the "gold standard" for DME
DME

Center involved

Not center involved
Focal laser treating non-foveal involved macular edema

Effective, initial treatment for DME that does not have foveal involvement, i.e., non-center involving DME
Paradigm Shift

Increasing evidence of the effectiveness of pharmacologic therapies.
Pharmacologic treatment:

**Anti-VEGF** (vascular endothelial growth factor)

**Corticosteroids**
Anti-VEGF Therapy

Ranibizumab (Lucentis) + prompt or deferred laser superior to laser alone with center-involved DME
Ranibizumab

Antibody fragment—all isoforms of VEGF-A

RISE & RIDE Trials

RISE 44.8% “3 line gainers”
RIDE 33.6% “3 line gainers”
Ranibizumab

RISE & RIDE Ranibizumab

*first line Rx for center involved DME-
improved vision through 36 months*
<table>
<thead>
<tr>
<th>RISE/RIDE</th>
<th>ETDRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% of patients gained 3 lines with <strong>Ranibizumab</strong></td>
<td>15% of patients gained 3 lines with <strong>Laser</strong></td>
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</tbody>
</table>
SS 60yo 20/400

Ranibizumab

Avastin/focal laser/Lucentis/focal laser/Lucentis

21 months

20/400

20/40
Bevacizumab

Full length antibody—all isoforms of VEGF-A
Off label for DME—widespread availability and low cost

*BOLT study* small number of patients with center-involved DME

32% gain 3 lines in 2 years
Afibercept

Recombinant fusion protein- activity against VEGF-A, VEGF-B, and placental growth factor

August 2014

VIVID/VISTA trials

33-40% gain 3 lines of vision in 2 years
“Head to head” Comparisons

**Ranibizumab (Lucentis)**
RISE/RIDE
40% gain in 3 lines in 2 years

**Aflibercept (Eylea)**
VIVID/VISTA q4wks then q8wks
33-40% gain in 3 lines in 2 years

**Bevacizumab (Avastin)**
BOLT trial (small study-80 patients)
32% gain in 3 lines in 2 years

DRCR.net Protocol T

Pivotal Trial for DME
Good News!

**REDUCTION** in treatment burden with injections over time (*DRCR.net*)...data through year 3—only 2-4 injections out of possible 13 were required! Anticipated that data through year 5 will demonstrate similar low treatment burden.

**BONUS** of decreasing the overall DR over time!

(*RISE/RIDE studies*) ...time of progression to PDR in treated eyes compared to sham (1% vs 12% to PDR) and 25% required no injections after 36 months (maybe related to DR improving over time!).
Anti-VEGF Agents

**Safe** in diabetics with no significant increase in BP, hemorrhagic events, or CVA.

May **modify long term outlook** for our patients with DME, hopefully resulting in **fewer injections** once we have controlled the disease.
Intravitreal VEGF Blockade

Most **efficacious** and **safest** treatment for center-involved DME

**Should be first-line treatment for center-involved DME**

M.B.
63 yo
DME s/p PPV OU

Lucentis x5, Eylea x3 OD

1/14 20/60 5/14 20/40+1 8/14 20/40+1 11/14 20/25+2

20/25+
66y.o. DMx2yrs., struggling with VA x2 yrs., DME/PDR/marked ischemia OU

1/11 Avastin/PRP

20/80-2

1/11 Avastin/PRP

6/400

1/11 Avastin/PRP

Avastin/focal laser

20/3

Avastin/focal laser

20/100
Add’l Focal laser+PRP OU Avastin

NO further Rx since 3/13

NO further Rx since 8/12

NO further RX
Corticosteroids

• Longer lasting and safer steroids with recent advances in pharmacotherapy
• Increasing role in treatment of DME
• **Unlikely to replace anti-VEGF Rx** as a first line agent
• But may add effective weapons in our armamentarium
Triamcinolone acetonide (TA)

Has been used off-label for DME

Use has declined as anti-VEGF Rx has increased, in part, due to risks of cataract and IOP elevation
Bioerodible dexamethasone intravitreal implant

