REVIEW ARTICLE

Anti-Vascular Endothelial Growth Factor Preparations in the Treatment of Retinopathy of Prematurity: Balancing Risks and Benefits

DEEPAK CHAWLA AND *BRIAN A DARLOW

*From Departments of Pediatrics, Government Medical College Hospital, Chandigarh, India, and *University of Otago, Christchurch, New Zealand.*

Correspondence to: Dr Deepak Chawla, Associate Professor, Department of PediatricsGovernment Medical College Hospital, Chandigarh, India. drdeepakchawla@hotmail.com

Need and purpose of review: *The standard of management of severe retinopathy of prematurity (ROP) is laser ablation of the peripheral retina. Intra-vitreal injection of anti- vascular endothelial growth factor antibodies has emerged as an alternative modality of treatment of ROP. The purpose of this review is to evaluate the current evidence on benefits and risks of using anti-VEGF antibodies for management of ROP.*

Methods: *PubMed and Cochrane Register of Clinical Trials were searched for studies evaluating role of anti-VEGF agents in ROP. No study design or language restriction was used. Data were extracted using a data extraction form and presented as a summary of key findings from different study types and designs.*

Results: Of 143 studies retrieved, 107 were found relevant and further screened. Seventy-three studies reporting original research were selected. These were divided into three categories: pharmacokinetics studies (*n*=5), observational studies without a control group (*n*=59) and clinical trials with a control group (*n*=9). The most commonly used agent was bevacizumab at a dose of 0.625 mg per eye. At this dose bevacizumab administration led to regression of ROP in the majority of cases with type 1 ROP but was associated with sustained reduction in systemic VEGF levels. The most common adverse event after anti-VEGF therapy was recurrence of ROP needing follow up for up to one-year postmenstrual age. Randomized controlled trials demonstrated better anatomical outcome with bevacizumab as compared to laser therapy. Studies lack evidence of long term effect of bevacizumab on retinal vessels, functional visual outcomes and extra-ocular effects.

Conclusion: Anti-VEGF agents are effective in causing regression of ROP. However, until adequately powered studies with long term follow-up and recording of more holistic outcomes are available, anti-VEGF agents remain an investigational drug in ROP and should be used only as part of clinical study.

Keywords: *Bevacizumab, Endothelium, Retinal Vessels, Treatment.*

Retinopathy of prematurity (ROP) is a vasoproliferative disorder observed in preterm neonates [1]. It results from arrested and aberrant development of retinal vessels. Most neonates with early stages of ROP show spontaneous regression. However, severe ROP involving the posterior retina or causing fibrovascular proliferation if not detected timely and if untreated can cause permanent loss of vision. Although the reported incidence of severe ROP varies with the degree of prematurity and level of neonatal care, about one-third of extremely preterm neonates can develop severe ROP. In middle-income countries, severe ROP has been reported even in moderately preterm neonates [2,3]. Worldwide, severe ROP is one of the commonest causes of childhood blindness [4].

A preterm neonate is born with retinal vessels growing from central disc but not yet reaching the peripheral parts of the retina. Normal retinal vascular growth is driven by production of various growth factors including the non-oxygen dependent insulin-like growth factor-1 (IGF-1), and the oxygen dependent vascular endothelial growth factor (VEGF) and erythropoietin [1]. After preterm birth, the hyperoxic postnatal environment and cessation of supply of essential nutrients from the placenta lead to decrease in levels of these growth factors. While the retinal vessels are in a stage of hyperoxia-induced developmental arrest, the rest of the retinal tissue keeps growing. With increasing postnatal age growing retinal tissues become hypoxic and start producing VEGF. This causes proliferation of aberrant vessels which leak readily, leading to formation of fibrovascular exudates and retinal detachment. Severe ROP is treated with laser ablation of the peripheral avascular retina. Laser ablation destroys the avascular retina producing VEGF resulting in regression of abnormal vessels. Early treatment of proliferative ROP with laser ablation leads to improved functional and structural outcomes as compared to late treatment [5]. However, peripheral retinal tissue is never vascularized and laser

ablation may not be able to preserve peripheral field of vision in zone I ROP [6]. In addition, there is increased prevalence of myopia and high myopia in ROP, requiring life time of management. An alternative modality of treatment of severe ROP has emerged in the form of antibodies to VEGF. Injected into the vitreous cavity, anti-VEGF antibodies can cause regression of abnormal vessels without destroying the peripheral retina. However, function of the peripheral retina thus preserved has not been established. Further, apart from its role in retinal vascular development, VEGF is needed for development of glomeruli, alveoli and parts of brain. This raises concern about possible adverse effects of suppression of normal ocular and systemic VEGF levels after intraocular administration of anti-VEGF antibodies. We herein review the literature on benefits and risks of using anti-VEGF antibodies for management of ROP (***Web Box* 1**).

