Retinopathy of Prematurity and Emerging Therapy

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Children’s Memorial Hermann Hospital
Disclosure Statement
Helen Mintz-Hittner, M.D.

I have no relevant financial relationships to disclose or conflict of interests to resolve.
FDA Disclosures

Dr. Mintz-Hittner has disclosed that her presentation involves comments or discussion of the investigational use of Bevacizumab: Anti-Angiogenic Agent; Anti-VEGF; Anti-Vascular Endothelial Growth Factor

Investigational New Drug Number: 101578
Number Clinical Trials: 00622726
UTHSCH: CPHS Number: HSC-MS-08-0036
Pathogenesis of ROP

Severe Retinal Dystrophy

Accelerated Retinal Detachment
Pathogenesis of ROP

At Risk

1st Exam

Premature birth

Normal Intrauterine Vessel Growth

Stage 0 ROP

Stage 1 ROP (Line)

Stage 2 ROP (Ridge)

Stage 3 ROP (Extensive fibrovascular proliferation)

Successful Treatment of Retinopathy

Immediately after therapy

Several weeks after therapy

Cryotherapy

Laser therapy

Bevacizumab therapy

Postmenstrual Age (weeks)

20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52

APROP onset

Stage 1 onset

Stage 2 onset

Stage 3 onset

Stage 4 (Partial retinal detachment)

Stage 5 (Total retinal detachment)

Neovascularization increases
Pathogenesis of ROP

- **Premature birth**
- **Normal Intrauterine Oxygen and VEGF**
- **Stage 0 ROP**
- **Stage 1 ROP (Line)**
- **Stage 2 ROP (Ridge)**
- **Stage 3 ROP (Extraretinal fibrovascular proliferation)**
- **Stage 4 (Partial retinal detachment)**
- **Stage 5 (Total retinal detachment)**
- **Cryotherapy**
- **Laser therapy**
- **Bevacizumab therapy**

**At Risk**
- Gestational ages at high risk for ROP

**1st Exam**
- First examination for ROP

**Phase II**
- Oxygen and VEGF Neovascularization increases

**Successful Treatment of Retinopathy**
- Immediately after therapy
- Several weeks after therapy

**Postmenstrual Age (weeks)**
- 20
- 22
- 24
- 26
- 28
- 30
- 32
- 34
- 36
- 38
- 40
- 42
- 44
- 46
- 48
- 50
- 52

**APROP onset**
- Stage 1 onset
- Stage 2 onset
- Stage 3 onset
International Classification ROP (ICROP) (Acute)
(Initial 8/1984)(Revisited 07/2005)

- Plus disease *
- Zone (I worse than III)
- Stage (5 worse than 1)
- [Clock hours]
International Classification ROP

References

### TABLE 1  Timing of First Eye Examination Based on Gestational Age at Birth

<table>
<thead>
<tr>
<th>Gestational Age at Birth, wk</th>
<th>Age at Initial Examination, wk</th>
<th>Postmenstrual</th>
<th>Chronologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31</td>
<td>9</td>
<td></td>
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<tr>
<td>23&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31</td>
<td>8</td>
<td></td>
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<tr>
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<td>31&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>32&lt;sup&gt;b&lt;/sup&gt;</td>
<td>36</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Shown is a schedule for detecting prethreshold ROP with 99% confidence, usually well before any required treatment.

<sup>a</sup>This guideline should be considered tentative rather than evidence-based for infants with a gestational age of 22 to 23 weeks because of the small number of survivors in these gestational-age categories.

