Anti-VEGF Evidence Based Management of ROP

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Retinopathy of Prematurity: The Life of a Lifetime Disease

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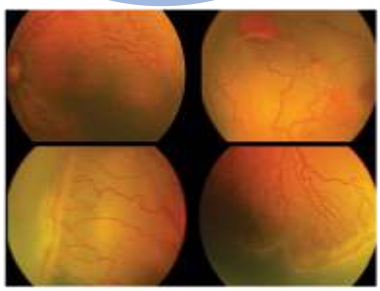
History

- Theodore Terry **1942**
  Retrolental Fibroplasia
- Owen and Owens **1949**
  Retinopathy of Prematurity/ Rush disease
- Dr. Hoeck **1949**
  Oxygen is the cause of ROP
- Leading cause of childhood blindness **1951**

CRYO-ROP
(1985-1986)

- It is the first study to deal with the management of ROP.
- Before the establishment of this study in 1985, more than **500 infants annually** were blinded by ROP in the United States alone.

Peripheral retinal ablation was performed when ocular findings indicated a risk approximately 50% for RD.

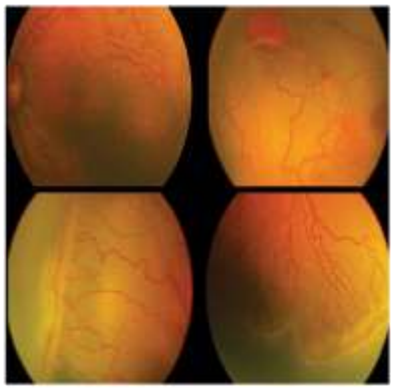


- To determine the **safety** and **efficacy** of trans-scleral cryotherapy of the peripheral retina in certain low birth-weight infants with retinopathy of prematurity (ROP) for reducing blindness from ROP.
- To determine the **long-term** outcome for eyes that had severe ("threshold") ROP, both with and without cryotherapy.

CRYO-ROP (1985-1986)

It is the first study to deal with the management of ROP.

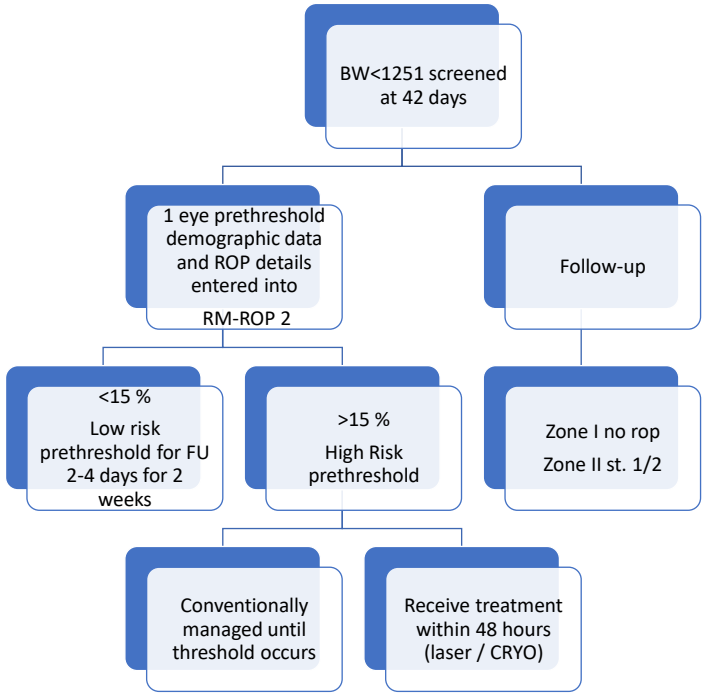
- Unfavorable anatomical outcome: 25.7% V.S 47.4 % .
- Unfavorable functional outcome: 35 % V.S 56.3 % .



Threshold disease

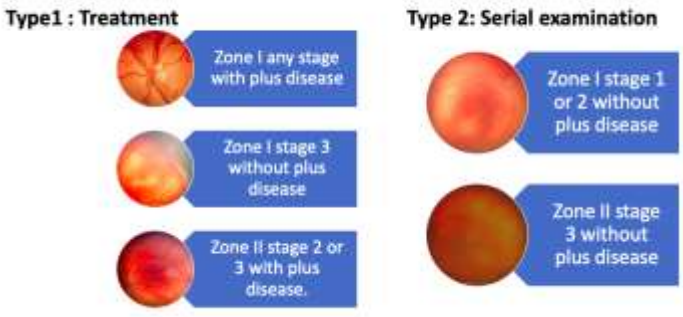
ETROP (2000-2002)

Whether early treatment in high risk pre-threshold ROP results in improved grating visual acuity and retinal structural outcomes compared to conventional treatment.



