Pros and Cons in the use of AntiVEGF therapy in ROP

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TRANSPUPILLARY DIODE LASER PHOTOCOAGULATION REMAINS THE GOLD STANDARD TREATMENT FOR SEVERE ROP IN ZONES III AND II (90% of the patients needing treatment)

AAO - American Academy of Ophthalmology
AAPOS - American Academy of Pediatric Ophthalmology
AAP - American Academy of Pediatrics
TREATMENT OF ROP IN ZONE I WITH LASER

ROP ZONE I (10% of the patients needing treatment)

• CRYO-ROP: 78% of the treated patients → unfavourable outcomes with laser around 40% of the treated patients → VA < 20/200 by 15 years of age

• ET-ROP: 55% of unfavourable outcomes with laser (VA < 20/200)

CRYO-ROP: results after 1988
ET-ROP: results after 2004
THE USE OF ANTI-VEGF THERAPY IN ROP

- Increasing popular treatment for ROP especially in South America
- It has been described as simpler, cheaper and more effective alternative to conventional laser therapy
- Without needing of general anesthesia or sedation

- **But is it really safe to inject na anti-cancer drug into eyes of a premature infant?**

- The use of anti-VEGF is widely debated among ophthalmologists and neonatologists
1st Clinical Trial 2011: BEAT-ROP STUDY

USE OF BEVACIZUMAB (AVASTIN) WITHOUT LASER FOR ROP

CONCLUSIONS:

• Intravitreal bevacizumab monotherapy, as compared with laser therapy in ROP stage 3+ showed a significant benefit for zone I but not zone II disease.

• Development of peripheral retinal vessels continued after intravitreal bevacizumab, but laser therapy led to permanent destruction of the peripheral retina.

• The trial was too small to assess safety.

THE SEARCH FOR A SAFER DRUG

OR A DRUG THAT ACTED LESS TIME SYSTEMICALLY

GREATER POSSIBILITY OF RECURRING THE DISEASE
PRÓS AND CONS IN THE USE OF ANTI-VEGF THERAPY IN ROP

1) Which is the best drug?
2) What is the ideal dose?
3) Which is the percentage of recurrence?
4) And if a retreatment is necessary?
   Use laser or a new injection?
5) Need for a longer follow-up time after injection?
6) Long-term patients safety?

will need a study with more than 2,800 patients
1) Which is the best drug?

Is Avastin the right choice of treatment for retinopathy of prematurity?

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BEVACIZUMAB VERSUS RANIBIZUMAB

- Ranibizumab may be a better alternative for premature infants, although it is almost 40 times more expensive. It has a much shorter half-life in serum and was developed for concerns of systemic adverse effects of bevacizumab, Ann Hellström says.

  Christoph Bührer is not so concerned about the longer half-life of bevacizumab.

- Not as we only give one or two injections. I would rather like to acknowledge Helen Mintz Hittner et al. for using bevacizumab and not ranibizumab in the BEAT-ROP study. By choosing the cheap anti-VEGF, it will be possible to use this treatment also in the developing world, he says.
Is Bevacizumab the Best Drug for Treatment?

**Bevacizumab (Avastin)**
- Most studies used Avastin (BEAT-ROP)
- Complete molecular Antibody containing FcRn fraction
- ½ life for elimination of the eye = 20 days
- Supress systemic VEGF for several weeks
- Less recurrence of the neovascularization

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**Ranibizumab (Lucentis)**
- Few studies in ROP at moment - Higher cost compared to Avastin
- Fragmento da molécula do Avastin without FcRn fraction
- ½ life for elimination of the eye = 2 hours
- Do not supress systemic levels of VEGF
- More recurrences of the neovascularization
Bevacizumab (Avastin) for retinopathy of prematurity: Wrong dose, wrong drug, or both?

Robert L. Avery, MD

After observing fellow eye effects and the sensitivity of preretinal neovascularization to anti-VEGF agents, I proposed the use of lower doses of bevacizumab or changing to ranibizumab when treating ROP to lower the systemic risk in this susceptible population. Subsequently, several
2) What is the ideal dose?

58 eyes - Success Definition: reducción del plus después de 5 días de la inyección and absence of recurrence in 4 weeks

RESULTS  Fifty-eight of 61 enrolled infants had 4-week outcomes completed; mean birth weight was 709 g and mean gestational age was 24.9 weeks. Success was achieved in 11 of 11 eyes at 0.25 mg, 14 of 14 eyes at 0.125 mg, 21 of 24 eyes at 0.063 mg, and 9 of 9 eyes at 0.031 mg.