<sup>b</sup>If necessary.
ROP Blindness Risk and Infant Mortality Rates

ROP Blindness Risk and Infant Mortality Rates

Screening Recommendations

• **Developed World**: $\leq 1500$ grams birth weight \textbf{OR} $\leq 30$ weeks gestational age at birth
  
  (Mean affected 700 grams birth weight)

• **Developing World**: $\leq 2500$ grams birth weight \textbf{OR} $\leq 34$ weeks gestational age at birth
  
  (Mean affected 1400 grams birth weight)
Screening References

- Pediatrics 2006;117:572-76.
- Pediatrics 2006;118:1324.(Errata)
Cryotherapy: CRYO-ROP-1988
Treatment: Threshold for CRYO-ROP
Laser Therapy: ETROP-2003
Treatment: Prethreshold for ETROP (Type I disease)
Rationale for Initial Treatment (Destructive Therapy)

• Laser the avascular retina to eliminate angiogenic factor, VEGF (vascular endothelial growth factor), by ablating the avascular retina.
Bevacizumab Therapy: BEAT-ROP-2011
Rationale for Initial Treatment
(Antigen-Antibody Therapy)

- Inject Bevacizumab into the vitreous to decrease angiogenic factor, VEGF (vascular endothelial growth factor), by rendering it inactive.
## Comparison of Treatment Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>CRYO-ROP</th>
<th>ETROP</th>
<th>BEAT-ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1988</td>
<td>2003</td>
<td>2011</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>800 grams</td>
<td>703 grams</td>
<td>664 grams</td>
</tr>
<tr>
<td>Gestational Age</td>
<td>26.3 wks</td>
<td>25.3 wks</td>
<td>24.3 wks</td>
</tr>
<tr>
<td>Zone I Cases</td>
<td>7%</td>
<td>40%</td>
<td>45%</td>
</tr>
<tr>
<td>Treatment (1st /2nd Eye)</td>
<td>Threshold / None</td>
<td>Prethreshold / Threshold</td>
<td>From Prethreshold through Threshold and beyond-both eyes</td>
</tr>
</tbody>
</table>

**Prethreshold**: Zone 1 ROP of any stage less than threshold; zone 2 ROP at stage 2+; zone 2 ROP stage 3 without plus; zone 2 ROP stage 3+ with fewer than the threshold number of sectors of stage 3+.

**Threshold**: Five or more contiguous or eight cumulative clock hours (30o sectors) of stage 3+ ROP in either zone 1 or 2.

**BEAT-ROP**: Included ROP from Prethreshold through Threshold and beyond.
### CRYO-ROP: The Fellow Eye was the Control (Not Treated)

<table>
<thead>
<tr>
<th></th>
<th>CRYO Treated Eye: Success</th>
<th>CRYO Treated Eye: Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treated Eye:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>Large numbers are here!!!</td>
<td>Treatment is Bad</td>
</tr>
<tr>
<td>Failure</td>
<td>Treatment is Good</td>
<td>Large numbers are here!!!</td>
</tr>
</tbody>
</table>

Large numbers are here in the non-treated eye, indicating that treatment is bad if the fellow eye is success and the treated eye is failure.
ETROP: The Fellow Eye was the Control (LATE Treated)

<table>
<thead>
<tr>
<th></th>
<th>Early Treated Eye: Success</th>
<th>Early Treated Eye: Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Treated Eye: Success</td>
<td></td>
<td>Treatment is Bad</td>
</tr>
<tr>
<td>Late Treated Eye: Failure</td>
<td>Treatment is Good</td>
<td></td>
</tr>
</tbody>
</table>
Treatment References

- NEJM 2011;364:603-615.
Patients at Greatest Risk: Zone I

2x the distance from the center of the disc to the center of the macula on the temporal side.

Many patients who have Zone I ROP become totally blind: many references!
# Preliminary Unfavorable Structural Outcomes: Zone I Eyes

<table>
<thead>
<tr>
<th>Study</th>
<th>CRYO-ROP Age of Rx: Control/Treated</th>
<th>ETROP 37.0 wk/35.2 wk</th>
<th>BEAT-ROP 33.7 wk/34.7 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Rx:</td>
<td>~/37 wk</td>
<td>24/111 (21.6%)</td>
<td>23/66 (34.8%)</td>
</tr>
<tr>
<td>Control Outcome</td>
<td>~ (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated Outcome</td>
<td>~ (33%)</td>
<td>12/111 (10.8%)</td>
<td>2/62 (3.2%)</td>
</tr>
</tbody>
</table>
When and How to Treat in Zone I

- Treat Type 1 ROP (ETROP):
  - Any stage ROP with plus disease.
  - Stage 3 without plus disease.

