Intravitreal Aflibercept for Diabetic Macular Edema: Subgroup Analysis by Baseline Demographics and Systemic Disease Characteristics

For the VIVID-DME/VISTA-DME Study Investigators

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Financial Disclosure

• Notice of Requirements For Successful Completion
  – Please refer to learning goals and objectives
  – Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours

• Conflict of Interest (COI) and Financial Relationship Disclosures:
  – Consultant for Genentech, Regeneron, Alcon, and Shire

• Off-Label Use:
  – Will discuss the off label use of bevacizumab for diabetic macular edema

Diabetic Eye Disease Is Increasing in Prevalence in the United States

• 1 of 4 leading causes of new blindness
• Leading cause of blindness in 20- to 74-year-old patients
• There was an 89% increase in diabetic retinopathy between 2000 and 2010

Diabetes is Associated With Serious Systemic Comorbidities

Prevalence of Microvascular and Macrovascular Complications in Diabetes Patients

Diabetic Retinopathy (DR)
16% of diabetic patients
15.6% of DR patients have DME

Diabetic Neuropathy
25% of diabetic patients have chronic pain

Diabetic Nephropathy
40% of diabetic patients have chronic renal disease

Diabetic Macular Edema (DME)
13.6% of patients with DR have DME

Diabetic Neuropathy
60-70% of people with diabetes have some form of nervous system damage

Ocular complications of diabetes include:

- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Glaucoma

Diabetes Directly Impacts Eye Health and Vision

Cataract
- 60% increased risk in patients with diabetes

Diabetic macular edema (DME)
- 13.6% of patients with DR have DME

Glaucoma
- 40% increased risk in patients with diabetes

Diabetic retinopathy (DR)
- 28.5% of adults (≥40 years old) with diabetes have DR

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Diabetic retinopathy (DR)
- 28.5% of adults (≥40 years old) with diabetes have DR
Diabetic Retinopathy

- Nonproliferative (NPDR): changes confined to retina
- Proliferative (PDR): changes outside the retina into the vitreous

Diabetic Retinopathy


Patients with Diabetic Macular Edema May Not Have Symptoms

- Patients should be referred for a retina (dilated) eye exam before any vision loss
- Symptoms and pain are often both absent in the early stages
- Vision loss can occur suddenly, and regular examinations are crucial to ensure treatment is obtained

Symptoms of DME include:

- Blurred Vision
- Double Vision
- Patchy vision loss

Patients with Diabetic Macular Edema Remain Untreated Or Undiagnosed

- 50% Patients unaware that their eyes have been affected by DME
- 44.7% Patients unaware that their eyes have been affected by DME

Patient’s Fear of Blindness

- 60% of Americans are more frightened of going blind than dying from heart disease, which is the leading killer of men and women
- 79% of Americans say that losing a loved one is more fearful than going blind
- Losing one’s eyesight is the worst thing that can happen to me

Impact of Vision Loss in Diabetes

Visual acuity:

- Miosis (farthest back loss)
- Miosis (farthest middle loss)
- Miosis (farthest front loss)

Diagnosis

- Capturing a retina image is only one part of the clinical diagnosis of DR and DME
- There are many ways to monitor retina health

- Color fundus photography
- Fluorescein angiography: normal and widefield
- Optical coherence tomography
Diabetic Macular Edema (DME)

Normal Macula: In the normal retina, light passes through 9 layers to reach the photoreceptors.

DME with Cysts in Fovea: Diffuse Edema: Increased thickness of the retina affects the ability of light to travel through the tissue to photoreceptors.

Interventions for Diabetic Macular Edema (DME)

Laser for Diabetic Macular Edema (n=155)
DRCR.net Protocol I
Ozurdex (Dexamethasone intravitreal implant approved) (n=853)
RISE/RIDE Study
Ranibizumab

Vitrectomy for Diabetic retinopathy
Vitrectomy + Laser anastomosis
VIVID/VISTA
Aflibercept
FAVOR
Iluvien (Fluocinolone intravitreal implant)

