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 EFFICACEY 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

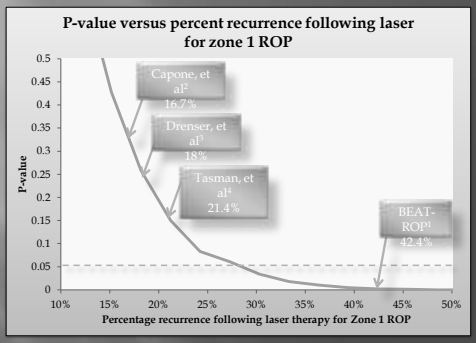
- BEAT ROP study
  - Showed no difference between laser and anti VEGF for zone 2 disease
  - Showed a statistically significant difference between laser and anti-VEGF (Avastin) for zone 1 disease

Why the difference ???

- 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…. difficult laser
- These 2 elements are important in understanding the results of this study

Laser vs. Anti-VEGF for zone 1 ROP

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



1. Mintz-Hittner, et al. NEJM 2011 February 17; 364(7):603–615.
2. Capone, et al. Am J Ophthalmol. 1993 Oct 15;116(4):444-50.
3. Drenser, et al. Retina. 2010 Apr;30(4 Suppl):S37-40
4. Tasman, et al. Ophthalmology. 2001 Sep;108(9):1644-6.

Anti-VEGF vs. Laser for zone 1 disease

This is a somewhat unfair comparison

1. The other study populations in these studies were not predominately Hispanic
2. 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%
3. 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?

BEAT-ROP study – Mintz-Hittner *N Engl J Med* 2011: 364; 603-615

This study was not powered to asses 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 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!

Agent	MW (KD)	Dose (mg)	Vitreous conc. (μM)	Vitreous Half-life (days)	Peak plasma Conc. (ng/mL)	Systemic half-life (days)
Pegaptanib	50	0.3	1.5	3.9	6-7	10
Ranibizumab	50	0.5	2.5	9	0.79-2.9	0.09
Bevacizumab	150	1.25	2.1	10	**20-687**	**20**

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?

Lee (*IOVS* 2011;52:ARVO E-abstract 3165). Preterm infants.

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).

Does intra-vitreal bevacizumab escape into the systemic circulation?

BEAT-ROP used ½ adult dose (0.625mg in 0.025ml)

Body of infant c. 1/50th adult

Vitreous volume less (1.6ml vs 4.0ml)

Sears (*Brit J Ophthalmol* 2008) estimates:

0.5-1mg bevacizumab intravitreal injection is **10,000 x** that needed to neutralize VEGF in vitreous in ROP cases.

following intravitreal injection, serum bevacizumab concentrations are **1,000 fold** higher (molar basis) than serum VEGF-A.

But - VEGF is produced and acts locally so blood concentrations do not accurately reflect levels of bioactive VEGF.

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 alveolisation

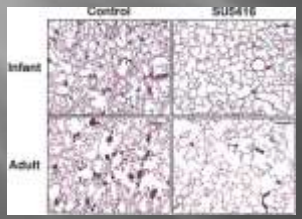
Key roles in bone growth, cardiac and kidney development

Are 6 main isoforms with different properties and actions

Actions of endogenous VEGF that might be adversely affected

Le Cras (*Am J Physiol Lung Cell Mol Physiol* 2002)

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

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

Conclusion

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

Conclusion

- With stadard 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