CURRENT TRENDS IN DIABETIC MACULAR EDEMA TREATMENT

Muge R. Keser, MD
DISCLOSURE

• No relevant financial interest or relationships
OBJECTIVES

• Current trends (evidence based)
• Review of clinical trials
  • Diabetic Retinopathy Clinical Research Network (DRCR)
    • Protocol T
  • Ozurdex MEAD Study Group
  • FAME
• Ongoing trials
  • Diabetic Retinopathy Clinical Research Network (DRCR)
    • Protocol V
    • Protocol U
• Future targets
DIABETIC RETINOPATHY:
A MAJOR PUBLIC HEALTH ISSUE

• ~25.8 million Americans have diabetes (8.3% of the U.S. population)¹

• Diabetic Retinopathy (DR) is the most common microvascular complication of diabetes² and increases with duration of diabetes
  • 28.5% of people with diabetes aged 40 years or older have DR¹
  - 1 in 12 with diabetes has advanced vision-threatening DR³

• Diabetes is the leading cause of new cases of blindness in working-aged Americans (ages 20-74)¹

### Classification of Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Non-Proliferative DR</th>
<th>Diabetic Macular Edema</th>
<th>Proliferative DR</th>
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</thead>
<tbody>
<tr>
<td>Microvascular damage</td>
<td>Swelling in central retina</td>
<td>End stage</td>
</tr>
<tr>
<td>• Chronic, occurring over years</td>
<td>• Accounts for most vision loss</td>
<td>• Neovascularization of retina</td>
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<tr>
<td>• Typically no significant vision loss, but progresses to DME and/or PDR</td>
<td>• Co-exists with NPDR and PDR</td>
<td>• High risk of severe visual loss</td>
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<td>• Similar damage occurs in other end-organ vascular beds</td>
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**More common**

Less severe

**Less common**

More severe
• Vascular endothelial growth factor (VEGF)
• Insulin-like growth factor-1
• Angiopoietin-2
• Stromal-derived factor-1, Fibroblast growth factor-2
• Tumor necrosis factor
VEGF-A IS A KEY MEDIATOR OF ANGIOGENESIS AND VASCULAR LEAKAGE

**ANGIOGENESIS**

- VEGF-A binding to VEGFR
- Receptor activation
- Signal transduction
- Gene expression

**VASCULAR LEAKAGE**

- VEGF-A binding to VEGFR
- Gene expression

Nucleus
**ANTI-VEGF AGENTS**

**Pegaptanib**
- **Aptamer**
  - Binds specifically only one VEGF-A isoform

**Bevacizumab**
- **Monoclonal antibody**
  - Binds all VEGF-A isoforms

**Ranibizumab**
- **Antibody fragment**
  - Binds all VEGF-A isoforms with a higher affinity than bevacizumab

**Aflibercept**
- **Fusion protein**
  - Binds VEGF-A with higher affinity than bevacizumab and ranibizumab
  - Also binds VEGF-B and PIGF

**Timeline**
- 2004
- 2005
- 2006
- 2011
- 2013
Diabetic Retinopathy Clinical Research Network

Aflibercept, Bevacizumab, or Ranibizumab for DME: Two-year Results

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

Change in visual acuity at 1 Yr (primary outcome) and 2 Yrs
- Adjusted for baseline visual acuity and multiple comparisons
- Multiple imputation for missing values, intent-to-treat principle
- Truncated to 3 SD from the mean

- Aflibercept vs. Bevacizumab
- Aflibercept vs. Ranibizumab
- Bevacizumab vs. Ranibizumab

- Visits were every 4 weeks during year-1 and 4 to 16 weeks during year-2, depending on treatment course
- Starting at the 6-month visit, focal/grid laser treatment was administered if DME persisted and was not improving
- Participants unmasked to treatment group following the publication of the 1yr primary results: though discouraged, decision could be made at that time to switch to a non-study anti-VEGF agent.
- Doses: aflibercept 2.0-mg; bevacizumab 1.25-mg; ranibizumab 0.3-mg
Mean Change in Visual Acuity Over 2 Years
By Baseline Visual Acuity Subgroup

20/32 to 20/40

- Aflibercept: +6.8, +7.8, +8.6
- Bevacizumab: +13.3
- Ranibizumab: +14.1, +16.1, +18.1