RESULTS

The most commonly investigated anti-VEGF antibody for treatment of severe ROP is bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody [7]. By binding to all isoforms of VEGF, bevacizumab inhibits VEGF receptor binding and signaling. Like any other IgG antibody, bevacizumab has a long half-life and can be detected in vitreous fluid and serum even 8 weeks after intra-ocular injection. Ranibizumab, a broken-down Fab component, is another less commonly used VEGF inhibitor. Ranibizumab has a shorter half-life. However, it is much costlier than bevacizumab [7].

Human Studies

Pharmacokinetic studies

In adults, intravitreal bevacizumab (IVB) is used most commonly in management of diabetic retinopathy [7]. The adult dose of IVB is 1.25 mg for each eye. In neonates, half of this dose (0.625 mg per eye) has been used in most of case reports and the largest randomized controlled trial. The rationale of using this dose is not clear and the correct choice is hampered by the lack of pharmacokinetic studies in neonates. Calculations of the volume of the eye and aqueous humor suggests that the size of a neonatal eye is one-third of adult size and a lower dose may be more appropriate [8].

IVB administration in neonates causes reduction of VEGF concentration in aqueous humor. However, it has now been established that bevacizumab leaks through the blood-retinal barrier and reaches not only the opposite untreated eye but also the systemic circulation. Kong, *et al*. [9] randomized 24 neonates with type 1 ROP into three treatment groups IVB at 0.625 mg or 0.25 mg per eye per dose or laser ablation. Serum levels of bevacizumab, free VEGF, and IGF-1 were measured before treatment and at 2, 14, 42, and 60 post-treatment days. Bevacizumab could be detected in the serum up to the last study measurement at 60 days and was accompanied by a dose-dependent reduction in serum VEGF levels. Serum IGF-1 levels were also reduced.

Hong, *et al*. [10] studied plasma concentration of VEGF, insulin growth factor, erythropoietin, pigment epithelium-derived factor and IgG1 in six neonates who received 0.6 mg of IVB for treatment of ROP. Plasma levels of VEGF, but not of other growth factors, were significantly reduced and remained low up to the last study measurement at 8 weeks. In another case series, Wu, *et al*. [11] measured serum levels of VEGF, VEGF receptors and various other anti-angiogenic growth factors in neonates who received IVB for treatment of type 1 ROP [11]. Similar to previous observations [10], VEGF levels were reduced for 8 weeks after IVB administration. A negative correlation was observed between serum levels of bevacizumab and VEGF [11]. Sato, *et al*. [12] have also reported elevated serum levels of bevacizumab and reduced serum levels of VEGF 2 weeks after 0.25 or 0.5 mg of IVB injection .

Thus, accumulating evidence (***Web Table* I**) suggests that IVB leads to sustained reduction in systemic VEGF levels. Evidence is needed on anatomical and functional effects of deficient VEGF levels on the development of various organs such as the lungs, kidneys, brain, injected eye and the contralateral eye.

Descriptive studies

The largest amount of evidence on the use of IVB stems from numerous case reports and case series without a control group. A total of 59 publications have reported experience with the use of anti-VEGF antibodies in 1205 eyes of 658 neonates (***Web Table* II**). Due to the lack of a comparison group, these studies cannot provide effect size of IVB *versus* laser ablation. In addition, evidence built on the basis of case reports has a high risk of bias due to possible publication bias. It is plausible that clinicians using IVB as an off-label drug for management of ROP may not report those cases in which IVB has been ineffective. However, the following key points emerge from these studies:

- Anti-VEGF treatment leads to a halt in neovascularization within 2-3 days. Complete resolution is expected within 2-3 weeks.
- The proportion of cases which respond to IVB varies in different studies with most studies reporting a good initial response in 90-100% cases. One of the largest case series reports outcome in a total of 253 eyes in 122

neonates with type 1 or worse ROP. Total regression was observed in more than 95% cases [14]. Those who did not respond showed complete regression after an additional 1-2 doses. Another study reported outcome in 162 eyes from 85 neonates with ROP [15]. Complete regression was observed in 143 eyes (88%). Fourteen eyes (9%) needed additional laser treatment.