- Treatment choices with severe ROP:
  - Current “standard of care”: Laser.
  - Severe cases: Consider Bevacizumab.
Consider Bevacizumab....

- If the infant is so ill that Laser may not be tolerated (on an oscillating ventilator).
- If vitreous hemorrhage obscures the view of the retina (preventing Laser).
- If the tunica vasculosa lentis is so dense that the irides will not dilate enough to perform Laser.
- If ROP is “typical” (Stage 3) but very severe or is “APROP” (rush disease).
Best Treatment for Patients with Severe Iris Neovascularization: Bevacizumab: 550 grams; 23 wk: Difference within 2 to 3 days:
Bevacizumab Monotherapy Compared to Laser Therapy for ROP

- Laser Therapy may cause posterior synechiae, hemorrhage, cataracts, and increased or decreased ocular pressure.
Bevacizumab Monotherapy Compared to Laser Therapy for ROP

- Laser Therapy destroys significant visual field in infants with Zone I ROP.
Bevacizumab Monotherapy Compared to Laser Therapy for ROP

• Laser Therapy often causes a high myopia in patients with Zone I ROP.
Literature: Bevacizumab for ROP

- **Salvage therapy:** after laser (very late—Stages 4B and 5).
- **Combination therapy:** with or after laser (earlier—Stages 3 or 4A).
Literature: Bevacizumab for ROP

- **Monotherapy**: (No laser) (Type 1 ETROP preferred).
- **Different details**: doses, volumes, gauge needles, etc.
Bevacizumab Monotherapy Compared to Laser Therapy for ROP

• Bevacizumab is effective more rapidly than Laser therapy:
  – Following Laser, 7-14 days for existing VEGF in the vitreous to diminish—for ROP to stop getting worse.
  – Bevacizumab immediately stops the effects of VEGF in the peripheral retina and in the vitreous.
Bevacizumab Monotherapy Compared to Laser Therapy for ROP

• Fragile infants do not require (re)-intubation pre-operatively. Infants often are discharged 2 weeks earlier following Bevacizumab than following Laser.

• Infants require fewer ophthalmic drops and the vitreous reaction is less post-injection than post-laser.
Specific Benefits of Bevacizumab Monotherapy for ROP

- There is a definitive end point ("completion" of vascularization).
- Usually only a single intravitreal injection of \( \frac{1}{2} \) the adult dose (0.625 mg in 0.025 ml) is required for each eye.
- (Perhaps \( \frac{1}{4} \) the adult dose could be used—but recurrences may be more frequent.)
Specific Benefits of Bevacizumab Monotherapy for ROP

- Bevacizumab enlarges the window of treatment.
- When you treat early (ETROP)—you do less damage when you give bevacizumab—many times the number of infants are receiving laser than is necessary.
Specific Benefits of Bevacizumab Monotherapy for ROP

• When you treat late (CRYO-ROP)—you still have a chance of getting a good outcome when you give bevacizumab—even when laser would not be possible or would not allow good structural or functional results.
Specific Benefits of Bevacizumab Monotherapy for ROP

- Bevacizumab is readily available and inexpensive—can be used worldwide.
- The infant vitreous is very viscous.
- Bevacizumab has a relatively long half-life.
Specific Benefits of Bevacizumab Monotherapy (without Laser)

• Bevacizumab is too large to easily penetrate the intact retina or to readily escape the eye—unless Laser Therapy has destroyed the retinal barrier. However, some does escape the eye.
BEAT-ROP Study

Bevacizumab Eliminates the Angiogenic Threat of Retinopathy Of Prematurity

[Response of Stage 3+ ROP to Intravitreal Bevacizumab]
BEAT-ROP Enrollment

150 Patients from 15 Centers

- Texas (10 centers = 128 patients)
- South Carolina (2 centers = 9 patients)
- California (1 center = 7 patients)
- Illinois (1 center = 5 patients)
- Colorado (1 center = 1 patient)
Patients Treated

2x or 3x the distance from the center of the disc to the center of the macula on the temporal side.