20/50 or Worse
Mean Change in OCT CST Over 2 Years

**Full Cohort**

2-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P<0.001$
- Aflibercept vs. Ranibizumab $P = 0.08$
- Ranibizumab vs. Bevacizumab $P = 0.001$

* $P$-values adjusted for baseline visual acuity, OCT central subfield thickness, and multiple comparisons
Conclusions

➢ Vision gains (from baseline) at 2 years were seen in all 3 groups with ~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 differences in 2-year vision outcomes 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 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
TRIALS ON THE HORIZON
Protocol V - Treatment for Central-involved DME in Eyes with Very Good Visual Acuity

Objective:
Compare the safety and efficacy of
1) prompt laser with deferred anti-VEGF
2) observation with deferred anti-VEGF
3) prompt anti-VEGF in eyes with center involved DME and good vision (defined as visual acuity $\geq$ 20/25).

Primary Outcome: proportion of eyes with a visual loss of at least 5 letters at 1 year, confirmed at 2 consecutive 4-week visits
Study Design

Randomized, multi-center clinical trial

At least one eye meeting **all** of the following criteria:
- Central-involved DME on OCT (Cirrus/Spectralis only)*
- VA letter score 20/25 or better*
- No prior treatment for DME

**Prompt** anti-VEGF

**Prompt laser + deferred anti-VEGF**

**Observation + deferred anti-VEGF**

Primary outcome: Proportion of eyes that have lost ≥5 letters of VA at 2 years

*Confirmed at 2 visits (screening and randomization 1-28 days apart)
The Diabetic Retinopathy Clinical Research Network

** PROTOCOL U **

Short-Term Evaluation of Combination Corticosteroid+Anti-VEGF Treatment for Persistent Central-Involved DME Following Anti-VEGF Therapy in Pseudophakic Eyes

Protocol Chair: Raj Maturi, MD
Objectives

- To assess short-term effects of combination steroid+anti-VEGF therapy on OCT retinal thickness and visual acuity in comparison with that of continued anti-VEGF therapy alone in pseudophakic eyes with persistent DME and visual acuity impairment despite previous anti-VEGF treatment.

- To provide more information needed for future conduct of a definitive phase III clinical trial.
Study Design

➢ Phase II, multicenter, controlled, participant-masked, clinical trial

➢ Duration of follow-up

Run-in Phase
12 Weeks

Randomized Phase
24 Weeks

Purpose
To ensure that enrolled eyes truly have “persistent DME” with decreased visual acuity despite prior anti-VEGF therapy.
OTHER ANTI-VEGF AGENTS IN CLINICAL TRIALS….

• Abicipar pegol
  • long-acting anti-VEGF A mono-DARPin®
  • small size, high potency and long intra-vitreal half-life

• Multicenter, Double Masked Phase 2 Clinical Trial Evaluating Abicipar Pegol for DME (PALM)
  • 28-week trial period
  • Abicipar with a 2-mg dose (and injected every 8 weeks, respectively every 12 weeks, following three monthly loading doses) demonstrated functional (BCVA) and anatomical (CRT) effects comparable with ranibizumab (Lucentis®) which was injected every 4 weeks into each eye

Profile was acceptable; mild-moderate intraocular inflammation, which resolved with treatment
Refillable rigid port delivery system (RPDS)

- Durable intravitreal implant
- Scleral incision in a one-time surgical procedure
- Refilled using a proprietary refill needle
- The timing for refills is currently being studied but at 4 to 6 months
- **Currently in a phase 2 clinical trial**, it could potentially replace intravitreal injections of Lucentis now normally given every 4 to 6 weeks.

**LADDER** – Phase 2, interventional, randomized, double-masked, active comparator, multi-center study
SUSTAINED-RELEASE INITIATIVE...

• Regeneron
  • Eylea (aflibercept) -- The formulation is in preclinical development

• Ocular Therapeutix
  • Tyrosine kinase inhibitors
  • Protein-based anti-VEGFs

• Alcon
  • small-molecule, single-chain antibody fragment brolucizumab (RTH258)

• pSivida
ALTHOUGH ANTI-VEGF APPEARS FLAWLESS IN MOST...