- The most common adverse event noted for an eye treated with IVB was recurrence of ROP. This has been reported in many studies in which treated infants have been followed up for one year after treatment. Recurrence of ROP leading to retinal detachment has been reported as late as 53 weeks of post-menstrual age, and in 5-10% cases. Therefore, IVB treated ROP eyes need to be monitored for progression of ROP or development of new areas of abnormal vascularization. This not only increases the number of retinal examinations needed but also the need for general anesthesia, especially in bigger infants where outdoor office examination may not be sufficient to look at the peripheral retina. If there is recurrence of ROP, prompt additional treatment (laser ablation, supplemental IVB or surgery) may be needed.
- Completion of retinal vascularization is delayed after use of IVB. An advantage over laser ablation; however, is that the peripheral retina is vascularized. However, as shown in the few studies with fluorescein angiography, these vessels have abnormal organization, are leaky, and need to be monitored [16].
- Other local adverse effects reported in the case reports include pre-retinal/vitreous hemorrhage, transient vascular sheathing, choroidal whitening suggestive of choroidal ischemia, cataract, and need of paracentesis to reduce the intraocular pressure after injection.
- The most commonly used dose of IVB has been 0.625 mg per eye. However, a few studies have used lower doses and have reported similar rates of regression of ROP [17]. As discussed above, IVB crosses through the blood-retinal barrier leading to prolonged suppression of systemic levels of VEGF. Future studies need to investigate the role of lower doses of IVB for management of ROP.
- Ranibizumab has a shorter half-life as compared to bevacizumab and theoretically should have lesser systemic effects. Very few studies have reported its use in ROP probably due to the prohibitively higher cost. Of the four case reports, two have reported complete regression of ROP in all cases and two have reported a 75-100% failure rate (***Web Table* II**).

Of note there is a lack of studies reporting functional visual outcome and neurological outcome at school age or beyond. Distressingly, despite use of anti-VEGF in hundreds of eyes, there is a lack of data on short and long-term outcomes like physical growth, structural changes in brain (*e.g.* brain volume in MRI), renal function tests and lung function tests.

Randomized controlled trials

The largest randomized controlled trial (RCT) on the use of IVB in ROP was published in 2011 [72]. The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) trial randomized 150 neonates with zone 1 or zone 2 posterior stage 3+ ROP to receive 0.625 mg of IVB or laser ablation therapy bilaterally. The incidence of recurrence of ROP was significantly lower in the IVB group (4% eyes *versus* 22% eyes). On subgroup analysis, a significant benefit of IVB was observed in zone 1 ROP only. Post-intervention macular dragging was observed in one neonate in IVB group and 22 in laser group. Retinal detachment was observed in two neonates of each group. Corneal transplant was needed in one neonate of laser group and cataract removal was needed in three neonates of laser group. At 2.5 years of age, degree of myopia and incidence of severe myopia were significantly lower in the IVB group [73]. The authors proposed that the anterior segment growth and therefore axial length of the eye is preserved in neonates who are treated with IVB. However, a number of issues have been raised about the BEAT-ROP trial:

- The primary outcome of the study, the incidence of recurrence of ROP, was assessed at 54 weeks of PMA. While this end-point was adequate for eyes treated with laser, it was not so for eyes treated with IVB. Recurrence of ROP has occurred later than 54 weeks PMA after IVB treatment in observational studies. Moshfeghi, *et al*. [74] highlight that statistically 47.7% of recurrences in IVB group would have occurred after the end-point of study [74].
- The primary outcome of the study was changed mid-way from "absence of recurrence of Stage 3+ ROP in Zone I or Zone II posterior by 54 weeks" to "recurrence of retinal neovascularization requiring retreatment by 54 weeks" [74]. This is especially important as the investigators assessing the primary outcome of the study were not blinded to the treatment assignment [75].
- The incidence of recurrence of ROP needing treatment in the laser treatment group was higher than the incidence expected from the literature. In addition, the study was not adequately powered to detect important differences in long-term neurological outcome [76].

- Bevacizumab was administered 2.5 mm posterior to limbus. At this location, in extremely preterm neonates, the pars plana is not fully developed and the injecting needle may pass through retina thus increasing the risk of retinal damage and detachment [74].
- Much observational data on the use of bevacizumab has emanated from middle- and low- income countries where relatively mature neonates are effected by severe ROP. Generalizing the safety profile of bevacizumab to smaller neonates enrolled in BEAT-ROP study may not be appropriate. Both the pharmacodynamics of bevacizumab and the integrity of blood-retinal barrier need to be studied in extremely preterm neonates in whom angiogenesis is still active in many organ systems [77].
- VEGF is needed for growth and development of many organs, including the lungs, brain, and kidneys as well as the retina. Therefore, short term structural outcomes may not predict long term functional success. It is worth noting that in the BEAT-ROP trial more deaths occurred in the IVB group (6.6% *vs* 2.2%), and four of these five deaths were due to respiratory failure [78].

