**ANTI-VEGF FOR ROP**
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**Financial Disclosures**
- None relevant to this talk

**Medico legal consideration of Anti-VEGF use in infants**
- Whenever a drug is used with a
- Different dose than in the label larger or smaller
- Different indication than the label
- Different age group children or infant
- This is Off Label use by all definitions

**Off label use of a compounded drug**
- NO FDA LIKE TESTING HAS BEEN DONE ON ANY ANTI-VEGF DRUG FOR ROP OR ANY DISEASE IN INFANTS AND CHILDREN FOR DOSING EFFICACY OR TOXICITY
- NOT FOR AVASTIN OR LEUCENTIS
- AVASTIN IS ALSO A COMPOUNDED DRUG

**Consent must include**
- Off label use lack of testing in infants
- Compounded drug consent as well

**Laser vs. Anti-VEGF for ROP**
- BEAT ROP study
  - Showed no difference between laser and anti-VEGF for zone 2 disease
  - Showed a statistically significant difference between laser and anti-VEGF (Avastin) for zone 1 disease
The population in the study was 67% Hispanic, a more difficult type of ROP to treat but may not represent the ethnic make up of the United States or much of the rest of the world.

The laser failure rate for zone 1 disease was 42% as defined by the study. These 2 elements are important in understanding the results of this study.

What if other zone 1 laser study treatment failure rates where used would the results still be significant?

These 2 elements are important in understanding the results of this study.

This is a somewhat unfair comparison. The other study populations in these studies were not predominately Hispanic. These other studies did not have a finite cut off for 2nd laser treatment in the Drenser study. 31% of eyes received a second laser treatment but the final failure rate was 18%. But still the results for Zone 1 disease would not be significant in BEAT ROP if these other values were used.

Is anti-VEGF therapy safe?


This study was not powered to assess side-effects or safety. 150 infants randomised.

Mortality:
- 7 deaths overall (3 zone I, 4 zone II ROP)
- Bevacizumab 5 (6.6%) vs Laser 2 (2.6%)
- 4/5 respiratory deaths vs 1/2 respiratory death

This difference was not significant but is clinically concerning and should be investigated further.

Is anti-VEGF therapy safe?

Reynolds (NEJM 2011 Editorial)

Despite the lack of evidence, stated: "It seems reasonable to assume that intravitreal bevacizumab is safe."

BUT

Neonatology has had many examples of therapies being adopted because of short term benefit ahead of proper studies:

• Uncontrolled oxygen - First epidemic of ROP
• Interferon for capillary haemangiomas - spastic diplegia
• Post-natal steroids to "wean" off ventilator - later cerebral palsy
Does intra-vitreal bevacizumab escape into the systemic circulation?

Yes it does!

<table>
<thead>
<tr>
<th>Agent</th>
<th>MW (KDa)</th>
<th>Dose (mg)</th>
<th>Vitreous conc. (µM)</th>
<th>Vitreous half-life (days)</th>
<th>Peak plasma Conc. (ng/mL)</th>
<th>Systemic half-life (days)</th>
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<td>Pegaptanib</td>
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<tr>
<td>Ranibizumab</td>
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<td>2.5</td>
<td>9</td>
<td>0.79-2.9</td>
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<tr>
<td>Bevacizumab</td>
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<td>1.25</td>
<td>2.1</td>
<td>10</td>
<td>20-687</td>
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</tr>
</tbody>
</table>

Tolentino M Surv Ophthalmol 2011

And see – Hård AL, Hellström A Acta Paediatrica 2011

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Does intra-vitreal bevacizumab escape into the systemic circulation?


Case series, 11 eyes, Intravitreal bevacizumab 0.62mg per eye

Concentration of plasma VEGF over next 8 weeks

Pre-injection 2050 pg/ml

at 1 week post 170 pg/ml

at 7 weeks post 50 pg/ml

Pieh (BJO 2008) reported median plasma VEGF-A concentrations at 32 weeks PMA of:

658 pg/ml when no ROP

904 pg/ml when ROP (untreated).

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Actions of endogenous VEGF that might be adversely affected


Newborn rats treated with single dose systemic VEGF receptor inhibitor Su-5416

Lungs develop reduced septation, large air spaces

pulmonary hypertension

This persists into adulthood

Looks like BPD

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### Actions of endogenous VEGF that might be adversely affected

**VEGF** has been described as

*“The Swiss Army Knife of vasoactive factors”*

- **VEGF** regulates normal angiogenesis in many organs and has many related roles
- In CNS: is neurotropic, neuroprotective, maintains BBB
- In lungs: important role in alveolarisation
- Key roles in bone growth, cardiac and kidney development
- Are 6 main isoforms with different properties and actions

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### Actions of endogenous VEGF that might be adversely affected


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Safety issues

- There have been no dosing studies to determine the lowest effective dose for anti-VEGF in ROP
- Leucentis also remains in the general circulation but for a much shorter time than Avastin

Safety issues

- All use of Anti-VEGF drugs for ROP or use in infants and children is off label and requires appropriate documentation and consent
- The FDA is looking at more rigorous testing of drugs for use in neonates and children

Future Studies

- It maybe impossible to access the real risk to pre term infants of anti-VEGF but by reducing exposure by a lower dose of a drug which leaves the body more quickly may be the best choice Novartis will likely be doing a labeling study for the EU for use of Leucentis in ROP to define the lowest dose and drug safety

How do I use anti-VEGF in ROP

- If I have exhausted laser with a good pattern usually more than one laser for APROP
- Then after a complete and open discussion of the potential benefits and unknown risks
- Then one injection prior to 40 weeks PMA due to presence of endogenous TGFbeta

Anti-VEGF use world wide

- Does anti-VEGF have value
- Certainly where no laser is available or a doctor who knows how to do the laser treatment YES
- If Laser is available and the doctor knows how to do the appropriate laser treatment and the population is less Hispanic I feel laser is safer for the infant

How else does primary anti-VEGF treatment for ROP change care

- Anti-VEGF therapy takes a disease with a predictable course and a finite follow up period and changes it to a disease with an easy treatment technique initially and an indefinite follow up course which can lead to very late retinal detachment making doctor examination and parent cooperation for follow up a difficult issue when it is needed for 6 months or more
Anti-VEGF treatment for ROP will most likely have a role in ROP management but until convincing safety data is available the right drug and the right dose is still in question.

Laser in my opinion is still standard primary therapy for ROP in most populations.

- With standard laser treatment and early 4A LS vitrectomy the failure rates of total retinal detachment are 1-2% with visions as good as 20/20 and average VA 20/55.

- To change these results a new treatment needs to be very safe and show a significant advantage I am not convinced Anti-VEGF does that in ROP.