CONS:

• Failure to respond to anti-VEGF therapy
• Compliance with regular appointment and injections
• Frequent injections increase the risk of potential complications

Ophthalmologists’ concept of DME has changed over the years
Inflammation is a major component
DME EVOLVES OVER TIME...

- Focal leakage → diffuse leakage → pigmentary changes → fibrosis

THE NEXT PARADIGM SHIFT

- Correlating these anatomic changes with physiologic progression
- Defining the multifactorial switch that fundamentally changes the disease from a permeability-driven disease to an inflammation driven disease
EFFICACY OF STEROIDS IN THE TREATMENT OF DME

Steroids inhibit:

• Recruitment of leukocytes
• Production of adhesion molecules
• Up-regulation of prostaglandins
• Accumulation of macrophages within the retina
• Action of VEGF and regulate its expression

Additionally:

• Stabilise the blood–retinal barrier
• Reduce capillary permeability by inhibiting leukocyte recruitment and enhancing the activity of endothelial cell tight junctions
OTHER INJECTABLES...

TRIESENCE
(Triamcinolone Acetonide)

OZURDEX
(dexamethasone)

ILUVIEN
(fluocinolone acetonide)
EVIDENCE FROM CLINICAL TRIALS OF BENEFICIAL EFFECTS OF INTRAVITREAL CORTICOSTEROIDS FOR DME

• DRCR.net Protocol I
  • Pseudophakic subgroup had a visual gain similar to the Ranibizumab groups

• FAME study
  • Fluocinolone Acetonide demonstrated benefits over 3 years

• MEAD study
  • Benefit of dexamethasone intravitreal implant over three year treatment period

Cataract and IOP rise are issues
The Diabetic Retinopathy Clinical Research Network

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

DRCR.net Protocol I

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
Mean Change in Visual Acuity* at Follow-up Visits:

Pseudophakic Eyes at Baseline

*Truncated ± 30 letters
• Dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan)

• Indicated for:
  • Macular edema secondary to retinal vein occlusion
  • Noninfectious uveitis
  • Diabetic macular edema (DME)

Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD), phase 3 study
Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema

David S. Boyer, MD, Young Hee Yoon, MD, PhD, Rubens Belfort, MD, PhD, Francesco Bandello, MD, Raj K. Maturi, MD, Albert J. Augustin, MD, Xiao-Yan Li, MD, Harry Cui, MS, Yehia Hashad, MD, Scott M. Whitcup, MD

Ophthalmology
Volume 121, Issue 10, Pages 1904-1914 (October 2014)
DOI: 10.1016/j.ophtha.2014.04.024
Phase III - MEAD Trial

**Study Visits**
- Screening, day -14 to -4
- Baseline, day 0
  - Safety assessments on days 1, 7, and 21 after treatment and each retreatment
  - Months 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39 (for patients treated at month 36 only)

**Condition to treat: DME**
- 1048 patients enrolled (1 eye/patient) and randomized to study treatment
- DEX implant 0.7 mg (N = 351)
- DEX implant 0.35 mg (N = 347)
- Sham (N = 350)

**Completed**
- Month 6: 330 (94.0%)
- Month 6: 331 (95.4%)
- Month 6: 276 (78.6%)
- Month 12: 292 (83.2%)
- Month 12: 305 (87.9%)
- Month 12: 221 (63.1%)
- Month 24: 254 (72.4%)
- Month 24: 264 (76.1%)
- Month 24: 174 (49.7%)

**Discontinued**
- Month 36: 226 (64.1%)
- Month 36: 230 (66.3%)
- Month 36: 152 (43.4%)
- Reason: 126
  - Ocular AE: 28
  - Nonocular AE: 17
  - Lack of efficacy: 23
  -Lost to follow-up: 11
  - Personal reason: 14
  - Protocol violation: 30
- Reason: 117
  - Ocular AE: 28
  - Nonocular AE: 20
  - Lack of efficacy: 25
  - Lost to follow-up: 12
  - Personal reason: 10
  - Protocol violation: 19
- Reason: 198
  - Ocular AE: 27
  - Nonocular AE: 12
  - Lack of efficacy: 84
  -Lost to follow-up: 18
  - Personal reason: 28
  - Protocol violation: 30