Zone I and Posterior Zone II: Measured Temporally
Figure 2. Enrollment, Randomization, and Follow-up of the 150 Study Infants.
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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</thead>
<tbody>
<tr>
<td>Randomized to Group</td>
<td>IVB Zone I</td>
<td>IVB Zone I</td>
<td>CLT Zone I</td>
<td>IVB Zone II</td>
<td>IVB Zone II</td>
<td>IVB Zone II</td>
<td>CLT Zone II</td>
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<tr>
<td>Patient</td>
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<td></td>
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<tr>
<td>Birth Weight (gms)</td>
<td>595</td>
<td>450</td>
<td>650</td>
<td>470</td>
<td>575</td>
<td>550</td>
<td>665</td>
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<tr>
<td>Gestational Age (wks)</td>
<td>24</td>
<td>23</td>
<td>28</td>
<td>23</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
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<tr>
<td>Ethnicity</td>
<td>Hispanic</td>
<td>Caucasian</td>
<td>Hispanic</td>
<td>Caucasian</td>
<td>African Am</td>
<td>African Am</td>
<td>Hispanic</td>
</tr>
<tr>
<td>PMA at Treatment (wks)</td>
<td>33.6</td>
<td>33.3</td>
<td>33.6</td>
<td>32.6</td>
<td>35.7</td>
<td>36.4</td>
<td>35.1</td>
</tr>
<tr>
<td>Hospitalized: Rx to</td>
<td>47</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>83</td>
<td>NA</td>
</tr>
<tr>
<td>Discharge (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged on Oxygen</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>PMA at Death (wks)</td>
<td>49.9</td>
<td>33.7</td>
<td>37.4</td>
<td>37.4</td>
<td>44.7</td>
<td>48.7</td>
<td>39.3</td>
</tr>
<tr>
<td>Cause of Death</td>
<td>Low Oxygen</td>
<td>Do Not Resuscitate</td>
<td>Sepsis (Coag Neg Staph)</td>
<td>Resp Failure</td>
<td>Resp Failure</td>
<td>Low Oxygen</td>
<td>Resp Failure</td>
</tr>
<tr>
<td>Location at Death</td>
<td>Off Monitor at Home</td>
<td>In Hospital</td>
<td>In Hospital</td>
<td>In Hospital</td>
<td>In Hospital</td>
<td>Off Monitor at Home</td>
<td>In Hospital</td>
</tr>
</tbody>
</table>
## BEAT-ROP Deaths

<table>
<thead>
<tr>
<th>Randomized to Group Patient</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Weight (gms)</strong></td>
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<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td><strong>Gestational Age (wks)</strong></td>
<td>24</td>
<td>28</td>
<td>23</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
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<tr>
<td><strong>Ethnicity</strong></td>
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<td>Caucasian</td>
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<td>33.6</td>
<td>33.6</td>
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<td>35.7</td>
<td>36.4</td>
<td>35.1</td>
</tr>
<tr>
<td><strong>Hospitalized: Rx to Discharge (days)</strong></td>
<td>47</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>83</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Discharged on Oxygen</strong></td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
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<tr>
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<td><strong>Cause of Death</strong></td>
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<td>Resp Failure</td>
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<td>Resp Failure</td>
</tr>
<tr>
<td><strong>Location at Death</strong></td>
<td>Off Monitor at Home</td>
<td>In Hospital</td>
<td>In Hospital</td>
<td>In Hospital</td>
<td>Off Monitor at Home</td>
<td>In Hospital</td>
</tr>
</tbody>
</table>
# BEAT-ROP Deaths