In another RCT, neonates with zone 1 or zone 2 posterior stage 3+ ROP were randomized to receive intravitreal pegaptanib or IVB with laser ablation (*n*=92 eyes of 46 infants), or laser therapy combined with cryotherapy (*n*=82 eyes of 41 infants) bilaterally [79]. A favorable anatomical outcome was observed significantly more commonly in the anti-VEGF group (90.2% eyes *vs* 62% eyes). No major side effects were reported. Retinal hemorrhages observed in both the groups resolved spontaneously. However, important details are missing in this report, including the method of randomization. The unfavorable outcome with laser therapy without IVB (38%) is much higher than expected from the literature.

Two more RCT comparing IVB with laser ablation have been published [80,81]. However, in both these studies, eyes of neonates were randomized so that one eye received IVB and contralateral eye received laser ablation. Even if IVB is injected in one eye, it is absorbed into systemic circulation and can be detected in the contralateral eye. Therefore, such studies have significant issues of contamination of the laser group. In the study by Lepore, *et al*. [80], 26 eyes of 13 neonates were randomized to receive IVB or laser. Fluorescein angiography was conducted before and 9 months after treatment. Even at 9 months post-treatment, the IVB group showed persistence of an avascular area and serious vascular abnormalities [80]. Retinal findings included vascular branching abnormalities, capillary dropout and macular changes. Moran, *et al.* [81] randomized 14 neonates with zone 1 or posterior zone 2 Stage 3 + ROP to receive 1.25 mg of IVB in one eye or laser ablation in contralateral eye. ROP regressed in all eyes. However, recurrence of ROP was observed more frequently in IVB treated eyes (21.4% *vs* 7.1%). The mean age of recurrence was higher in the IVB group (51 weeks PMA *vs* 37 weeks PMA) indicating the need for longer follow up [81].

Retrospective cohort studies

Five studies have retrospectively compared outcomes in neonates given IVB or treated with laser ablation (***Web Table* III**). Results are similar to those observed in RCT. Of note, Araz-Ersan, *et al*. [82] reported retinal detachment in 22% eyes, and Hwang, *et al*. [83] reported more frequent recurrence of ROP (14% *vs* 3%) in the IVB group. Araz-Ersan, *et al*. [82] also reported neuro-developmental outcome of their study cohort at 2 years of age. Neurological examination and cognitive development were comparable in the two groups.

In the absence of RCTs of IVB that are adequately powered to detect longer term systemic effects, one source of information is from large neonatal networks. A retrospective comparison of neurodevelopmental outcome at 18-22 months of age in infants of <29 weeks gestation in the Canadian Neonatal Network (CNN) born in 2010-11, who had acute ROP treated with either standard laser therapy or intravitreal bevacizumab injection, has been reported in abstract form [84]. Eighty-two infants received laser treatment and 32 bevacizumab, in most cases as monotherapy. Bevacizumab treated infants had significantly lower motor scores after adjustment for confounding factors [84].

SUMMARY AND UNANSWERED QUESTIONS

Intravitreal anti-VEGF therapy looks to be a promising therapy for the management of ROP. Treatment with IVB injection takes less time, needs less learning skills and causes less pain or ocular inflammation. As there is no need to buy and maintain costly laser equipment, anti-VEGF therapy can potentially improve accessibility and timeliness of treatment of ROP.

Intravitreal anti-VEGF therapy preserves the peripheral retina. Evidence from comparative studies indicates that it may be associated with better structural and functional outcomes. However, as the peripheral retina is preserved and can start producing VEGF again, ROP can recur and if undetected can lead to retinal detachment and loss of vision. Therefore, neonates managed with anti-VEGF agents require more frequent hospital visits, longer follow up until at least 1 year of postmenstrual age, more often general anesthesia and newer skills to diagnose and manage the recurrences that appear different from laser

related recurrences. Despite hundreds of eyes been treated with anti-VEGF therapy there are many issues which need to be addressed before it use can be recommended as the primary mode in management of ROP.

Effect on organ development: Apart from promoting vascular growth in eyes during the perinatal period, VEGF plays a role in development of glomeruli, alveoli and parts of the brain. It is not known how structure and function of these organs are affected in neonates who have systemic elevation of anti-VEGF and decrease of VEGF levels sustained for at least 2 months after a single intraocular injection of anti-VEGF. Evidence from one network data analysis suggests increased risk of motor developmental problems in neonates who received IVB [84]. There is an urgent need to further investigate the long-term effects of this therapy on cognition and related neurological functions.