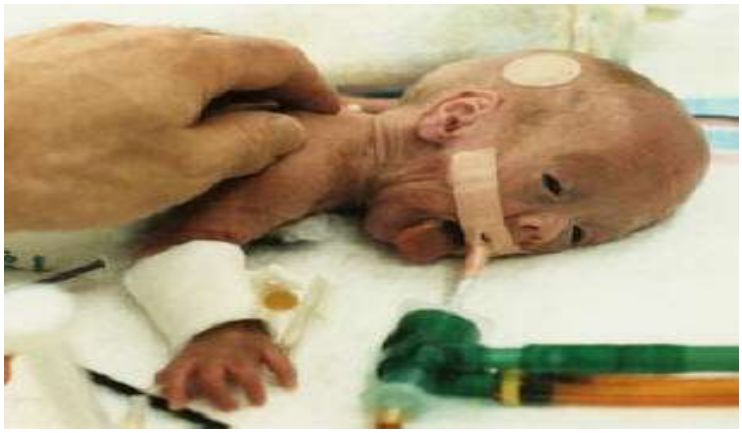
ETROP (2000-2002)

- **Unfavorable visual acuity outcome : 14.5 % V.S 19.5 %**
- **Unfavorable structural outcome : 9.1 % V.S 15.6 %**

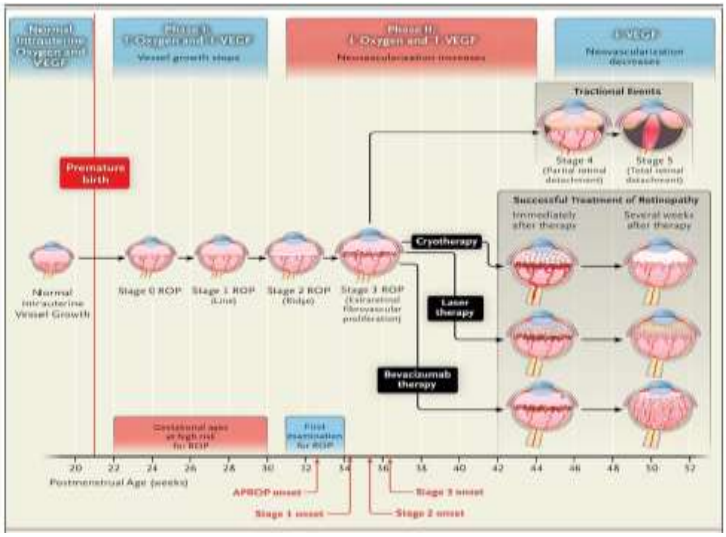


DESPITE OF THE GOOD OUTCOME OF ET-ROP STILL THERE IS POOR FUNCTIONAL AND STRUCTURAL OUTCOME

I AM ALREADY SUFFERING!!



Anti- VEGF Agents



Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity

- Retina:
March 2008 - Volume 28 - Issue 3 - pp S13-S18
doi: 10.1097/IAE.0b013e3181644ad2
Articles

Off-Label L **Conclusions:** Off-label use of bevacizumab appears to be useful as a salvage treatment for ROP when laser treatment is precluded. It improves dilation, quiets the disease when visibility is difficult, and temporizes the disease until laser can be supplemented. Threshold

LALWANI, GEETA A. MI JOHNSON, ROSE A. RN;

- Retina:
July/August 2011 - Volume 31 - Issue 7 - pp 1239-1247

Intravitreal Conclusion: Intravitreal bevacizumab may serve as a supplemental therapeutic agent for severe laser-refractory retinopathy of prematurity or as monotherapy when media opacities preclude diode laser photocoagulation or the patient is too sick for lengthy laser treatment. Prematurity

Block ROP
Pan-VEGF Blockade (2006-2009)

- To assess the safety and tolerability of bevacizumab in infants with APROP who had failed conventional laser therapy.
- A second phase of the BLOCK-ROP study targets Type-1 threshold ROP to demonstrate non-inferiority of intravitreal bevacizumab compared with standard-of-care laser.

