ANTI-VEGF
PRO-CONTRO

Elena Piozzi

Terapia con anti-VEGF

- La terapia della ROP è basata sulla diminuzione dei livelli di VEGF che possiamo avere con:

  1) completa ablazione della retina avascolare che produce VEGF

  2) inattivando VEGF con la terapia medica

Retinopathy of Prematurity: Two Distinct Mechanisms That Underlie Zone 1 and Zone 2 Disease

JOHN T. FLYNN, MD, AND TAILOI CHAN-LING, PHD

proaches to therapy must be considered. On an experimental basis, studies that are directed at the inhibition of pathologic vasculogenesis (zone 1 ROP) might take a direction other than ablative therapy. For example, with the use of agents such as bevacizumab[39,40] or imatinabmesylate,[41–43] monoclonal antibodies may inhibit tyrosine kinase proteins and attack the process of abnormal vasculogenesis upstream from $VEGF_{165}$.

(Am J Ophthalmol 2006;142:46–59. ©

Bevacizumab/Avastin

- Farmaco che inibisce l'attività del VEGF(A)
- Anticorpo Monoclonale completo (non è un frammento come invece ranibizumab/lucentis)
- Alto peso molecolare (149 kd)

Bevacizumab/Avastin caratteristiche

- Minor capacità di penetrazione nello spessore retinico (minor possibilità di interferire nel normale sviluppo retinico)
- Scarsissima possibilità di uscire dall'occhio rimanendo intrappolato nel gel vitreale del prematuro

- **Intravitreal Injection of Bevacizumab Vs. Conventional Laser Treatment in Type 1 ROP** Tuesday, May 03, 2011,

Fernando Molle1A, Domenico Lepore1A, Antonio Baldascino1A, Carmine Angora1A, Lorenzo Orazi1A, Monica M. Pagliara1A, Carmen Giannantonio1B, Velia Purcaro1B, Patrizia Papacci1B, Costantino Romagnoli1B.

A

- A Department of Ophthalmology, BDepartment of Pediatrics, 1Catholic University, Rome, Italy.

- All inborn babies with type 1 zone 1 ROP and therefore eligible for laser photoablation following the ETROP indications were included in the study.
- 7 babies (14 eyes) with a mean BW of 606.7gr (range 450-840) and a mean GA of 25.8wks (range 23-29) were enrolled.

- At the time of treatment the first eye was randomized for intravitreal injection of 0.5mg di Avastin in a 0.02 ml BS solution; the second eye, used as control, was randomized for conventional laser photoablation of the peripheral avascular retina.

- Binocular indirect ophthalmoscopy (BIO) and digital Retcam were performed before treatment and every 3 days while digital FA at treatment and every 2 wks until discharge. After discharge from NICU, BIO was performed every 2 wks until 52nd wk of PMA and then monthly until 1 years of age. Babies underwent FA, cyclopegic refraction and IOP measurement at 6 month and at 1 year of age under general anaesthesia.

RISULTATI

- One eye of the laser group progressed to stage 4b and therefore results considered unfavourable according to CryoROP. Remaining 6 eyes showed positive results.
- None of the eyes treatment with a single IVB progressed to retinal detachment but showed an incomplete vascularisation of the peripheral retina.
- Furthermore all but one eyes showed some fluorangiographic abnormalities either at the periphery or at the posterior pole.

CONCLUSIONI

- The IVB seems to be able to stop the progression to retinal detachment. Some concerns for the use of IVB in type 1 zone 1 arise from the FA study. Long term follow-up is needed to evaluate the effect of bevacizumab on panretinal development

Adverse Events After Off Label Intravitreal Bevacizumab In The Treatment Of Retinopathy Of Prematurity, May 03, 2011,

Olivia Baldivieso Hurtado1, Gerardo García-Aguirre1, Virgilio Morales Cantón1, Hugo Quiroz-Mercado2, R.V. Paul Chan3, María Ana Martínez-Castellanos1. 1Retina and Vitreous, Asociacion para Evitar la Ceguera en Mexico, Cuidad de Mexico, Mexico; 2Retina and Vitreous, University of Colorado Hospital, Denver, CO; 3Retina and Vitreous, Weill Cornell Medical Center, New York, NY.

