Evolution of Treatment in DME

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Novartis Symposium
AOS 2019

DME

➢ Pathophysiology of the disease
Role of VEGF in the pathophysiology

DIABETES

CHRONIC SUBCLINICAL INFLAMMATION

MICROVASCULAR DAMAGE

CHRONIC HYPERGLYCEMIA

METABOLIC RESPONSE

BREAKDOWN OF THE INNER BLOOD-RETINAL BARRIER

ISCHEMIA

LEAKAGE

VEGF

NEOVASCULARIZATION

MACULAR EDEMA

Boyer DS, ADA 71st Scientific sessions, San Diego, California, 2011

DIAGNOSIS OF DME

OCT is the Tool

Fluorescein Angiography is rarely needed
Normal OCT Appearance
Medical Management of DME
Laser Photocoagulation
Steroids Injections
ANTI VEGF Injections
Laser photocoagulation

- **Laser photocoagulation**

  - It was the standard treatment between 1985 and 2010 — as it helps to slow fluid leakage and **reduces** the amount of fluid in the retina (Macular Edema).  
  - **Stabilizes** / prevents further vision loss.  
  - Recommended for *Clinically significant Macular Edema* without centre involvement or with centre involvement in mild cases.

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DME: diabetic macular edema

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First Publications

1985

ETDRS study

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Arch Ophthalmol 1985; 103:1796–806
EDTRS classification

- The classification was mainly based on clinical diagnosis to detect thickening

- FA was only useful to detect the type of leakage,

- whether it was focal or diffuse to define type of laser being used.

- For focal edema, focal laser was applied to the site of leakage,

- whereas in diffuse type a grid laser was performed.

CSME Criteria for Laser treatment of DME : ETDRS 1
CSME Criteria for Laser treatment of DME : ETDRS 2

![Image of CLINICALLY SIGNIFICANT MACULAR EDEMA](image1)

**Figure 5-8**: CSME. Hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina. (Courtesy of the ETDRS.)

CSME Criteria for Laser treatment of DME : ETDRS 3

![Image of CLINICALLY SIGNIFICANT MACULAR EDEMA](image2)

**Figure 5-9**: CSME. A zone of thickening larger than 1 disc area if located within 1 disc diameter of the center of the macula. (Courtesy of the ETDRS.)
Response to Laser: Focal vs Diffuse

- The ETDRS found NO difference in the response to laser photocoagulation when comparing eyes with focal leakage or eyes with ‘intermediate to diffuse’

- Similar results with photocoagulation were reported by Blankenship et al in another large scale study.

Why was Laser beneficial? less drop in Vision

- 50% reduction of patients who develop moderate to severe visual loss

- 2X number of patients who can reach 6/12

- Doing Laser for DME cases was considered beneficial?
Results of the ETDRS Trial

Limitations and complications of laser

- Complications\(^4,5\)
  - Foveal burn
  - Central visual field defects
  - Colour vision abnormalities
  - Retinal fibrosis
  - Spread of laser scars
Role of VEGF in the pathophysiology

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Medical Management of DME

Laser Photocoagulation

Steroids Injections

ANTI VEGF Injections
Protocol B: IVTA vs Laser study *

Retreatment no more often than every 4 months

Results of DRCR PROTOCOL B: IVTA vs LASER

VA change in 3 years
Conclusions: **Steroids Injection for DME**

- There was no **long-term** benefit of intravitreal triamcinolone relative to focal/grid photocoagulation for patients with DME.
- Rather, visual acuity outcomes **slightly favored the laser group** compared with either of the two triamcinolone groups.