- In this randomized three-armed trial:
  - 0.75 mg intravitreal bevacizumab in one eye and laser treatment in the fellow eye;
  - 0.625 mg intravitreal bevacizumab in one eye and laser treatment in the fellow eye;
  - laser photocoagulation in both eyes.

BEAT-ROP (2008-2011)

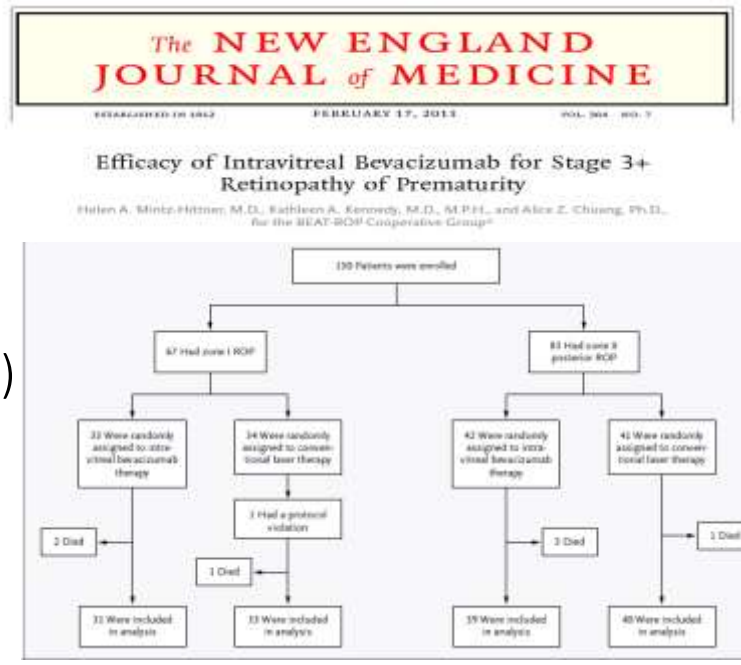


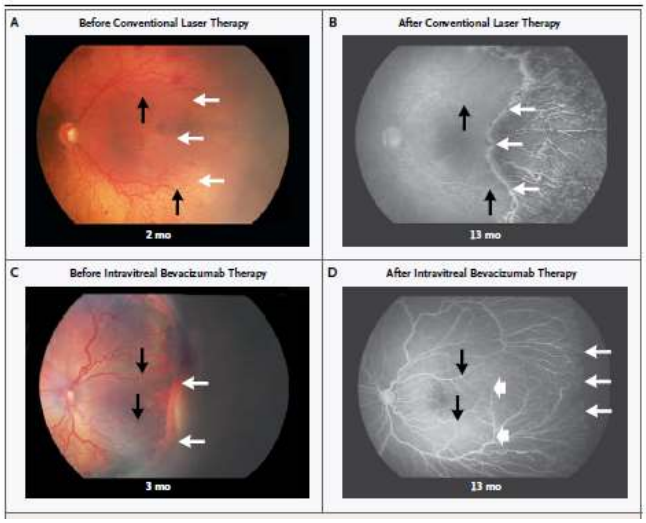
Table 2. Ocular Outcomes in the 143 Survivors at 54 Weeks' Postmenstrual Age.*

Variable	Zone I ROP (N=64)		Zone II Posterior ROP (N=79)	
	Intravitreal Bevacizumab (N=31)	Conventional Laser Therapy (N=33)†	Intravitreal Bevacizumab (N=39)	Conventional Laser Therapy (N=40)
Recurrence of ROP (primary outcome) — no. of patients (%)				
None	29 (94)	19 (58)	37 (95)	35 (88)
In one eye	2 (6)	5 (15)	0	1 (2)
In both eyes	0	9 (27)	2 (5)	4 (10)
Eyes affected — no.	2	23	4	9
Odds ratio for recurrence with bevacizumab (95% CI) [P value]				
Per zone	0.09 (0.02–0.43) [0.003]		0.39 (0.07–2.11) [0.27]	
For zones I and II combined	0.17 (0.05–0.53) [0.002]			
Interval from treatment to recurrence — wk‡	19.2±8.6	6.4±6.7	14.4±0.8	6.8±4.2
Vitrectomy — no. of eyes	0	13	2	0
Structural outcomes of recurrence — no. of eyes				
Macular dragging	1	16	0	6
Retinal detachment	0	2	2	0
Complications requiring intraocular surgery — no. of eyes				
Cornea opacity requiring corneal transplant	0	0	0	1
Lens opacity requiring cataract removal	0	0	0	3

* Plus–minus values are means ±SD. Of the 150 infants enrolled, 7 died before 54 weeks: 5 before hospital discharge and 2 after discharge; 2 had been receiving intravitreal bevacizumab for zone I retinopathy of prematurity (ROP), 1 conventional laser therapy for zone I ROP, 3 intravitreal bevacizumab for zone II posterior ROP, and 1 conventional laser therapy for zone II posterior ROP.