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Phase III - MEAD Trial

![Graph showing patients with ≥15 letters gain at final visit.](attachment:image.png)

- **DEX Implant 0.7 mg** (n = 351)
  - 22.2%
  - *P < 0.001*

- **DEX Implant 0.35 mg** (n = 347)
  - 18.4%
  - *P = 0.018*

- **Sham** (n = 350)
  - 12.0%
ILUVIEN

- A fluocinolone acetonide (FAc) intravitreal implant 0.19 mg (Iluvien, Alimera Sciences)
- Indicated for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP
- Offers particular promise for patients with long-standing DME refractory to other treatments, as well as difficult-to-treat vitrectomized eyes

Fluocinolone Acetonide for Diabetic Macular Edema (FAME) trials
Patients with DME and:
- ≥ 1 previous laser trx
- BCVA ≥ 19 and ≤ 68 letters
- TD-OCT center point ≥ 250 μm

Additional laser therapy allowed after week 6
Retreatment any time after month 12 (if eligible)
Study ends

Randomization 2:2:1
N = 956

Month: 0 6 12 18 24 30 36

ILUVIEN
- 0.2 μg/d FAc (n = 376)
- 0.5 μg/d FAc (n = 395)
Control: sham injection (n = 185)

BCVA, best corrected visual acuity; DME, diabetic macular edema; TD-OCT, time domain optical coherence tomography.

* At masked investigator’s discretion.
* If BCVA loss ≥ 5 letters or retinal thickening ≥ 50 μm from best reading in previous 12 months.
Percentage of Patients With ≥ 15-Letter Improvement Over Baseline

- Control (n = 185)
- 0.2 μg/d FAc (n = 376)

Primary readout:
- Control: 16.2%
- FAc: 28.7%

Month 24:
- Control: 16.2%
- FAc: 28.7%

Month 36:
- Control: 18.9%
- FAc: 28.7%

P-values:
- Control vs. FAc: P = 0.002
- Control vs. FAc: P = 0.018

References:
FLUOCINOLONE ACETONIDE FOR DIABETIC MACULAR EDEMA (FAME) TRIALS

- FAc 0.19 mg intravitreal implant (Iluvien, Alimera Sciences) improves and slows progression of diabetic retinopathy

In the complete FAME data set at month 36:
31% of sham-controlled eyes and 17% of the fluocinolone acetonide 0.2 µg/day treated eyes progressed to PDR ($p < 0.001$) with a mean of 1.3 injections of the implant
DISADVANTAGES INCLUDE CATARACT AND IOP RISE.

- After three years, incisional glaucoma surgery was needed:
  - 4.8% of patients in the low-dose group
  - 8.1% of patients in the high-dose group
ROLE OF LASER THERAPY…

Conventional laser
• Has advanced to offer clinicians with more options:
  • Grid patterns
  • Improvements in spot size
  • Wavelength modifications
• Complications remain:
  • Loss of visual acuity
  • Reduction in color, night, and contrast vision
  • Choroidal neovascularization
  • Epiretinal fibrosis
Blanching that results from the intense heat
Kills tissue
Creates scars that expand with time

Is there concern that laser photocoagulation will cause additional inflammation in patients with inflammation-driven DME who do not respond to anti-VEGF therapy?
TISSUE-SPARING MICROPULSE TECHNOLOGY

- Low-intensity, high-density laser applications
- Envelopes of repetitive short pulses
- Can be paired with the 810 nm and newer 577 nm lasers

Intracellular anti-angiogenic & restorative biological factors without producing visible signs of laser treatment
HOW THEY DIFFER...