- Retrospective analysis of the records of 195 patients with ROP (stage 3, threshold, pre-threshold, 4a and 4b) who underwent IB (0.05cc or 0.03cc) in the period from September 2005 to October 2010.
- Baseline characteristics of each infant and adverse events during and/or after treatment were collected. Follow up of the injection was at least of 3 months

RISULTATI

We had a total of 52 (26.6%) local adverse events: four (2%) patients with stage 4 had worsening of the retinal detachment, 2 of these required pars plana vitrectomy and final visual outcome was 20/400 or worse. In the beginning of the study the dose we applied was 0.05cc. Since 23 eyes required paracentesis after elevation of intraocular pressure (IOP), we modified the dose to 0.03cc and lowered the IOP elevation rate.

EFFETTI AVVERSI
Locali

- Two (1%) patients had peripheral fibrous avascular membrane, 3 (1.5%) intravitreal hemorrhage that resolved without vitrectomy, 8 (4.1%) have avascular extreme periphery, and 12 (6.1%) sub-conjunctival hemorrhage.

EFFETTI AVVERSI Sistemici

- 3 (1.5%) patients died: one secondary to sepsis by P. aeruginosa 2 months after injection, one by neuro-infection after placement of a ventriculo-peritoneal shunt valve 6 months after injection, and one by multi-organic dysfunction secondary to transfusion blood one week after injection. Twenty two (11.2%) patients had some degree of psychomotor development retardation, after birth and before the injection; 14 patients (7.1%) presented apnea and 6 (3%) respiratory distress syndrome, 1 patient (0.5%) had Down's syndrome and 1 (0,5%) dysmorphic

CONCLUSIONI

- The use of IB appears to be safe and effective for type 1 prethreshold and threshold ROP, presenting with a limited number of treatable ocular adverse events. However, once the retina is detached (Stage 4a or worse) retinal detachment may be more likely to progress. With regard to systemic adverse events, we believe that systemic abnormalities in children treated with IB for ROP may be a sequelae of prematurity itself and not related to the medication. Longer follow up is needed of prospective multicenter studies to determine the safety profile for the use of IB