<table>
<thead>
<tr>
<th>Randomized to Group Patient</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>7</th>
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</thead>
<tbody>
<tr>
<td>Birth Weight (gms)</td>
<td></td>
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<tr>
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<tr>
<td>Hospitalized: Rx to Discharge (days)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Discharged on Oxygen</td>
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<td>NA</td>
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<tr>
<td>PMA at Death (wks)</td>
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<td>37.4</td>
<td>44.7</td>
<td>39.3</td>
</tr>
<tr>
<td>Cause of Death</td>
<td>Do Not Resuscitate</td>
<td>Sepsis (Coag Neg Staph)</td>
<td>Resp Failure</td>
<td>Resp Failure</td>
</tr>
<tr>
<td>Location at Death</td>
<td>Off Monitor at Home</td>
<td>In Hospital</td>
<td>In Hospital</td>
<td>Off Monitor at Home</td>
</tr>
</tbody>
</table>

For patient 5, the cause of death is listed as Severe Sepsis (Coag Neg Staph) following a diagnosis of Sepsis. Additionally, the location at death is specified as In Hospital.
Documentation by RetCam
Photographs—First ROP RCT

RetCam Shuttle

RetCam 3

19” flat panel display
New ergonomic hand piece
Large work surface
Pull out keyboard with soft-key controls
Fluorescein Angiography Module
Wrap-around cord holster
Storage drawers
Photo and text printer
Tri-function foot control
RetCam Photography for Timely Accuracy

- Allowed confirmation of Stage by a second ophthalmologist with electronic transmission of images quickly before treatment.
- Made sure of randomization to the correct arm of the study (Zone I or Posterior Zone II) (objective measurement from the RetCam photograph—not easy with the infant moving.)
- Images could be taken by a doctor, nurse, technician or just a hospital photographer—the doctor’s schedule did not delay diagnosis.
RetCam Photography for Sequential Images over Time

Imaging of Retinopathy of Prematurity in study patients:

Documented disease development before treatment; identified skipped areas; recorded response to treatment; documented recurrence when observed before re-treatment; allowed objective determination of the final anatomical outcome.
RetCam Photography for Parents

• Following teaching with RetCam images:
  – Parents could understand better why their infant needed treatment and the consequences of untreated disease.
  – Parents consented more willingly—rapport with the staff was established.
  – Parents understood the need for follow-up and complied better with repeated outpatient examinations
Preparation of Intravitreal Bevacizumab: Compliance with USP Chapter 797 Guidelines

Prepare in credentialed pharmacy with sterile technique.
Intravitreal Injections of Bevacizumab for Neonates

31 gauge needle (5/16”)

0.025 ml (0.625 mg)

0.3 ml Insulin Syringe with 0.5 Unit Marks
(Note: 2.5 Insulin Units = 0.025 ml)
Intravitreal injections of Bevacizumab

- The lens of the **very** immature infant with ROP is **very** large (blue).
- It is worse to **hit the lens** on the way in (sharp trauma) or out (blunt trauma) than to **enter the peripheral, undifferentiated, neuroblastic retina**
Normal Inner Retinal Vasculogenesis

Vitreous Surface: Retinal Vessels

Vitreous Surface: Retinal Vessels

20 wk

25 wk

30 wk

35 wk

40 wk

Scleral Surface: Choroidal Vessels
Table 2. Ocular Outcomes in the 143 Survivors at 54 Weeks’ Postmenstrual Age.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zone I ROP (N=64)</th>
<th>Zone II Posterior ROP (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravitreal Bevacizumab (N=31)</td>
<td>Conventional Laser Therapy (N=33)†</td>
</tr>
<tr>
<td>Recurrence of ROP (primary outcome) — no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>29 (94)</td>
<td>19 (58)</td>
</tr>
<tr>
<td>In one eye</td>
<td>2 (6)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>In both eyes</td>
<td>0</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Eyes affected — no.</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Odds ratio for recurrence with bevacizumab (95% CI) [P value]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per zone</td>
<td>0.09 (0.02–0.43) [0.003]</td>
<td></td>
</tr>
<tr>
<td>For zones I and II combined</td>
<td></td>
<td>0.17 (0.05–0.53) [0.002]</td>
</tr>
<tr>
<td>Interval from treatment to recurrence — wk‡</td>
<td>19.2±8.6</td>
<td>6.4±6.7</td>
</tr>
<tr>
<td>Vitrectomy — no. of eyes</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Structural outcomes of recurrence — no. of eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular dragging</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Complications requiring intraocular surgery — no. of eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornea opacity requiring corneal transplant</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lens opacity requiring cataract removal</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Laser: 760 gm; 24 wk at birth