Conventional laser

Micropulse laser

*MicroPulse* allows the tissue to *cool between pulses*, minimizing or preventing tissue damage.
TREX-DME 1-year Outcomes

Randomized Trial of Treat and Extend Ranibizumab with and without Navigated Laser for Diabetic Macular Edema

John F. Payne, MD, Charles C. Wykoff, MD, W. Lloyd Clark, MD, Beau B. Bruce, MD, PhD, David S. Boyer, MD, David M. Brown, MD

Ophthalmology
Volume 124, Issue 1, Pages 74-81 (January 2017)
DOI: 10.1016/j.ophtha.2016.09.021

Purpose
To compare monthly dosing with a treat and extend algorithm using ranibizumab 0.3 mg with and without angiography-guided macular laser photocoagulation for center-involving diabetic macular edema (DME)
TREX-DME 1-year Outcomes

3 cohorts:
- Monthly
- Treat and Extend without laser (TREX)
- Treat and Extend with angiography guided laser (GILA)

All eyes received monthly ranibizumab (0.3mg) x4mo
At week 12, begin treat and extend if CRT \leq 325\mu m
If CRT > 325\mu m, continue monthly injections

Treat and extend algorithm for extending, maintaining, or reducing treatment interval on the basis of the central retinal thickness (CRT) measurements
Locally weighted regression (LOESS) analysis for change in visual acuity over time.
Locally weighted regression (LOESS) analysis for change in central retinal thickness (CRT) over time

- Mean CRT improvements were similar
- No significant difference among cohorts in mean CRT
TREX-DME 1-year Outcomes

TREX and GILA cohorts experienced a statistically significant and clinically meaningful reduction of 2.4 and 3 treatments, respectively, when compared with monthly dosing at 1 year.

Adding a mean of 2.9 navigated laser photocoagulation sessions did not significantly reduce treatment burden of injections at 1 year.

Locally weighted regression (LOESS) analysis for treatment interval for the 3 cohorts.
Diabetic Macular Edema: The Role of MicroPulse Laser Therapy in the Anti-VEGF Era

An excellent first-line treatment for patients who do not want injections, or those with limited disease.

BY ELIAS REICHEL, MD, AND ADAM H. ROGERS, MD

Case Example

Male patient with excessive exudation and clinically significant DME in both eyes, but especially in the right eye.

Pre MicroPulse: Patient received a few anti-VEGF and Kenalog treatments, but repeated or recurrent macular edema occurred within a few months, and within 6 weeks of any anti-VEGF. TxCell-Guided MicroPulse was delivered with 200 µm spot, 200 ms duration, 400 mW, 5% duty cycle, 7x7 grid with confluent, zero spacing.

At 7 months post 2 MicroPulse treatments: Vision improved 1 line, and reduction in fluid was visible on OCT.
HELPFUL ALGORITHM
Future targets…

- **RO6867461** (Hoffmann-La Roche) -- bispecific antibody that blocks both VEGF and Ang2 -- **BOULEVARD** study, Phase II
- **ALG-1001** (Luminate, Allegro Ophthalmics) -- First-in-class anti-integrin peptide  
  **DEL MAR** Phase IIb
- **Sunitinib** -- tyrosine kinase inhibitor blocks VEGFs, PDGFRs, c-MET, and DLK (**MICROPARTICLES**)  
- **REGN910-3** (Regeneron) -- antibody directed solely against Ang2
**PURPOSE:** To demonstrate the non-inferiority of ALG-1001 to bevacizumab, which was defined as a difference of 3 or fewer letters in the mean change in the BCVA at 20 weeks after treatment.
Example #2: Luminate

Baseline

Study Week 16
(8 weeks post load)

Study Week 20
(12 weeks post load)
Future targets…

- **AKB-9778** (Aerpio Therapeutics) – First-in-class Tie2 activator
  - Small molecule responsible for endothelial cell stabilization
  - Dosed at 15mg BID **subcutaneously** (Alone or in combination with RANIZIMUMAB) improves retinopathy over 3 months

- **Teprotumumab** --blocks activation of IGF-R1 by both IGF-1 and IGF-2
  - Intravitreal levels of IGF-1 and 2 are elevated in PDR
  - **Intravenous infusion**

- **ASP-8232** – inhibits plasma VAP-1 activity
  - VAP-1 activity associated with diabetic macular edema
  - VAP-1 Inhibition in Diabetes (VIDI) study, ongoing Phase 2 study

**Indian J of Ophthalmology**
DIABETIC RETINOPATHY IS A COMPLEX DISEASE

- Investigational efforts will make management of this common, yet challenging condition more effective and cost-efficient
- Introduction of new products into the treatment algorithm will be exciting and rewarding
- Therapies in the pipeline will continue to increase the number of patients we can treat with better outcomes
THANK YOU