- **Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity.**

Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group

N.Engl J Med 364;67 Feb17,2011

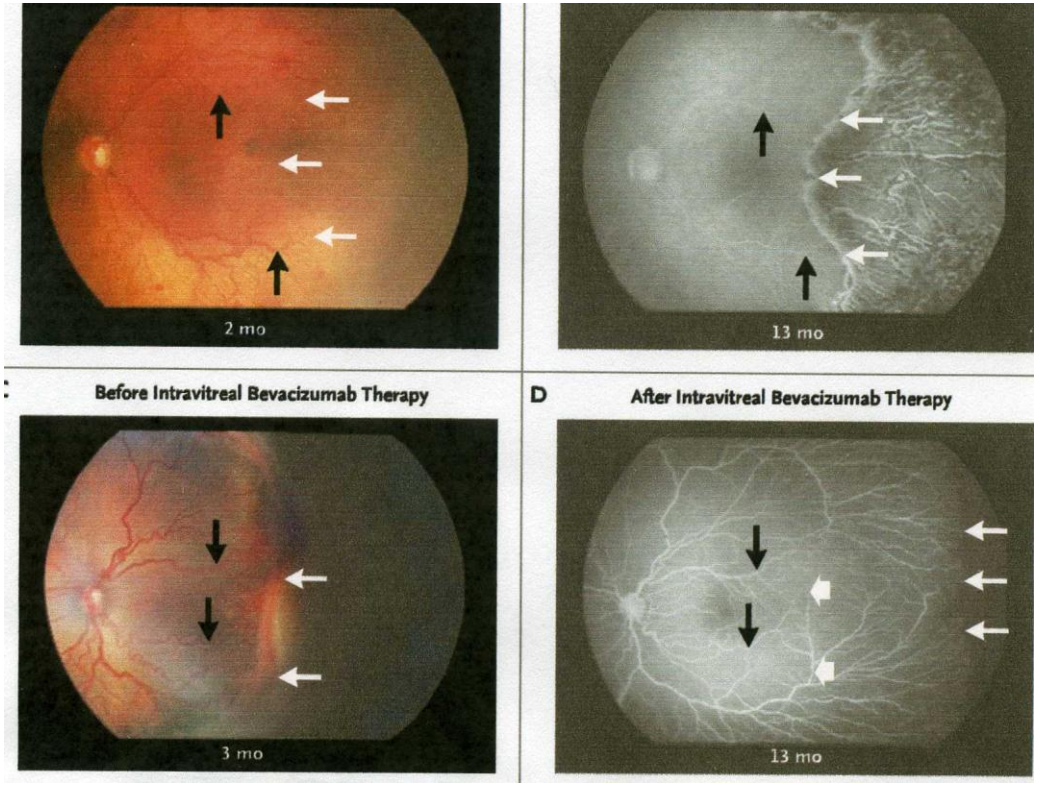
METODI

- We conducted a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) retinopathy of prematurity.
- Infants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally.
- The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age.

RISULTATI
Recidiva post-trattamento

- We enrolled 150 infants (total sample of 300 eyes); 143 infants survived to 54 weeks' postmenstrual age, and the 7 infants who died were not included in the primary-outcome analyses.
- Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], P=0.002). A significant treatment effect was found for zone I retinopathy of prematurity (P=0.003) but not for zone II disease (P=0.27)

STADIO 3 zona I



Dopo bevacizumab i vasi avanzano, ma perifericamente la retina non vascolarizza completamente

Ricorrenza della malattia

16±4.6 6 occhi Bevacizumab

6.2±5.7 32 occhi Laser

Attenzione :

follow-up più attento e prolungato

Sicurezza

- Lo studio è limitato
- Necessitano 2800 prematuri per valutare in modo statisticamente significativo la mortalità
- Un campione più numeroso per valutare tossicità locale e sistemica

CONCLUSIONI

- Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease.
- Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina.
- This trial was too small to assess safety. (Funded by Research to Prevent Blindness and others;)

Vantaggi

- Uso rapido
- Non necessita di curva di apprendimento
- Meno costoso

Limiti

- Off-label
- Follow-up più lungo
- Sicurezza???

Pre-Trattamento

Necessità di stabilire criteri uniformi di

- Timing
- Dose
- Modalità (Ret-Cam+Fag)

