Bevacizumab: Treatment for ROP

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Disclosure Statement

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

FDA Disclosures

This presentation involves comments or discussion of the investigational use of Bevacizumab: Anti-Angiogenic Agent: Anti-Vascular Endothelial Growth Factor
Pathogenesis of ROP

Accelerated Retinal Detachment

Severe Retinal Dystrophy

At Risk

1st Exam

1st Exam

Normal Intrauterine Oxygen and VEGF

Premature birth

Normal Intrauterine Vessel Growth

Stage 0 ROP

Stage 1 ROP (Line)

Stage 2 ROP (Ridge)

Stage 3 ROP (Extraretinal fibrovascular proliferation)

Cryotherapy

Laser therapy

Bevacizumab therapy

Successful Treatment of Retinopathy
Immediately after therapy
Several weeks after therapy

Tractional Events

Stage 4 Retinal detachment
Stage 5 (Total retinal detachment)

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 3 onset

XX

XX

Pathogenesis of ROP

*
# 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>
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</th>
<th>ETROP</th>
<th>BEAT -ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Rx:</td>
<td>None/ 37 wk</td>
<td>37.0 wk/35.2 wk</td>
<td>33.7 wk/34.7 wk</td>
</tr>
<tr>
<td>Control/</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>(33%)</td>
<td>24/111 (21.6%)</td>
<td>23/66 (34.8%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>(33%)</td>
<td>12/111 (10.8%)</td>
<td>2/62 (3.2%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></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 case: **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:
Rationale for Initial Laser Treatment (Destructive Therapy)

- Laser the avascular retina to eliminate angiogenic factor, VEGF (vascular endothelial growth factor), by ablating the avascular retina.
Laser Therapy **Zone II**: ETROP-2003
Laser Therapy **Zone I**: ETROP-2003
Rationale for Initial Bevacizumab Treatment (Antigen-Antibody Therapy)

- Inject Bevacizumab into the vitreous to decrease angiogenic factor, VEGF (vascular endothelial growth factor), by rendering it inactive.
Bevacizumab Therapy in Zone II: BEAT-ROP-2011
Bevacizumab Therapy in Zone I: BEAT-ROP-2011
Vitreous Surface: Retinal Vessels

Normal

Inner Retinal Vasculogenesis

Scleral Surface: Choroidal Vessels
Vitreous Surface: Retinal Vessels and Vascular Precursors

Arrested
Inner
Retinal
Vasculo-
genesis

Scleral Surface: Choroidal Vessels

25 wk
54 wk
BEAT-ROP Study

Bevacizumab Eliminates the Angiogenic Threat of Retinopathy Of Prematurity

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

- RetCam Imaging: before, 1 week, 1 month, 6 months, and 12 months.
- Half of the infants were given 0.625 mg (0.025 mL) sterile Bevacizumab with a 31 gauge, 5/16 inch needle attached to a 0.3 mL syringe.
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
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 for Neonates

• 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.
Vitreous Surface: Retinal Vessels

Normal Inner Retinal Vasculogenesis

Scleral Surface: Choroidal Vessels
BEAT-ROP Results

• Primary ocular outcome: Recurrence of ROP in one or both eyes requiring re-treatment before 54 weeks (≈ 6 months) post menstrual age.

• This “change in protocol” was to make recurrence a variable with 3 possible outcomes. (This change was made by the DSMB.)

• Infants could not go to retinal detachment without attempted re-treatment (IRB decision).
<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)</td>
<td>[0.003]</td>
</tr>
<tr>
<td>For zones I and II combined</td>
<td></td>
<td></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>
Successful Laser: 760 gm; 24 wk at birth

2 months

13 months
Successful Bevacizumab:
495 gm; 24 wk at birth

3 months

13 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.
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).
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.
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

- 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.
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 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.
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.