Macular Laser: Standard of Care Treatment for DME Since 1985

- Early Treatment of Diabetic Retinopathy Study (ETDRS) 1
  - Showed macular laser photocoagulation effective for DME
  - Decreased risk of significant (3-line) visual acuity loss by 50%
- Relatively few patients experience significant visual acuity improvement with laser, and improvements typically occur slowly
  - ~15% rate of 3-line improvement at 2 years in recent studies 2,3

VEGF in Human Ocular Fluids

VEGF (ng/mL)

- aqueous fluid
- vitreous fluid
- mean

VEGF in Human Ocular Fluids

- No Proliferative Diseases
  - DM, Without PDR
  - DM, QR-PDR
  - CRVO, active

- Iris NV, regressed
- Iris NV, active

VEGF in Human Ocular Fluids

Stewart MW. Inflamm Allergy Drug Targets. 8/8/2015


How Are These Drugs Delivered?

Affinity and binds VEGF-B, PlGF intermediate half-life

MW: 115 (~150 kDa)

Mouse

N = 333

6.3-7.5

Patients With Diabetic Retinopathy (%)


Diabetic Retinopathy: More Prevalent with Duration of Diabetes

Little is known regarding the effect of baseline systemic characteristics on anti-VEGF treatment outcomes for diabetic macular edema (DME)

Several studies have demonstrated the importance of glycemic control in DME and diabetic retinopathy.1,4

In a retrospective case study review of 124 patients with DME, we reported data supporting an association between glycemic control and visual and anatomic outcomes with anti-VEGF therapy.3

Using data from the phase 3, here we assess in a larger patient population whether any systemic factors influenced VA improvement with aflibercept in patients with DME

Goals of This Analysis

AADE15

AADE15

AADE15

AADE15
**Study Design**

Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320

- IAI = intravitreal aflibercept injection
- N=406 (VIVID)
- N=466 (VISTA)

**Primary Endpoint:**

Week 52

**Mean change in BCVA**

**Key Secondary endpoints**

Change in OCT
Change in Diabetic Retinopathy Severity Scale (DRSS)

Continued treatment through Year 3

Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320

**Objectives**

- To examine outcomes at Week 100 based on select baseline characteristics –
  - Demographics (age, gender, race)
  - Systemic characteristics (BMI, renal impairment, ischemic heart disease, cerebrovascular disease, hypertension)
- To investigate relationships between baseline quartiles of HbA1c and change in outcomes from baseline to week 100

**Outcomes at Week 100**

- At week 52, IAI demonstrated significant superiority in functional and anatomic endpoints over laser in both VIVID and VISTA, with similar efficacy in the 2q4 and 2q8 groups despite the extended dosing interval in the 2q8 group
- At 100 weeks, IAI sustained its 52-week superiority over laser in visual and anatomic outcomes, with a similar efficacy in the 2q4 and 2q8 groups, in both VIVID and VISTA
- There were no clinically relevant differences between the 2q4, 2q8, and laser groups in terms of frequency (5.2%, 3.8%, and 5.9%, respectively) or pattern of ocular serious adverse events

**Effect of Baseline Systemic Characteristics**
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>VIVID 8</th>
<th>VIVA 2q4</th>
<th>VISTA 6</th>
<th>VISTA 2q8</th>
<th>IAI-2q4</th>
<th>IAI-2q8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>63.9 (8.6)</td>
<td>62.6 (8.6)</td>
<td>64.2 (7.8)</td>
<td>61.7 (8.7)</td>
<td>63.1 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Gender (Women), n (%)</td>
<td>54 (40.9%)</td>
<td>53 (39.0%)</td>
<td>47 (34.8%)</td>
<td>69 (44.8%)</td>
<td>67 (43.5%)</td>
<td>73 (48.3%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>106 (80.3%)</td>
<td>109 (80.1%)</td>
<td>106 (78.5%)</td>
<td>131 (85.1%)</td>
<td>128 (83.1%)</td>
<td>125 (82.8%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.8%)</td>
<td>0</td>
<td>1 (0.7%)</td>
<td>16 (10.4%)</td>
<td>16 (10.4%)</td>
<td>19 (12.6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>25 (18.9%)</td>
<td>27 (19.9%)</td>
<td>27 (20.0%)</td>
<td>3 (1.9%)</td>
<td>5 (3.2%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>HbA1c, mean % (SD)</td>
<td>7.7 (1.26)</td>
<td>7.8 (1.46)</td>
<td>7.7 (1.43)</td>
<td>7.6 (1.68)</td>
<td>7.9 (1.65)</td>
<td>7.9 (1.56)</td>
</tr>
<tr>
<td>Proportion w/ &gt;8%, n (%)</td>
<td>42 (31.8%)</td>
<td>55 (40.4%)</td>
<td>44 (32.6%)</td>
<td>45 (29.2%)</td>
<td>57 (37.0%)</td>
<td>57 (37.7%)</td>
</tr>
</tbody>
</table>