POST-TRATTAMENTO

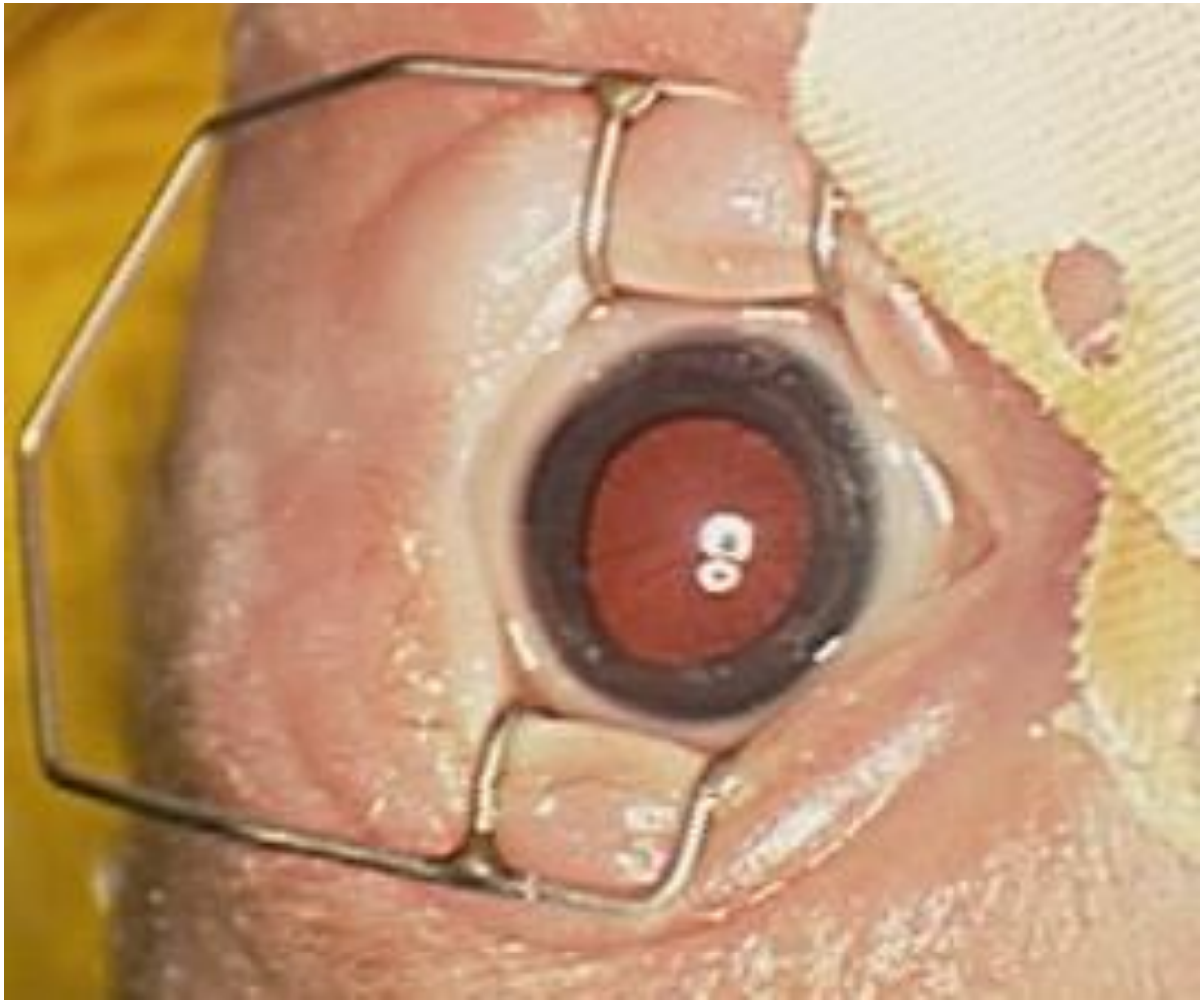
Criteri uniformi

- Durata
- Frequenza
- Modalità (Ret-cam +FAG)
- Gestione della recidiva