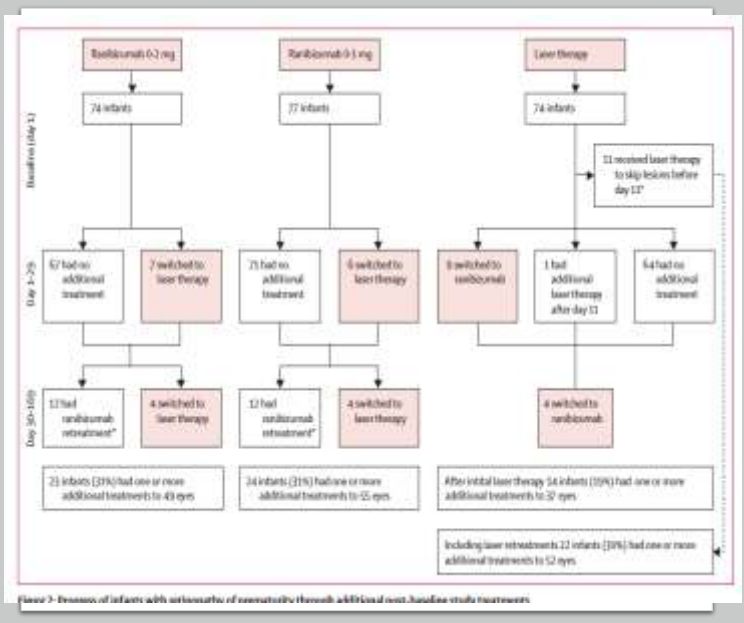
† One infant who had been randomly assigned to undergo conventional laser therapy for zone I ROP was instead given intravitreal bevacizumab (a protocol violation). In analyses, we followed the intention-to-treat principle and assumed that treatment was successful in both eyes (i.e., no recurrent disease with conventional laser therapy).

‡ The interval from treatment to recurrence for both zones considered together was 16.0±4.6 weeks for 6 eyes after intravitreal bevacizumab therapy versus 6.2±5.7 weeks for 32 eyes after conventional laser therapy.



RAINBOW (2015-2019)

- Aim: Prospective superiority multicentric trial to compare two doses of ranibizumab and laser for type 1 ROP
  - Survival without active ROP
  - Unfavorable structural outcome
  - Treatment switch



Ranibizumab compared to laser for treatments of infants born prematurely with retinopathy of prematurity

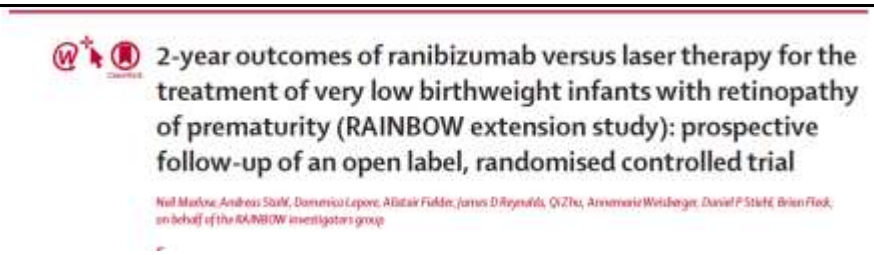
RAINBOW (2015-2019)

- Results: higher success rate
- Unfavorable structural outcome
  - ETROP 9.1 %
  - Rainbow laser 10%
  - Rainbow 0.2 mg ranibizumab 1.43%
    - Vascular dragging
    - Macular folding
    - Macular ectopia
    - Macular detachment

- Conclusion: In the treatment of ROP, ranibizumab 0·2 mg might be superior to laser therapy, with fewer unfavorable ocular outcomes than laser therapy and with an acceptable 24-week safety profile.

Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial

	Ranibizumab 0·2 mg	Ranibizumab 0·1 mg	Laser therapy
Patients entered	74	77	74
Patients with known primary outcome*	70	76	68
Treatment success†	56 (80%)	57 (75%)	45 (66%)
Reason for not meeting primary objective‡			
Active ROP present§	0	3	0
Unfavourable structural outcome¶	1	5	7
Treatment switch‖	11	13	18
Death of infant	4	4	4



2-year outcomes of ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW extension study): prospective follow-up of an open label, randomised controlled trial

Neil Marlow, Andreas Stahl, Domenico Lepore, Alistair Fielder, James D Reynolds, Qi Zhu, Annemarie Weisberger, Daniel P Stahl, Brian Fleck, on behalf of the RAINBOW investigators group

- No new serious retinal findings up to 2 years of age
- high myopia (worse than –5 dioptres) was more common following laser therapy compared with ranibizumab.
- **Implications of all the available evidence**

The use of ranibizumab to treat retinopathy of prematurity is safe and efficacious up to 2 years of age.

FIREFLEYE (2019-2022)

Original Investigation
July 26, 2022

Effect of Intravitreal Aflibercept vs Laser Photocoagulation on Treatment Success of Retinopathy of Prematurity
The FIREFLEYE Randomized Clinical Trial

- Q: is treatment with a 0.4-mg dose of intravitreal aflibercept noninferior to laser photocoagulation?
- Multicentric for type 1 ROP
- The primary outcome was the proportion of infants without active ROP and unfavorable structural outcomes 24 weeks after starting treatment (assessed by investigators). The requirement for rescue treatment was considered treatment failure.

FIREFLEYE: Aflibercept non-inferiority

- Treatment success : 85.5% IVA vs 82.1% with laser
- Rescue treatment : 4.8% IVA vs 11.1% laser
- The serious adverse event rates were
  - OCULAR 13.3% IVA vs 7.9 Laser
  - Systemic 24.0 % IVA VS 36.8 Laser in
  - Three deaths, which occurred 4 to 9 weeks after intravitreal aflibercept treatment, were considered unrelated to aflibercept by the investigators.
- **Conclusions and Relevance** aflibercept compared with laser photocoagulation did not meet criteria for noninferiority with respect to the primary outcome of the proportion of infants achieving treatment success at week 24. **FIREFLEYE NEXT (2020-2025)**

BUTTERFLEYE (2019-2022)

- Primary Outcome Measures:

Proportion of patients with **absence of active** retinopathy of prematurity (ROP) and of **unfavorable structural outcomes**

- Secondary Outcome Measures :
  - Proportion requiring **rescue** treatment modality
  - Proportion of patients with **recurrence** of ROP
  - Proportion of patients with **ocular** treatment-emergent **adverse events** (TEAEs) and serious adverse events (SAEs)
  - Proportion of patients with **systematic** TEAEs and SAEs

BUTTERFLEYE: Efficacy of Aflibercept vs Laser **(2019-2022)**

Clinical Studies

Results

Results from week 52 of chronological age in the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT studies are shown in Table 12 below. EYLEA was not demonstrated to be non inferior to Laser treatment.

Table 12: Efficacy Outcomes at Week 52 Chronological Age in BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT Studies

Full Analysis Set	BUTTERFLEYE		FIREFLEYE	
	EYLEA	Laser	EYLEA	Laser
Efficacy Outcomes	N=93	N=27	N=75	N=38
Proportion of patients with absence of active ROP and unfavorable structural outcomes (%)	80%	78%	79%	82%
Adjusted Difference[a] (%) (95.1% CI)	1.8% (-16, 19)		-1.9% (-17, 13)	

- Percentages Rounded to account for limited significant figures
- Secondary endpoints removed

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REGENERON®

February 8, 2023 at 6:45 PM EST

EYLEA® (AFLIBERCEPT) INJECTION APPROVED AS THE FIRST PHARMACOLOGIC TREATMENT FOR PRETERM INFANTS WITH RETINOPATHY OF PREMATURITY (ROP) BY THE FDA

