EYE CARE ISSUES IN THE PREMATURE INFANT
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Ross Eye Institute
University at Buffalo

Questions for Today
- Who should be screened?
- When should they be screened?
- Who are the responsible parties?
- What are the obligations of primary care practitioners?
- What is new in the treatment of ROP?
- What is the natural ocular history of premature infants with and without ROP?

SCREENING

Screening Guidelines for Acute ROP - When
- Initial exam
- Subsequent exams
- Concluding exam

Initial Exam

<table>
<thead>
<tr>
<th>Gestational Age at Birth, wk</th>
<th>Age at Initial Examination, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>23</td>
<td>10</td>
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<td>24</td>
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<td>28</td>
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<td>29</td>
<td>10</td>
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<tr>
<td>30</td>
<td>10</td>
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<tr>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>32</td>
<td>10</td>
</tr>
</tbody>
</table>

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

Subsequent Exams

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Initial Exam Date</th>
<th>Subsequent Exam Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Doe</td>
<td>10/5/2011</td>
<td>10/15/2011</td>
</tr>
<tr>
<td>Jane Smith</td>
<td>10/10/2011</td>
<td>10/20/2011</td>
</tr>
</tbody>
</table>

(If necessary)
Conclusion of Exams
- Zone III retinal vascularization without previous zone I or II ROP
- Full retinal vascularization
- PMA of 45 weeks and no prethreshold ROP or worse
- Regression of ROP
- These rules do not apply post-treatment

Responsible Parties

Responsible Parties
- Hospital (Admitting; Transferring; Receiving)
- Neonatology team
- Ophthalmology
- Primary care practitioners who accept premature infants into their practice
- Parents

Screening - Who
- Premature infants with BW ≤ 1500 grams
- GA ≤ 30 weeks

Obligations
- Any caregiver who provides care for these infants or accepts such infants into their practice should be familiar with the ROP screening guidelines and be willing to act on them and appropriately document such action.

Later Onset Sequelae of Prematurity
- Myopia
- Amblyopia
- Strabismus
- Retinal detachment
- Glaucoma
- Cataract
Background

- 2004: Bevacizumab efficacy proven for CA. FDA approval.
- 2005: Ranibizumab efficacy proven for AMD
- 2006: Bevacizumab achieves wide-spread off-label use for AMD
- 2011: CATT Trial – Bz and Rz found to be equivalent in nearly all categories

Chemistry of Bevacizumab

- Full monoclonal antibody
- Large molecule (150 KD)
- Long half-life (5-10 days)
- Systemic circulation 1:1000
- Anti-VEGF

Pharmacokinetics of Bevacizumab

- IVB and ROP
  - Rescue
  - Combination
  - Monotherapy

Pharmacokinetics of IVR

- Monkey – Gaudreault, 2005
- Rabbit – Bakri, 2007
- Half-life 3 days
- High retinal concentration (3:1)
- Serum concentration very low

Pharmacokinetics of IVB

<table>
<thead>
<tr>
<th>Compartiment</th>
<th>t1/2 (days)</th>
<th>tmax (days)</th>
<th>Cmax (µg/ml)</th>
<th>% of Vitreous</th>
<th>AUC (µg/ml*day)</th>
<th>Exposure to Bevacizumab % of Vitreous Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous</td>
<td>4.32</td>
<td>4</td>
<td>4.09</td>
<td>1400</td>
<td>5300</td>
<td>---</td>
</tr>
<tr>
<td>Aqueous</td>
<td>4.88</td>
<td>3</td>
<td>37.7</td>
<td>14.4</td>
<td>295</td>
<td>8.9</td>
</tr>
<tr>
<td>Serum</td>
<td>6.66</td>
<td>8</td>
<td>3.32</td>
<td>36.8</td>
<td>54</td>
<td>1.6</td>
</tr>
</tbody>
</table>

AUC = area under curve; Cmax = maximum concentration; tmax = time to attain maximum concentration; t1/2 = half-life.
Samples were taken from the aqueous and vitreous of the injected eye.
Bakri et al, 2007
Small Series
- Law, et al, 2010
- Mintz-Hittner & Kuffel, 2008

Randomized Trials
- BEAT-ROP, 2011

Assessment
- Efficacy
- Safety
- Practicality

CLT vs. IVB

<table>
<thead>
<tr>
<th></th>
<th>CLT</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone I</td>
<td>44%</td>
<td>6%</td>
</tr>
<tr>
<td>Zone II post.</td>
<td>12%</td>
<td>5%</td>
</tr>
</tbody>
</table>

BEAT – ROP

<table>
<thead>
<tr>
<th>Disease Recurrence (infants)</th>
<th>CLT</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone I</td>
<td>44%</td>
<td>6%</td>
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<tr>
<td>Zone II post.</td>
<td>12%</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomic Abnormality (eyes) inc/recurrence</th>
<th>CLT</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone I</td>
<td>88/73</td>
<td>1/2</td>
</tr>
<tr>
<td>Zone II post.</td>
<td>7/9</td>
<td>2/4</td>
</tr>
</tbody>
</table>

CLT
- Effective
- Established
- Expensive
- Labor intensive
- Mild field loss
- Cataracts
- Zero systemic effect

IVB
- Effective
- Controversial
- Cheap
- Easy
- Minimal field loss
- No ocular complications
- ??? Systemic effect

Study Flaws
- Recurrence vs. lack of regression
- Infants vs. eyes
- Sample size too small for safety
- No visual results
- Unmasked design
Safety Issues
- Eye – minimal
- Systemic – potentially profound

Systemic Effects
- Molecular half-life
- Serum concentration and pharmacokinetics
- Blood – retinal barrier
- Reduced VEGF plasma levels
- Cause and effect

Systemic Concerns
- PVL; BPD; SD
- ATE
- Renal Thrombotic Microangiopathy

ATE Events
- Ranibizumab
- Bevacizumab

ATE Mechanism
- Decreasing VEGF
- Increases inflammation
- Increases plaque instability
- Decreases endothelial cell proliferation
- Increases adhesion to endothelium
- Decreases collateralization
- BZ – VEGF complexes may activate platelets

Systemic Safety
- Little direct evidence
- Speculation revolves around circulating Bz and
  - Tiny weight
  - Developing organs
  - PVL; BPD; SD
- Comparison to other antiangiogenesis drugs (e.g. interferon)
Conclusions
- IVB is more practical
- IVB is safe to the eye
- IVB is highly efficacious
- IVB systemic safety is unclear and controversial
- IVB is associated with late recurrences (up to 54 weeks)
- IVB administration must be properly timed

Personal Recommendations
- Treatment of choice for:
  - Zone I ROP
  - AP – ROP
  - Zone II or worse ROP with V.H. or media opacity

“Use of [IVB] must include informed consent that is based on a discussion of the known and unknown risks versus the risk of blindness.”