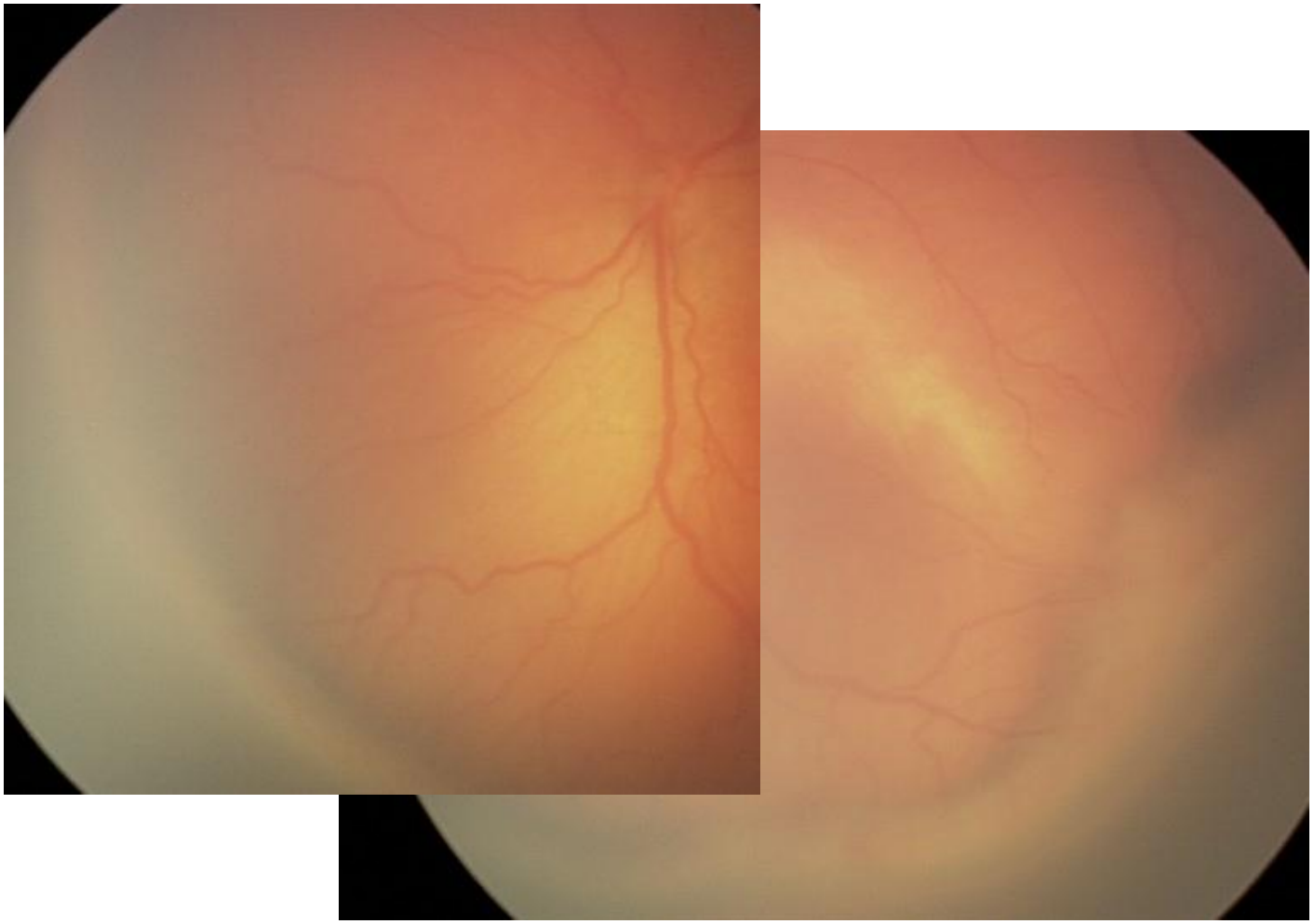
Caso clinico

- 24+2 settimane
- 680 gr
- Laser terapia alla 31ª sett. in OO
- Avastin alla 32ª sett. in OO

