Bevacizumab and ROP: Review of an RCT

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UHW
Sections

- ROP
- VEGF and its involvement in the pathogenesis of ROP
- Details of the study (BEAT-ROP)
  - Methods
  - Results
  - Conclusions
- Limitations/controversies
- Systemic side effects
- Conclusions and recommendations
Retinopathy of Prematurity
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Demarcation line separates avascular from vascularized retina</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Ridge arising in region of demarcation line</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Extraretinal fibrovascular proliferation/neovascularization</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Partial retinal detachment</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Total retinal detachment</td>
</tr>
<tr>
<td>Pre-plus disease</td>
<td>More vascular tortuosity than normal, but insufficient for diagnosis of plus disease</td>
</tr>
<tr>
<td>Plus disease</td>
<td>Vascular dilation and tortuosity of at least two quadrants of the eye</td>
</tr>
</tbody>
</table>
Vascular Endothelial Growth Factor (VEGF)
VEGF

- Vascular endothelial growth factor
- Mitogen
- Critical rate-limiting step in physiological and pathological angiogenesis & angiogenic sprouting
- Five isomers; VEGF$_A$ involved in angiogenesis
- Several isoforms (VEGF-A$_{121, 145, 165, 183, 189, 206}$)
- Two receptors (VEGFR-1, VEGFR-2)
- HIF-1$\alpha$ key regulator, also inflammatory cytokines
Roles

• Physiological
  – Embryonic vasculogenesis and angiogenesis
  – Early postnatal development (esp kidneys)
  – Skeletal growth and endochondral bone formation
  – Ovarian angiogenesis (follicular growth and the development of the corpus luteum)
  – Regulates foetal lung maturation and surfactant production

• Pathological
  – Solid tumors and hematologic malignancies
  – Intraocular neovascular syndromes
  – Inflammation and brain edema
  – Polycystic ovary syndrome
VEGF in the eye

• VEGF is produced by retinal pigment epithelial cells, neurons, glial cells, endothelial cells, ganglion cells, Müller cells, and smooth muscle cells

• Angiogenesis, vasodilatation (NO), increased capillary permeability, monocyte chemotaxis
BEAT-ROP Study
BEAT-ROP Study Methods

• Prospective
• Controlled (laser treatment as standard)
• Randomised (computer controlled)
• Stratified (by zone) a-priori
• Unmasked (care givers and assessors). Post-hoc validation of enrolment and primary outcome by Reading Centre experts
Methods

• **Eligibility**: infants with 3+ disease in zone I or II

• **Primary outcome** treatment failure: the recurrence of neovascularization in one or both eyes arising from the retinal vessels and requiring retreatment by 54 weeks postmenstrual age (as derived from ET-ROP trial)
Scientific basis

• Laser therapy successful in 50% of Zone I and 80% of Zone II ROP

• However, permanent destruction of peripheral retinal cells
  – Loss of peripheral vision
  – Myopia

• Numbers: 24/group for zone I
  50/group for zone II
150 Patients were enrolled

67 Had zone I ROP

33 Were randomly assigned to intravitreal bevacizumab therapy
- 2 Died
- 1 Died
- 31 Were included in analysis

34 Were randomly assigned to conventional laser therapy
- 1 Had a protocol violation
- 33 Were included in analysis

83 Had zone II posterior ROP

42 Were randomly assigned to intravitreal bevacizumab therapy
- 3 Died
- 39 Were included in analysis

41 Were randomly assigned to conventional laser therapy
- 1 Died
- 40 Were included in analysis
<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>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></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>
Results and discussion

• Significant efficacy of intravitreal bevacizumab for zone I disease but not for zone II posterior disease (recruitment target not met for zone II)

• No infant intubated for injection (all needed intubation for laser therapy)

• Underpowered to detect safety of drug (mortality/toxicity)
Limitations and Controversies
Limitations/Controversies

• Significant risk of investigator bias
• Intravitreal injection not “straightforward” procedure
• Only short-term structural complications studied; long-term functional data needed
• Lack of safety data; possible adverse effects in neonates (see later)
• Monotherapy for a multifactorial disease
Attrition bias

7 infants died

5
  In hospital

2
  Laser group
    1 due to respiratory failure
    1 due to sepsis

3
  Bevacizumab group

2
  Bevacizumab group
    4 due to respiratory causes
    1 “do-not-resuscitate”

2
  At home
Time to recurrence - Zone I

Bevacizumab (mean 34.5±1.4 weeks)
- 35.1 - 37.9 weeks
- 43.7 - 46.5 weeks
- 52.3 - 55.1 weeks
- 60.9 - 63.7 weeks
- 69.5 - 72.3 weeks

Laser (mean 33.7±1.6 weeks)
- 38.5 - 41.7 weeks
- 45.2 - 48.4 weeks
- 51.9 - 55.1 weeks
Time to recurrence

- For 2SD, failure in the bevacimab group may not occur until 72.3 weeks, 18.3 weeks after primary end-point (54 weeks)
- 47.7% failures in bevacizumab group would be after primary endpoint for 2SD
- Almost all failures in laser group within primary endpoint, even for 2SD

- Bevacizumab alters disease course and recurrences are delayed
- Primary endpoint should be any recurrence, not a time-point. This was not reported.
- Exercise caution in use of bevacizumab before long-term data published
Systemic side-effects
VEGF inhibition in newborn period (animal data)

- Extensive apoptotic changes in the vasculature of neonatal but not adult mice

- Renal failure resulting in increased mortality

- Stunted growth (failure of chondrocytes at growth plates) and ovarian failure

- Lack of lung maturing and decreased surfactant production resulting in RDS
Systemic side-effects of VEGF-blockade

Systemic absorption (adult data)

- Ranibizumab: short serum half-life (6 hours); not detected in contralateral eye
- Bevacizumab: serum half-life 20 days; serum conc 20-687ng/ml (normal serum VEGF conc 100pg/ml)
- Intra-ocular bevacizumab lowers blood VEGF conc 117-fold in 1 day and 4-fold upto 1 month later

Systemic absorption (infant data)

- Even higher levels of bevacizumab and lower levels of VEGF noted in preterm infants (n=11) with ROP

Anti-VEGF molecules

- Pegaptanib: aptamer of VEGF$_{165}$ but now discontinued
- Bevacizumab (Avastin): full length murine-derived humanised monoclonal antibody with two VEGF binding sites (148kD).
  
  **Cost $50/dose**

- Ranibizumab (Lucentis): affinity-enhanced (5-20 fold) Fab fragment of bevacizumab (48kD)
  
  **Cost $2029/dose**

- Afibercept (VEGF Trap-eye): binding sequences of VEGFR-1 & -2 on an Fc backbone (90kD). 140 fold higher affinity for VEGF compared to ranibizumab
Conclusions and Recommendations
Conclusions

• Bevacizumab may be an effective treatment for Zone I ROP.
• Usefulness for zone II ROP uncertain
• Delayed recurrences requiring longer-term follow-up
• No systemic safety data yet
• Long-term follow-up study awaited (not before 2015/2016)
Recommendations

• Use with caution (?do no harm)
• Consider lower dose (effective in DR)
• Use ranibizumab (short half-life); however, 20-times more expensive
• Basis for co-ordinated surveillance study by creating a register, both for recurrences and for systemic safety monitoring
References - 1

References - 2

References - 3