Effect of Baseline
Systemic Characteristics

Conclusions

- At week 100, improvements in vision achieved with IAI 2q4 and 2q8 were significantly greater than laser and consistent among subgroups of patients with differing race and variable systemic disease control at baseline.

Objectives
Post-Hoc Sub-analyses

- To investigate the relationships between baseline HbA1c (using quartiles) and change from baseline at week 100 within each treatment group for:
  - Best-Corrected Visual Acuity (BCVA)
  - Central Retinal Thickness (CRT)
  - HbA1c

- To investigate the similarity of these relationships between the treatment groups.

Methods
Post-Hoc Sub-analyses

- Analyses focused on comparison within each treatment group.
- Treatment Groups:
  - Laser
  - IAI (2q4 and 2q8 combined)
- HbA1c partitioned by quartile using all data available at baseline.
- Repeated measures models used to report summary measures.
- Least square means reported.
Baseline Characteristics
Within HbA1c Quartiles

<table>
<thead>
<tr>
<th>Quartile</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range for HbA1c Quartiles</td>
<td>4.5% - &lt; 6.7%</td>
<td>6.7% - &lt; 7.4%</td>
<td>7.4% - &lt; 8.6%</td>
<td>8.6% - &lt; 9.7%</td>
</tr>
<tr>
<td>N</td>
<td>233*</td>
<td>206</td>
<td>209</td>
<td>208</td>
</tr>
<tr>
<td>Caucasian (White), %</td>
<td>84.12</td>
<td>83.50</td>
<td>76.56</td>
<td>83.65</td>
</tr>
<tr>
<td>Age, years</td>
<td>63.52</td>
<td>64.34</td>
<td>62.7</td>
<td>60.74</td>
</tr>
<tr>
<td>Body Mass Index, Kg/M²</td>
<td>29.38</td>
<td>29.96</td>
<td>31.46</td>
<td>31.38</td>
</tr>
<tr>
<td>Central Retinal Thickness, µm</td>
<td>513</td>
<td>496</td>
<td>528</td>
<td>462</td>
</tr>
<tr>
<td>BCVA, ETDRS Letter Score</td>
<td>60</td>
<td>60</td>
<td>59</td>
<td>60</td>
</tr>
</tbody>
</table>

Baseline characteristics within quartiles were similar for the laser and IAI groups.

VIVID: Excluded uncontrolled diabetes mellitus, as defined by HbA1c >12%.; VISTA: Excluded Uncontrolled diabetes mellitus in the opinion of the investigator.

Patterns Observed
IAI Group

Mean Change in BCVA by Baseline HbA1c Quartiles

Mean Change in CRT by Baseline HbA1c Quartiles

ETDRS; Compared to baseline

Laser Q1 Q2 Q3 Q4

Mean Change in BCVA by Baseline HbA1c Quartiles

Mean Change in CRT by Baseline HbA1c Quartiles

ETDRS; Compared to baseline

Laser Q1 Q2 Q3 Q4
Compared to Change in HbA1c

<table>
<thead>
<tr>
<th>Q1</th>
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<tbody>
<tr>
<td>0.0</td>
<td>0.1</td>
<td>0.6</td>
<td>0.4</td>
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</table>

Mean Change in HbA1c at Week 100 by Baseline HbA1c Quartiles

- HbA1c Range: 4.5% to < 6.7% 6.7% to < 7.4% 7.4% to < 8.6% 8.6% to 1

Rescue Treatment Experience Through Week 100

<table>
<thead>
<tr>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
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<td>23.8</td>
<td>29.1</td>
<td>30.3</td>
<td>30.5</td>
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Summary of Laser Group