CONCLUSIONS AND RELEVANCE A dose of bevacizumab as low as 0.031 mg was effective in 9 of 9 eyes in this phase 1 study and warrants further investigation. Identifying a lower effective dose of bevacizumab may reduce the risk for neurodevelopmental disability or detrimental effects on other organs.
3) Which is the percentage of recurrence?

2011 - BEAT-ROP: RECURRENCE OF NEOVASCULARIZATION ??

6% in Avastin
(mean BW 615 g / GA 24 weeks)

X

27% in laser
(mean BW 657 g / GA 24 weeks)

REACTIVATION AFTER USE OF RANIBIZUMAB (Lucentis) IN ROP

Clinical Ophthalmology

Intravitreal ranibizumab as a primary or a combined treatment for severe retinopathy of prematurity

57 eyes / 29 patients
BW = 1,280 g
GA = 29.5 weeks
Severe ROP Zones I and posterior II
mean PCA at treatment
37.2 ± 2.2 weeks
75.4% Regression of ROP
53.4% Recurrence of neovascularization
By 3 to 15 weeks after injection 52/54 wks
REACTIVATION OF RETINOPATHY OF PREMATURITY AFTER RANIBIZUMAB TREATMENT

RYAN K. WONG, MD, SASHA HUBSCHMAN, BS, IRENA TSUI, MD

In summary, we examined the use of anti-VEGF agents for the treatment ROP. A significant number of infants treated with ranibizumab developed reactivation and required laser treatment; whereas no cases of eyes treated with bevacizumab had reactivation. In addition, we report the first case of bilateral effect of unilateral intravitreal ranibizumab for the treatment of retinopathy of prematurity. Although the shorter half-life of ranibizumab may make it an attractive option when concerned about systemic absorption, it may also translate into higher chance of reactivation when compared with infants treated with bevacizumab. Our findings suggest that infants treated with ranibizumab may need more frequent follow-up than those treated with bevacizumab. More and longer term data are still needed.

Supplemental Laser Post Injection

All 6 eyes treated with ranibizumab eventually required supplemental laser therapy (Table 2). Three eyes (Infants 2 and 4) had reactivation and continued progression of ROP. Two eyes (Infant 6) had reactivation, subsequent regression, but persistent Zone III avascularity. One eye (Infant 1) did not have reactivation but exhibited persistent Zone III avascularity.

Two eyes (Infant 3) treated with bevacizumab also exhibited persistent Zone III avascularity eventually requiring laser. The 2 remaining eyes (Infant 5) treated with bevacizumab eventually vascularized and did not require laser.
Variation +0.75 D / - 3.50 D (12 months/5 year follow-up)

Myopia is a multifactorial challenge

1) Myopia of the prematurity per se
2) Myopia of spontaneously regressed ROP
3) Myopia of peripheral retinal ablation by photocoagulation

BEAT-ROP Study

Mean - 1.50 D - SD +/- 3.50 D Bevacizumab (Avastin)
Mean - 8.50 D - SD +/- 7.50 D Laser photocoagulation
COMPLICATIONS OF THE INJECTION OF ANTI-VEGF IN INFANTS

ADULTS with ARMD: endophthalmitis

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PRETERM INFANTS with ROP: traumatic cataract

- Very short axial length of the preterm eye
- Proportional higher volume of the preterm lens
- Distance from limbus to the Pars plicata
- High IOP over the optic nerve head
- Risk in to increase the complications of ROP if applied > 36 weeks of PCA
1) Laser or Anti-VEGF?

Christoph Bührer has a different opinion.

- Just because laser has been historically used as opposed to bevacizumab doesn’t mean it is superior. It has just been known for a longer period of time. Laser treatment is irreversible, whereas anti-VEGF isn’t. With laser you take away parts of the retina to save other parts of the retina, whereas with bevacizumab you are not destroying anything. If bevacizumab doesn’t work you still have the option of laser, but if you have already damaged the retina by laser you cannot redo it. Another positive thing with bevacizumab is that you avoid central anaesthesia, and by doing that you do something good for the brain, he says.

ROP in ZONE I: ANTI-VEGF

ROP in ZONE II: ANTI-VEGF PRÓS e CONS

ROP in ZONE III: Always LASER
ANTI-VEGF: BETWEEN THE 35th and 36th WEEKS OF PCA

LASER: BETWEEN THE 36th and 38th WEEKS OF PCA
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