Ozurdex
for DME (MEAD Study)
.... 22% 3 line gainer 2 yrs

Figure 1. Ozurdex has a <0.4-mm diameter, the inside dimension of a 22-gauge needle.
Sustained-release nonbioerodible Fluocinolone acetonide

*Fame Study* showing benefits over 3 years for DME but increased risks of cataract and IOP elevation – *Iluvien* (Alimera)

29% 3 line gainer over 2 years
Combination Therapy for DME

All “3 line gainers”!
Statistically achieve significant improvement of 15 letters (3 lines)
vs sham
# Combination Therapy for DME

<table>
<thead>
<tr>
<th>3 line gainers</th>
<th>Other side of the story</th>
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<tr>
<td><strong>Ranibizunab</strong> (Lucentis)</td>
<td>60% not 3 line gainers</td>
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<tr>
<td>40% 2yrs. (RISE/RIDE)</td>
<td></td>
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<tr>
<td><strong>Aflibercept</strong> (Eylea)</td>
<td>60-66% not 3 line gainers</td>
</tr>
<tr>
<td>33-40% 2 yrs. (VIVID/VISTA)</td>
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</tr>
<tr>
<td><strong>Bevacizumab</strong> (Avastin)</td>
<td>68% not 3 line gainers</td>
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<tr>
<td>32% 2 yrs. (BOLT)</td>
<td></td>
</tr>
<tr>
<td><strong>Dexametasone</strong> (Ozurdex)</td>
<td>78% not 3 line gainers</td>
</tr>
<tr>
<td>22% 2 yrs. (MEAD)</td>
<td></td>
</tr>
<tr>
<td><strong>Fluocinolone acetonide</strong> (Iluvien)</td>
<td>71% not 3 line gainers</td>
</tr>
<tr>
<td>29% 2 yrs. (FAME)</td>
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Rationale for Combination Rx

Despite several medications now approved for treatment of DME more than 50% of the time 3 line gain is not achieved with any one of them!
Next Step if Monotherapy not Optimal

Switching

or

Adding
DME/Multifactorial Disease

Not purely *VEGF driven*

*Inflammatory* cytokines and chemokines, e.g. interleukins 6 and 8 – not affected by anti-VEGF but susceptible to steroids
Inflammation plays a role as well in diabetic retinopathy and macular edema!
Corticosteroids affect multiple mediators of inflammation, including VEGF
Combination Therapy

• Combination Rx may be helpful for patients who are unresponsive or have a suboptimal response to anti-VEGF agents.

• Combination Rx works by targeting multiple factors in the inflammatory cascade.

• Combination Rx an option for “difficult to treat” patients.
PB 68y.o. 1/12 DME OD only

Avastin x11, Focal laser x1, IVTA x1, Lucentis x17, Ozurdex x1
Vitrectomy Surgery

Its role in management of DME not clear-
limited evidence combining vitrectomy with intravitreal anti-VEGF agents, corticosteroids, and/or laser photocoagulation to Rx refractory DME-small non-randomized uncontrolled case
Vitrectomy Surgery

Effectively reduces retinal thickness but **visual outcomes less consistent!**
Summary of Current Management Strategies

• Optimal control of blood sugar, blood pressure, serum lipids, and body mass index
• Medications, e.g. oral glitazones assoc. DME
• Non-center involved DME- ETDRS laser
• Center-involved DME: paradigm shift from focal/grid laser to intravitreal anti-VEGF as first-line treatment
• DME refractory to anti-VEGF Rx, intravitreal corticosteroids may be added
• PPV/membranectomy with center-involved DME and vitreomacular traction or epiretinal membrane, when pharmacoRx unsuccessful
Finally

- Data from DRCRnet protocol T should better define differences among various anti-VEGF agents.

- More data needed to better define the ideal timing of various treatments, as well as the potential for combination Rx regimens to achieve better clinical outcomes and/or reduced treatment burden compared with monotherapy.