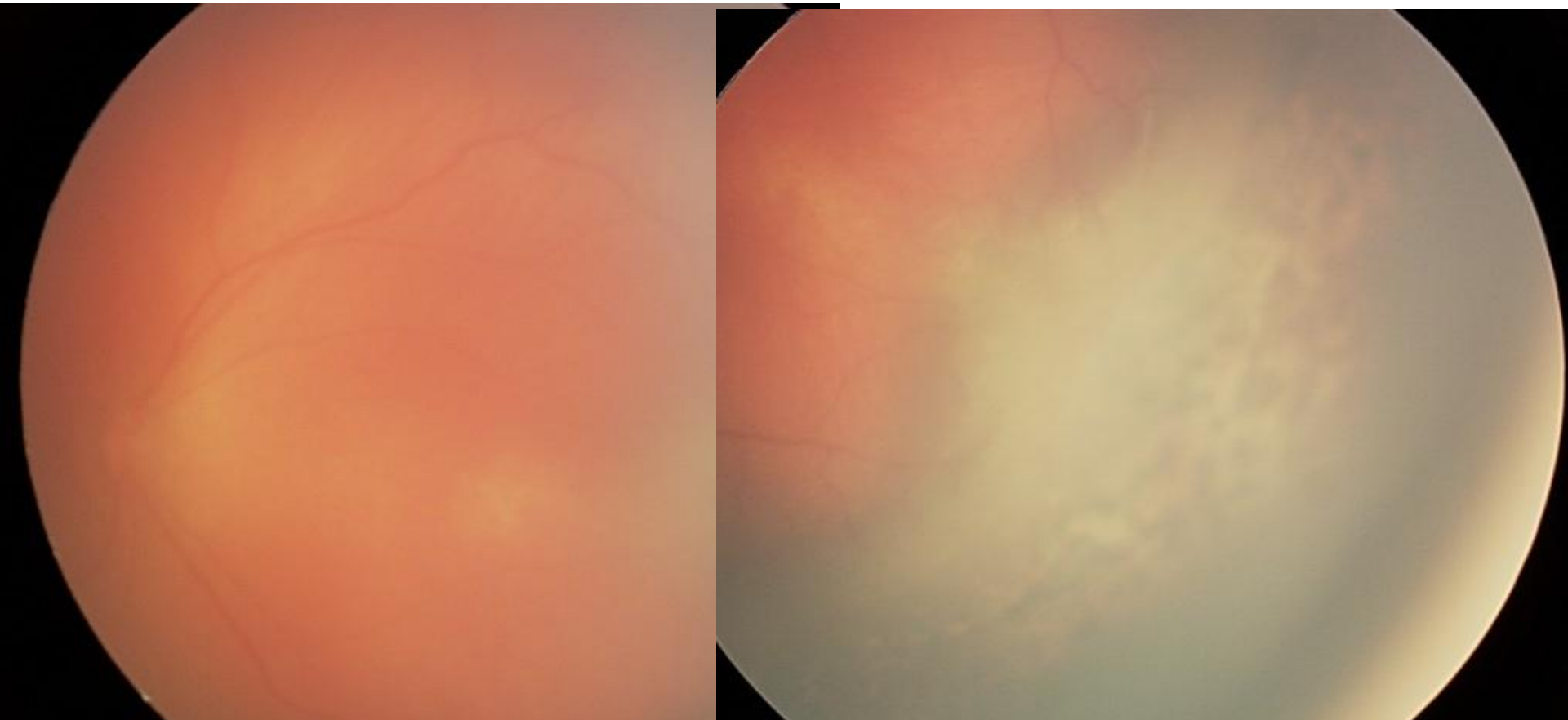
Prelaser OS



Prelaser OS

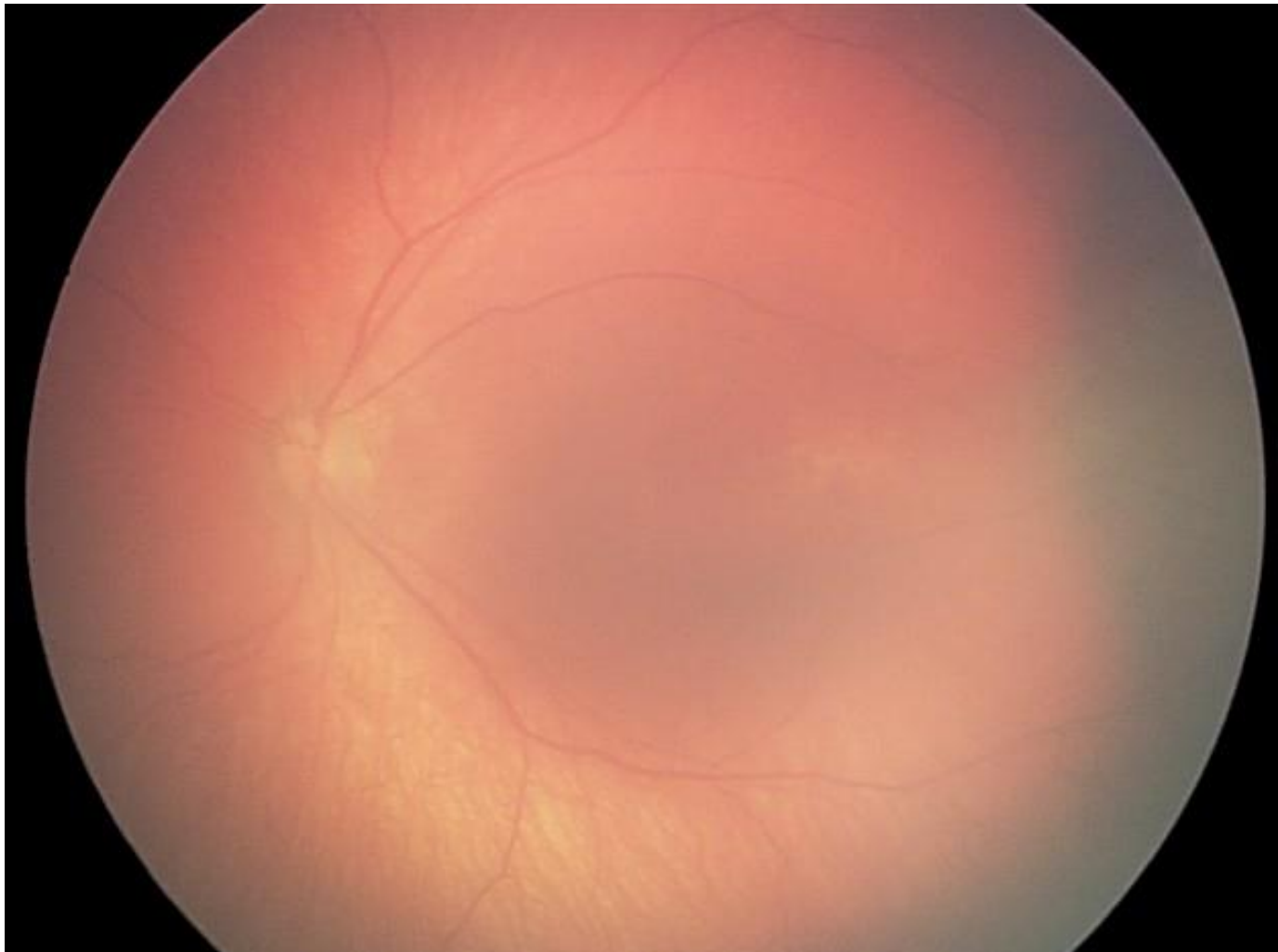


Post laser OS