**IOP elevation in Steroid injections Protocol B**

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>TA 1 mg</th>
<th>TA 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 mmHg rise in IOP @ anytime in 3 yrs</td>
<td>4 %</td>
<td>18 %</td>
<td>33 %</td>
</tr>
<tr>
<td>IOP&gt;30 mmHg</td>
<td>1 %</td>
<td>9 %</td>
<td><strong>21 %</strong></td>
</tr>
<tr>
<td>% on IOP lowering drugs @ end of 3 yrs</td>
<td>3 %</td>
<td>2 %</td>
<td><strong>12 %</strong></td>
</tr>
<tr>
<td>Glaucoma procedure</td>
<td>0 %</td>
<td>0 %</td>
<td>1.5 %</td>
</tr>
</tbody>
</table>
Cataract in Steroid injections Protocol I

Cumulative Probability of Cataract Surgery

Intravitreal Steroid Sustained-release Implants

Ozurdex Implant
Ozurdex (Allergan)

MEAD study: 3 years / DEX implant

1048 patients enrolled (1 eye/patient) and randomized to study treatment

<table>
<thead>
<tr>
<th>DEX implant</th>
<th>DEX implant</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7 mg (N = 351)</td>
<td>0.35 mg (N = 347)</td>
<td>(N = 350)</td>
</tr>
</tbody>
</table>

Retreatment no more often than every 6 months
MEAD study (whole study)

Mean change VA

MEAD study (Pseudophakic only)

Mean change VA: Pseudophakic
Cataract surgery incidence: MEAD / DEX Implant

- DEX 0.7 mg → 59.2%
- DEX 0.35 mg → 52.3%
- Sham → 7.2%

Steroids: Why consider it?

- Cheap (but not implants)
- Result temporary for few months
- High incidence of cataract (59%)
- Drop of vision after few months
- Glaucoma (Common complication)

- How does Anti VEGF compare to Steroids??
Role of VEGF in the pathophysiology

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Medical Management of DME

Laser Photocoagulation
Steroids Injections
ANTI VEGF Injections
Evolution of Anti VEGF drugs Protocols

➢ Anti VEGF Management Protocol
- VA Based ?
- OCT Based ?
Monthly injections given & suspended when:

- Monthly treatment until maximum VA is achieved then observe.
  - ‘Maximum VA’ is defined as VA stable for three consecutive monthly assessments while on ranibizumab treatment

Retreatment is initiated when:

- Injection resumed if loss of VA due to DME
  - Monthly injections administered until stable vision for three consecutive monthly assessment while on ranibizumab treatment
  - VA again stable for three consecutive visits
Change in VA from baseline

2 year results

After 3 injections of anti-VEGF both eyes
➢ Before & After 3 injections = VA 6/12

Baseline VA is a strong predictor of VA gains

No cross-trial comparisons unless studies are prospectively designed in a head-to-head manner

Could there be a ‘ceiling effect’?
Medical Management of DME

- Laser Photocoagulation
- Steroids Injections
- ANTI VEGF Injections

Why Not Use both Anti VEGF & Laser ??

- Adding laser may benefit??
  - Improve vision ??
  - Reduce injections number??
Mean change in BCVA: RESTORE

3 year results

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

- Ranibizumab 0.5 mg (n = 83)
- Ranibizumab 0.5 mg + laser (n = 83)
- Laser (n = 74)

Core study assessment
Interim Analysis
Full analysis/Study completion

Reduced need for injections ??

Mean number of injections

- Ranibizumab 0.5 mg
- Ranibizumab 0.5 mg + laser
- Laser + ranibizumab PRN from 12 months

Laser at first then + ranibizumab PRN from 12 months

19% to 25% of patients did not require any ranibizumab injections during the extension study.
Changes in How we Perceive DME

Taboos Broken

➢ Focal vs Diffuse DME:
  • Why?
    o Focal Laser vs Grid Laser
    o Anti VEGF injections?

Mean change in BCVA from baseline to Month 12 by baseline DME type

<table>
<thead>
<tr>
<th>Focal</th>
<th>DIFFUSE</th>
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<tbody>
<tr>
<td>ranibizumab 0.5 mg</td>
<td>ranibizumab 0.5 mg+laser</td>
</tr>
<tr>
<td>(n=63)</td>
<td>(n=68)</td>
</tr>
<tr>
<td>ranibizumab 0.5 mg+</td>
<td>ranibizumab 0.5 mg+laser</td>
</tr>
<tr>
<td>laser (n=52)</td>
<td>(n=46)</td>
</tr>
<tr>
<td>laser (n=52)</td>
<td>laser (n=52)</td>
</tr>
</tbody>
</table>

