Lessons from the ETROP Study: Where do We go From Here?

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What is ROP?
- A disease of premature infants wherein retinal vessels fail to develop to the ora serrata
- Instead, vessel growth ceases and neovascularization can occur at the leading arcade of vessels
- Most of the time ROP regresses without treatment
- In some infants, retinal detachment can occur
ROP Treatment Prior to 2003
- Treat at threshold: Zone I or II; stage 3 for 5 continuous or 8 cumulative hours, and plus disease
- Findings from the CRYO-ROP Study
- Reduced blindness from 50% to 25%
- Myopia, low vision, strabismus remained serious problems

ROP Treatment After 2003
- Treat Type 1 (Zone I or II, plus disease; or Zone I stage 3)
- Watch Type 2 to progression and treat or regression

ROP 2010
- Findings published in 2003 confirmed in 6 years visual acuity testing
- Caveat that there is a trend to less favorable outcome if type 2 is treated early
- Awaiting visual fields reports/cs/Teller acuity

Problems with Eyes Treated at Prethreshold and Threshold
- High rate of myopia (63%) and high myopia (25%; >5D)
- Visual acuity outcomes are not great
- Astigmatism in 25% (>1.5 D)
- Strabismus 23%
- Visual field loss
Shift Attention to Prevention: abc’s of ROP

- A=avastin
- B=beta blockers
- C=cytokines

What is VEGF?

- First described as vascular permeability factor by Dvorak\(^1\)
- Purified and cloned in 1989 by N Ferrara\(^2\)
- Member of a family of angiogenic and lymphangiogenic growth factors:
  - VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PIGF*
- Secreted by a variety of cells in response to hypoxia/ischemia and other signals
- Increases vascular permeability
- Induces neovascularization

Avastin

- ASRS meeting, 07/05
  - MARINA results presented
  - Intravitreal Avastin data
- Lucentis approval 12 mo away
- Rapid adoption of Avastin
- No randomized, controlled trial completed to date
- Common uses of Avastin
  - AMD
  - Retinal edema associate with
    - Retinal vascular occlusion
    - Diabetic retinopathy
- Black box warnings
  - GI perforation
  - Hemorrhage (including GI, CNS)
  - Wound healing complications
- “The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established”

Avastin for ROP

- Case series
  - Retrospective
  - Non-comparative
- Stage 3 ROP
  - Zone I
  - Posterior zone II
- Intervention
  - Avastin 0.625mg (0.025mL)
  - 1 injection
  - No laser
- Outcome
  - 100% success
  - No complications

Conclusions

- Anti-VEGF injection therapy may become an additional treatment option for ROP
- Appropriate dose is yet to be determined
- Systemic safety profile yet to be determined
- At least one report of a late retinal detachment
- Reports of persistent avascular retina

B-Blockers for Prevention of ROP

- ROP occurs far less commonly in African American children c/w Caucasian
- B-Blockers (systemic) cure cutaneous hemangiomas (which are much more common in premature infants)

B-Blocker Polymorphisms

It has been shown in several large clinical trials that African-American infants are less likely to develop ROP, and less likely to have the disease progress. One possible explanation for this invokes beta-adrenergic receptor polymorphisms that exist in many African-Americans as protective against ROP. These polymorphisms cause variations in response to B-blocker treatment in African-Americans in conditions such as heart failure, because the effect of the polymorphism is to render the person already “blocked.” If this beta-blockade status were true in ROP, then it would suggest a reason for relative immunity to the disease in African-American infants.
**B-Blockers and the Eye**

- Less effective for glaucoma in African-Americans
- Effect on retinal vessels largely unexplored
- Study Design Issues: treat one eye, some of the drug may get into circulation and treat the other eye

**Cytokines that Control Homeostasis**

- TBDN-1: a novel n-acetyl transferase that controls the integrity of cell membranes and plays a role in downregulating protein production/cellular metabolism
- Present in healthy retinal endothelial cells
- Missing in neovascular eye disease

**Evidence pointing to mechanism**

- **Tubedown associates with cortactin and controls permeability of retinal endothelial cells to albumin**
  
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**Tbdn suppressed in neovascular retinal disease**

- **Tubedown-1 in Remodeling of the Developing Vitreal Vasculature in Vivo and Regulation of Capillary Outgrowth in Vitro**
  

- **Suppressed Expression of Tubedown-1 in Retinal Neovascularization of Proliferative Diabetic Retinopathy**
  
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- **Tubedown-1 (Tbdn-1) suppression in oxygen-induced retinopathy and in retinopathy of prematurity**
  
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IgF; VEGF, and ROP

- Work of Lois Smith
- Hypothesize that IgF-1 is suppressed at birth with concomitant suppression of VEGF
- IgF-1 remains suppressed in proportion to infant’s growth
- Eventually other factors take over and VEGF is suppressed in too much abundance leading to ROP

Treatment

- Offer IgF-1 to infants who grow poorly after birth
- Monitor infant growth

Conclusion

- Rate of retinal detachment from ROP is < 10% in the worst eyes; those randomized in the ETROP Study
- Treatment prevents blindness but visual acuity results/myopia/field loss remain important issues
- Need treatments to prevent ROP