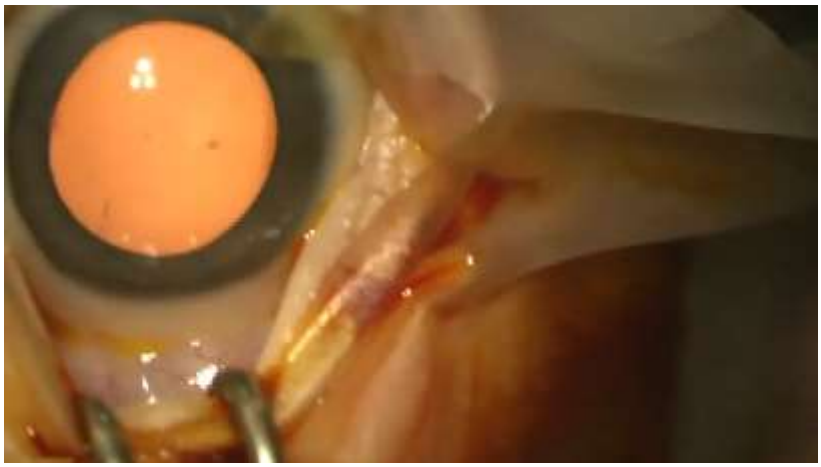
ROP is a leading cause of childhood blindness worldwide

EYLEA now approved to treat five retinal conditions caused by ocular angiogenesis

ROP LANDMARK STUDIES

- CRYO-ROP (1985-1986)
- ET-ROP (2000-2002)
- BEAT-ROP (2008-2011)
- RAINBOW (2015-2019)
- FIREFLEYE & BUTTERFLEYE (2019-2022)
- FIREFLEYE NEXT (2020-2025)

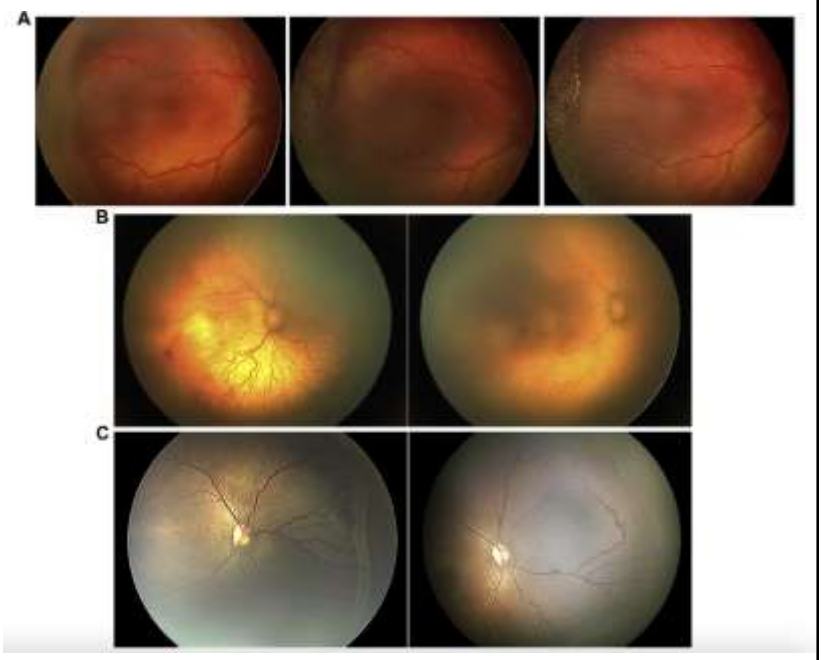
How to inject



Follow-up

- Signs of regression

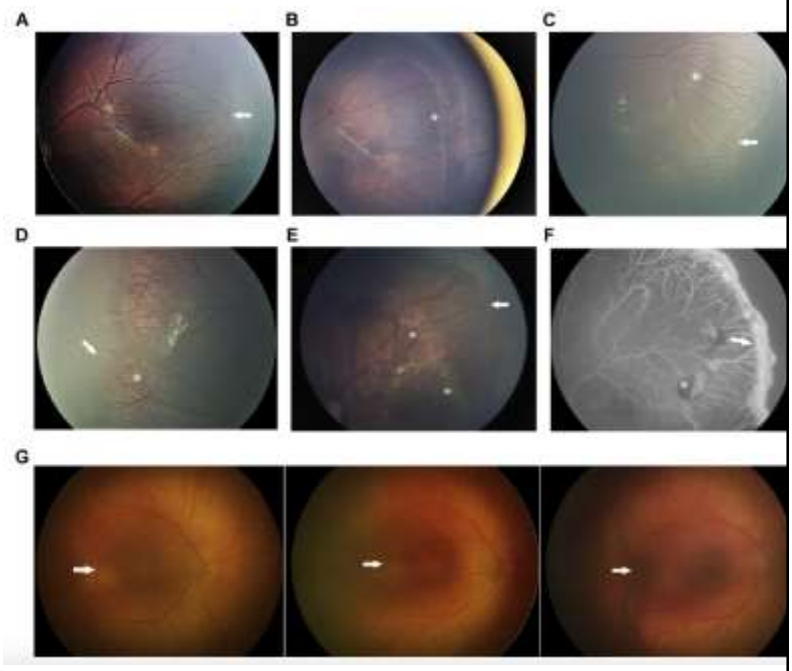
1. Plus disease
2. Hemorrhage
3. Neovasulariztion
4. Ridge colour
5. Peripheral vascularization