2 months

13 months
Laser: 650 gm; 22 wk at birth

2 months

11 months
Bevacizumab: 495 gm; 24 wk at birth

3 months

13 months
Bevacizumab: 570 gm; 24 wk at birth

2.5 months

18 months
Primary Outcome

- **Primary Failure:** Development of Recurrence of ROP: (Stage 3 with Plus) Requiring 2 or more Laser or 2 Bevacizumab Treatments (Good vision still possible). The IRB would not allow patients to remain untreated knowingly until retinal detachment occurred.
Bevacizumab (Avastin) Therapy is Dose Related

• **Too much:**
  – Stops Growth into Vitreous, and *permanently*
  – Stops Growth forward into Avascular Retina

• **Too little:**
  – Temporarily stops all growth, but sooner or later
  – Neovascular growth *recurs* into vitreous (from two sites)

• **Just right:**
  – *Stops Growth into Vitreous, and temporarily:*
  – *Stops Growth into Avascular Retina, but soon:*
  – *Growth into Avascular Retina Continues!*
Bevacizumab: 650 gm; 24 wk at birth (Zone I) Recurrence-LE-Stage 3+

33.7 wks PMA

81.9 weeks PMA
Bevacizumab: 490 gm; 24 wk at birth (Zone I) Recurrence-RE-Stage 3+

34.6 weeks PMA

82 weeks PMA
Laser Recurrence Right Eye: Retreated "Successfully"
Bevacizumab Recurrence Right Eye: Retreated “Successfully”
Unintended Outcome

• **Total Failure:** Development of Retinal Detachment: (Stage 4a to 4b or Stage 5 with Membranes) Requiring Vitrectomy (Usually a serious decrease in vision).
Laser Recurrence Right Eye: Post Vitrectomy
Bevacizumab Recurrence Left Eye: Requiring Vitrectomy
Why Dose/Ocular Volume May Need to Be Larger to Treat ROP

- Extraretinal fibrovascular proliferation results in higher vitreous levels of VEGF with rapidly advancing ROP compared to lower vitreous levels of VEGF with slowly progressive ARMD (age related macular degeneration).
- Dose cannot be related to ocular volume alone—must consider amount of VEGF in the vitreous with severe ROP.
What Will the Be the Effect of a Higher Dose/Ocular Volume on the Peripheral Retina?

- One half of the adult dose compared to one quarter of the adult dose may make:
  - Peripheral retina may not grow out as far (linear extent) or as fast (time sequence).
  - Recurrences less frequent.
  - Recurrences occur later.
What Will Be the Effect of a Higher Dose/Ocular Volume on VEGF Levels Systemically?

• Some Bevacizumab will exit the eye; however, much of the drug will combine with high vitreous levels of VEGF.
Specific **Ocular** Complications of Bevacizumab

- **No ocular complications** demonstrated in animal models or human case reports:
- Must be vigilant for immediate traumatic events: lens rupture or dislocation, retinal tears, etc.
- Must be vigilant later for cataracts, retinal detachment, endophthalmitis, etc.
Specific Ocular Toxicity of Bevacizumab

• Rat model supports Bevacizumab (Hartnett)
• Case report demonstrates no toxicity in neonate (22wks; 350 gm)
First Histopathology of ROP Patient Treated with Bevacizumab

• 22 wks gestational age; 350 gms birth weight.
• Not vascularized to the macula.
• Aggressive Posterior-ROP: RUSH disease.
• Too sick to tolerate Laser therapy—which would have left almost no visual field and/or caused cataracts due to iris neovascularization.
• Patient treated at 31 + 41 wks (0.50 mg; 0.02 ml)
• Patient died at 52 wks; parents donated eyes.
Right Eye-Posterior/Central Retina