- Clear association between change in BCVA and CRT with levels of HbA1c
  - Decreasing change in VA with increasing HbA1c
  - Increasing CRT with increasing HbA1c
  - Increasing rate of rescue with increasing HbA1c

- Pattern seen at Week 52 reflected at Week 100

Patterns Observed IAI Group

Mean Change in BCVA by Baseline HbA1c Quartiles
Mean Change in CRT by Baseline HbA1c Quartiles

Mean Change in HbA1c at Week 100 by Baseline HbA1c Quartiles

Rescue Treatment Experience Through Week 100

Summary of IAI Group
- No clear association between change in VA or CRT or rescue rate with levels of HbA1c
- Lack of meaningful correlations at week 52 replicated at week 100

How do Patterns in the Laser and IAI Groups Compare?
Mean Change in BCVA by Baseline HbA1c Quartiles

Mean Change in CRT by Baseline HbA1c Quartiles

Mean Change in CRT at Week 100 by Baseline HbA1c Quartiles

Rescue Treatment Experience Through Week 100

Strengths and Limitations Post-Hoc Sub-analysis

- **Strengths**
  - Large sample size from controlled phase 3 studies

- **Limitations**
  - Post-hoc analyses, subgroups were not pre-defined
  - Analyses limited to relationship with only baseline HbA1c
Summary
Post-Hoc Sub-analysis

- In eyes treated with laser, increasing baseline HbA1c levels associated with:
  - Decreasing mean change from baseline BCVA at weeks 52 and 100
  - Decreasing mean change from baseline CRT at weeks 52 and 100
  - Increasing rescue rate with increasing HbA1c

- In eyes treated with IAI, there was no meaningful correlation between increasing baseline HbA1c levels and visual and anatomic outcomes.

- In both treatment groups, slight mean change in baseline HbA1c at week 100 were somewhat dependent (increasing) on baseline HbA1c
  - HbA1c increase consistently higher in laser group compared to IAI group

Safety

SAE = serious adverse event; AE = adverse event.

Safety Overview through Week 100

<table>
<thead>
<tr>
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<th>Laser</th>
<th>IAI 2q8</th>
<th>IAI 2q4</th>
<th>ALL IAI</th>
<th>N 133 136 135 271 154 155 152 307</th>
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</thead>
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<tr>
<td>Any APTC event</td>
<td>2 (1.5%)</td>
<td>2 (1.5%)</td>
<td>4 (3.0%)</td>
<td>6 (2.2%)</td>
<td>9 (5.8%) 8 (5.9%) 5 (3.7%) 13 (4.8%)</td>
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<tr>
<td>Non-fatal MI</td>
<td>1 (0.8%)</td>
<td>1 (0.7%)</td>
<td>0</td>
<td>1 (0.4%)</td>
<td>4 (2.6%) 3 (2.2%) 0 3 (1.1%)</td>
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<tr>
<td>Non-fatal stroke</td>
<td>0</td>
<td>1 (0.7%)</td>
<td>2 (1.5%)</td>
<td>3 (1.1%)</td>
<td>2 (1.3%) 3 (2.0%) 2 (1.3%) 5 (1.6%)</td>
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<td>Vascular deaths</td>
<td>1 (0.8%)</td>
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**Anti-platelet Trialists’ Collaboration-defined Arterial Thromboembolic events include non-fatal stroke, non-fatal MI, and vascular death as adjudicated by a masked committee. Safety analyses set.**
Conclusions

- Improvements in vision achieved with IAI 2q4 and 2q8 were significantly greater than laser and consistent among subgroups of patients with differing race and variable systemic disease control at baseline.

Effect of Baseline HbA1c –
- In eyes treated with laser, increasing baseline HbA1c levels were associated with decrease in visual and anatomic outcomes.
- In eyes treated with IAI, there was no association between increasing baseline HbA1c levels and visual and anatomic outcomes.
- In both treatment groups, slight mean change in baseline HbA1c at week 100 were somewhat dependent (increasing) on baseline HbA1c.
- HbA1c increase consistently higher in laser group compared to IAI group.

Thank you!