International Classification of Retinopathy of Prematurity, Third Edition

Follow-up

- Reactivation
  1. Neovascualrization
  2. Ridge
  3. Hemorrhage
  4. Detachement



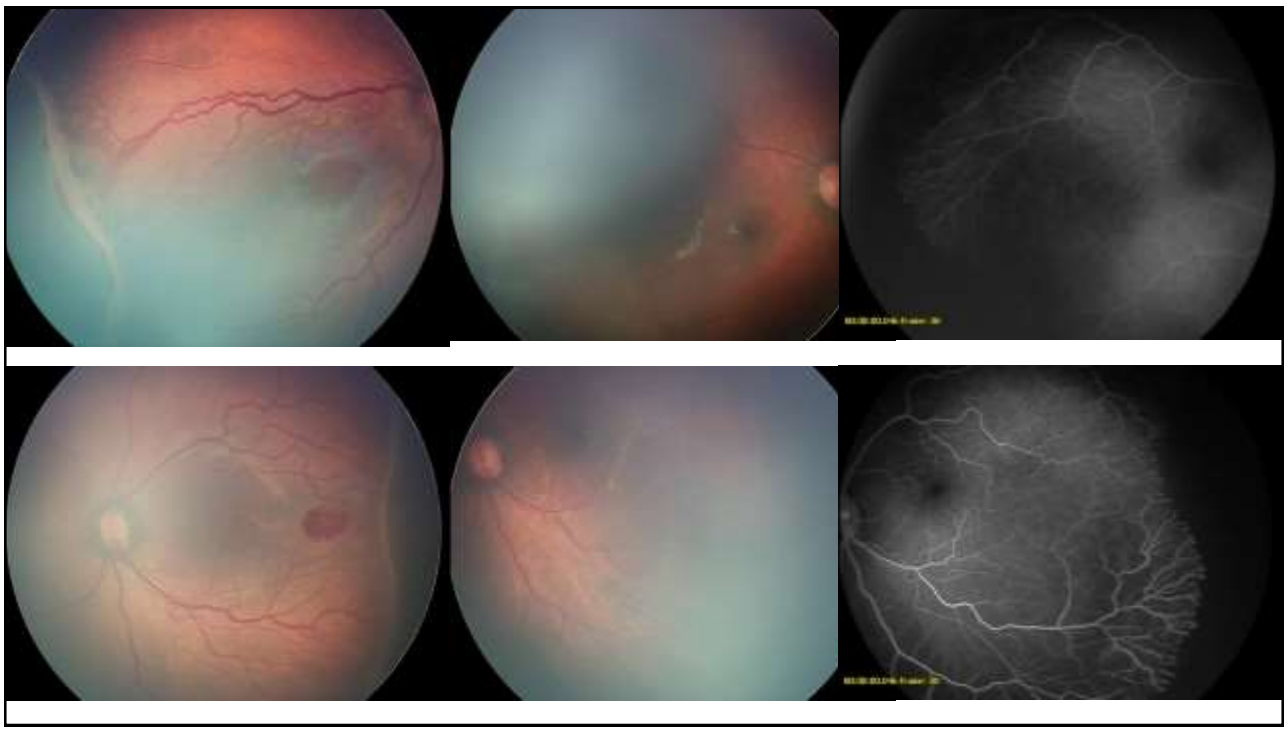
International Classification of Retinopathy of Prematurity, Third Edition

AMERICAN ACADEMY OF OPHTHALMOLOGY®

International Classification of Retinopathy of Prematurity, Third Edition

Persistent avascular retina (PAR)
Chronic vascular arrest

- More than 2DD (disc diameter) of peripheral avascualr retina



TREAT
vs
OBSERVE

Management

- Ablation therapy
  - Cryotherapy
  - Laser photocoagulation
- Scleral buckling
- Pars-plana vitrectomy
- Anti-VEGF Therapy

Scan me

Time is