Low and higher power views of posterior retina. Notice the intact layers of the retina without necrosis, inflammation or scarring, including intact photoreceptors consistent with non-toxic effect. (There is retinal detachment and a crack in the inner retina associated with artifact of processing of the tissue)
Low and higher power views of peripheral retina. Notice the intact layers of the retina without necrosis, inflammation or scarring, including intact photoreceptors consistent with non-toxic effect. Notice the cellularity in the area of inner blood vessels seen in ROP. (There is retinal detachment consistent with artifact of processing of the tissue)
Specific **Systemic** Toxicity of Bevacizumab

- No **systemic toxicity studies** have prospectively investigated the effects of Bevacizumab on the brain, lung, kidney, etc. in animal models or human case reports (no reports of systemic toxicity to date).
Be Careful of Pharmacokinetic Literature: Bevacizumab and VEGF Levels

- Different routes of administration: intravenous, intravitreal, subconjunctival or topical.
- Different sources of specimens: plasma, aqueous, vitreous, subretinal fluid.
Be Careful of Pharmacokinetic Literature: Bevacizumab and VEGF Levels

- Different animal species: mouse, rat, rabbit, pig, monkey, human.
- What are the minimal/maximal levels of VEGF that permanently affect development of brain, lung, kidney, etc.??
Be Careful of Pharmacokinetic Literature: Bevacizumab and VEGF Levels

• Different **subject ages**: adults, older children, term infants, **preterm infants**. (When injected? How many injections? When sampled? How many times sampled?)

• Must include **sample times beyond peak level**.
Be Careful of Pharmacokinetic Literature: Bevacizumab and VEGF Levels

• Different ROP Stages: may or may not have had Stage 3 equivalent (May be Stages 4 or 5).

• Laser may or may not have been applied prior to Bevacizumab.
Be Careful of Pharmacokinetic Literature: Bevacizumab and VEGF Levels

- **Needle** may have been large (greater diameter) (Reflux).
- **Injection volume** may have been large (Increased IOP may cause leakage.)
Serum VEGF vs Time

![Graph showing the time course of serum VEGF before and after intravitreal Bevacizumab. The graph indicates a significant decrease in serum VEGF levels from pre to 2 weeks post-injection.]

Serum Concentrations of Bevacizumab and VEGF in Infants with Retinopathy of Prematurity

Serum Concentrations of Bevacizumab and VEGF in Infants with Retinopathy of Prematurity

- The best study to date, but......
- Laser Therapy given prior to Bevacizumab Injection.
- Samples taken for only 14 days.
What’s Needed:

• Better Pharmacokinetic Study: **Human, plasma** samples (including days **beyond peak** levels), from **preterm infants** who were given a **small volume and dose of intravitreal Bevacizumab** for Vision Threatening ROP that had previously **not been treated with Laser** using a **31 gauge needle**.
What’s Needed:

- Large, prospective, randomized, controlled, clinical trials looking for Bevacizumab efficacy and toxicity. (Study different doses, and different Anti-VEGF substances).

- Registry of infants receiving Bevacizumab including Zone II ROP to follow for immediate complications (minutes after injection), recurrence (weeks following injection) and long term toxicity (years following injection).
What’s Needed

• **Survival**—real deaths related to **Bevacizumab**:
  – not infants “DNR” taken off ventilator support.
  – not infants at home taken off monitors and oxygen.

• **Study organs vascularizing late in gestation**:
  – Brain (development—multiple aspects);
  – Lung (pulmonary hypertension, poor pulmonary function);
  – Kidney (systemic hypertension, proteinuria)
Conclusions

• Intravitreal Bevacizumab Monotherapy, as compared with Laser Therapy, in infants with Vision Threatening ROP in Zone I showed a significant treatment benefit.

• The peripheral retinal vessels continued to develop following Bevacizumab Monotherapy, but Laser Therapy led to permanent destruction of the peripheral retina.
Conclusions

• But, safety has not been established.
• “Off-label” Bevacizumab Monotherapy requires written consent, sterile technique, and a trained ophthalmologist to do adequate treatment and follow-up.