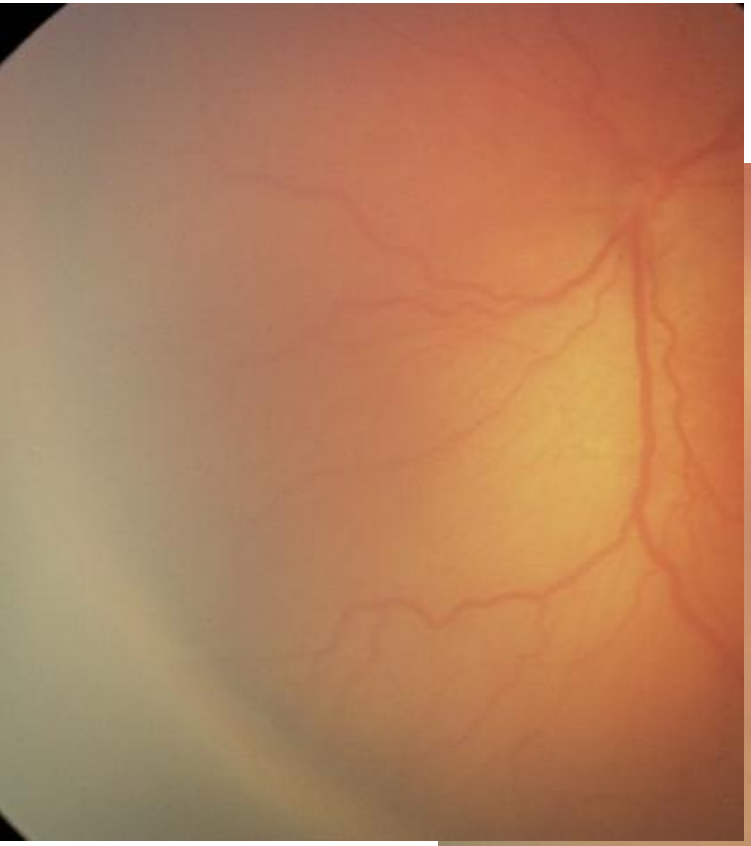


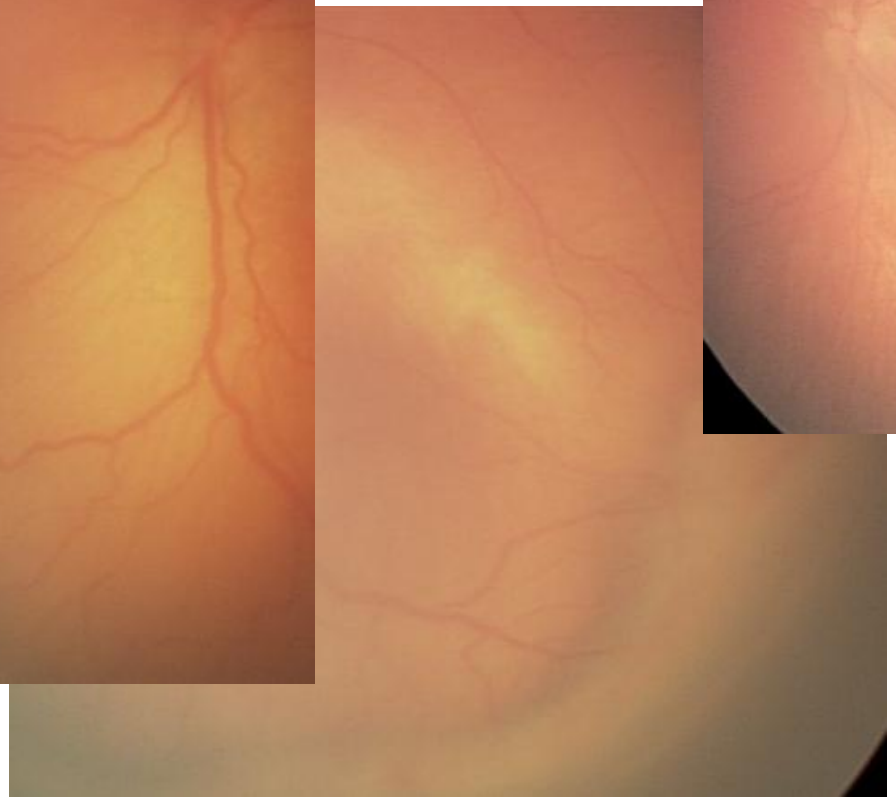
Post avastin OS

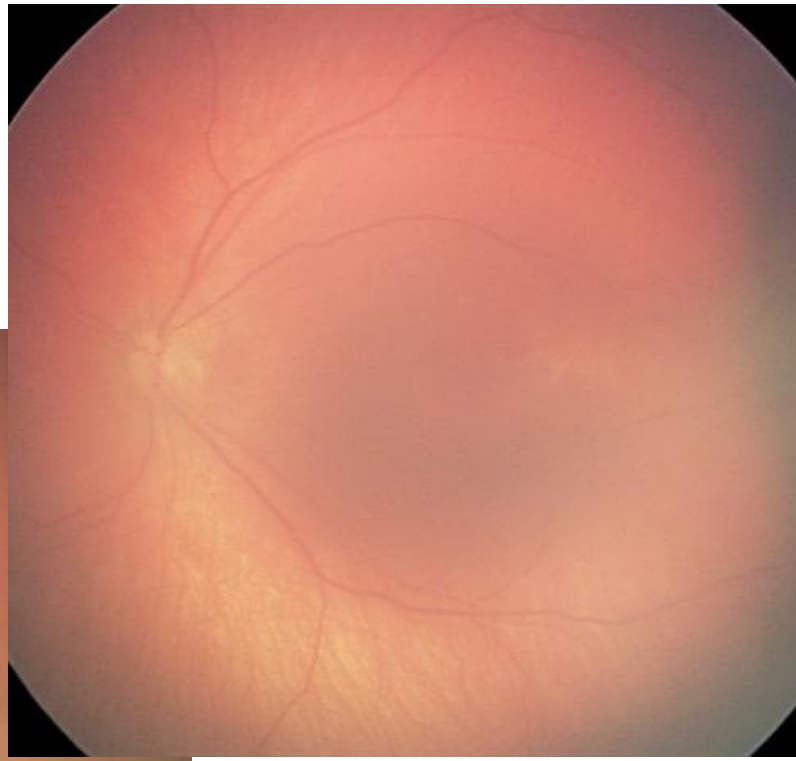
- Marcata riduzione del plus



Pre OS post







Post avastin OS

- Marcata riduzione della tunica vasculosa