VA change

Month

0 1 2 3 4 5 6 7 8 9 10 11 12

-10 -8 -6 -4 -2 0 2 4 6 8 10

Full analysis set/LOCF
BCVA: best corrected visual acuity; VA: visual acuity; LOCF: last observation carried forward

Mitchell P et al.
Ophthalmology
2011;118:615-625
Changes in How we Perceive DME
Taboos Broken

➢ CSME or Not?
  • Meaningless in the era of OCT
  • Only to Perform Laser (Rare)
  • The Question is:
    o CiME vs non-CiME

NEW Generations do NOT understand why we are still mentioning CSME,
or considering Focal vs Diffuse,
or ordering FLA (no need)
Decreasing use of FA in managing DME

- IN 1998 audit of DME management, only 19.5% of British ophthalmologists treating DME with focal laser obtained a FA before treatment.
- In a 2007 study from the DRCR.net, 50% of eyes were managed without FA.
- DRCR quote: 'Any system of classifying DME that relies on FA will suffer from inutility by the majority of clinicians who avoid this ancillary study in their management of the condition.'

This trend to use FA may change if some evidence of usefulness in treating and predicting outcome is discovered'

Changes in How we Perceive DME

Taboos Broken

- New Questions:
  - Which Drug?
  - When Do we Stop?
  - Is it going to Last Forever ....
DRCR Protocol T

➢ Comparing drugs
➢ Avastin & Lucentis & Eylea
➢ Included changes in OCT to the stable point of Vision in Follow up

Monthly injections suspended when:

➢ Monthly treatment until maximum VA is achieved
➢ If changes in OCT >10% , then continue injection
➢ ‘Maximum VA’ is defined as VA stable for three consecutive monthly assessments while on ranibizumab treatment

RVO, retinal vein occlusion; VA, visual acuity
wAMD, wet age-related macular degeneration
Retreatment is initiated when:

- Injection resumed if loss of VA due to DME
  - Monthly injections administered until stable vision and
  - NO change in OCT for three consecutive monthly assessment while on ranibizumab treatment
  - VA again stable for three consecutive visits

Decrease in VA due to DMO

Visit
Visit
Visit
Visit
Visit

VA
Injection recommended
Injection not recommended

Mean 12-month visual acuity scores in Protocol T are inconsistent with previous studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline BCVA</th>
<th>Mean BCVA change from baseline to Month 12</th>
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<tr>
<td></td>
<td>54.7 ETDRS letters</td>
<td>12.5 ETDRS letters</td>
</tr>
<tr>
<td></td>
<td>57.5 ETDRS letters</td>
<td>10.9 ETDRS letters</td>
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<td></td>
<td>56.9 ETDRS letters</td>
<td>11.9 ETDRS letters</td>
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<tr>
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<td>56.9 ETDRS letters</td>
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<td>58.8 ETDRS letters</td>
<td>9.7 ETDRS letters</td>
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<td>10.7 ETDRS letters</td>
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<td>59.6 ETDRS letters</td>
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<td>65.1 ETDRS letters</td>
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Similar VA gains in overall population between aflibercept and ranibizumab at 2 years

At Year 1, the improvement was greater, but not clinically meaningful, with aflibercept than with the other two drugs. At Year 2, the difference in VA gain between aflibercept and ranibizumab was no longer significant (p = 0.47), indicating that a dose of ranibizumab that is 60% of the 0.5 mg ex-U.S. approved dose produced equivalent VA gains over 2 years to the full aflibercept 2.0 mg dose.


Updates in Treatment

➢ Are we going to inject forever?
  • 5 Years Protocol I DRCR
Take Home message

- **Anti VEGF** is the Best modality
- **Laser** is Better than **NO** treatment
- Laser does not **ADD** to Anti VEGF
- Depend on **VA** and consider **OCT** changes
- **All** Drugs are effective
- DME will **not** last Forever
- Nearly **ALL** DME will be gone in **3-5 Y**
- Those who **inject** will end up **BETTER**
ALEXANDRIA OPTHALMOLOGY SUMMIT

8 - 10 April, 2020
Radisson Blu Hotel
Alexandria, Egypt

See you NEXT YEAR

AOS 2020

Save THE DATE

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