Anti-VEGF agent, dose and timing: The majority of evidence on anti-VEGF agents exists with 0.625 mg of bevacizumab. Whether a lower dose, repeat doses or use of different agents (like ranibizumab) can be associated with lower systemic levels and similar beneficial effects in the eye is yet to be seen. The timing of administration of anti-VEGF agents may be crucial. If administered after fibro-vascular proliferation has set in, they may cause contraction of the fibro-vascular membrane and retinal detachment [69].

Long-term retinal development: Limited evidence suggests that retinal vessels which develop into peripheral retina are not normal, and have abnormal branching pattern and capillary drop-out. What happens to these vessels into adulthood, especially if child grows up to be diabetic, is unknown. This is of special importance to countries like India where a large proportion of preterm neonates also have intrauterine growth restriction and are prone to development of metabolic syndrome later in life [88].

Operational implementation: If anti-VEGF therapy is effective and free from serious side-effects, its implementation requires significant challenges in settings with limited resources. Anti-VEGF therapy is costly; frequently vials are shared among many neonates needing treatment. This significantly increases the risk of complications due to infections thus offsetting at the population level any benefit accrued from use of anti-VEGF. As compared to neonates treated with laser therapy, neonates treated with anti-VEGF need longer follow-up.

Until these important issues are addressed, despite being effective in causing regression of ROP, anti-VEGF remains an investigational drug and should be used only as part of a clinical study. Research needs to examine whether it can be recommended as an alternative therapy to parents of neonates with severe ROP. There may be instances of its off-label use in exceptional circumstances like non-availability of laser therapy, non-visualization of the retina, as rescue therapy in laser-failed cases or delayed presentations. We recommend that a national registry should be maintained on the use of anti-VEGF therapy for treatment of ROP and neonates should be followed up until at least 18-24 months of age for recording visual and neurodevelopmental outcomes.

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REFERENCES

1. Hellström A, Smith LEH, Dammann O. Retinopathy of prematurity. Lancet. 2013;382:1445-57.
2. Sanghi G, Dogra MR, Katoch D, Gupta A. Demographic profile of infants with stage 5 retinopathy of prematurity in North India: Implications for screening. Ophthalmic Epidemiol. 2011;18:72-4.
3. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: Ten year data from a tertiary care center in a developing country. Indian J Ophthalmol. 2007;55:331-6.
4. Darlow BA. Retinopathy of prematurity: New developments bring concern and hope. J. Paediatr. Child Health. 2015;51:765-70.
5. Early Treatment For Retinopathy Of Prematurity Cooperative Group null. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol Chic Ill 1960. 2003;121:1684-94.
6. Quinn GE, Dobson V, Hardy RJ, Tung B, Palmer EA, Good WV, *et al*. Visual field extent at 6 years of age in children who had high-risk prethreshold retinopathy of prematurity. Arch Ophthalmol Chic Ill 1960. 2011; 129:127-32.
7. Stewart MW. The expanding role of vascular endothelial growth factor inhibitors in ophthalmology. Mayo Clin Proc. 2012;87:77-88.
8. Spandau U. What is the optimal dosage for intravitreal bevacizumab for retinopathy of prematurity? Acta Ophthalmol (Copenh.). 2013;91:e154.
9. Kong L, Bhatt AR, Demny AB, Coats DK, Li A, Rahman EZ, *et al*. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. Invest Ophthalmol Vis Sci. 2015;56:956-61.
10. Hong YR, Kim YH, Kim SY, Nam GY, Cheon HJ, Lee SJ. Plasma concentrations of vascular endothelial growth factor in retinopathy of prematurity after intravitreal bevacizumab injection. Retina Phila. 2015;35:1772-7.

11. Wu W-C, Lien R, Liao P-J, Wang N-K, Chen Y-P, Chao A-N, *et al*. Serum levels of vascular endothelial growth factor and related factors after intravitreous bevacizumab injection for retinopathy of prematurity. JAMA Ophthalmol. 2015;133:391-7.
12. Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahashi-Shima C, *et al*. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol. 2012;153:327-33.e1.
13. Nonobe NI, Kachi S, Kondo M, Takai Y, Takemoto K, Nakayama A, *et al*. Concentration of vascular endothelial growth factor in aqueous humor of eyes with advanced retinopathy of prematurity before and after intravitreal injection of bevacizumab. Retina Phila. 2009;29:579-85.
14. Yetik H, Gunay M, Sirop S, Salihoglu Z. Intravitreal bevacizumab monotherapy for type-1 prethreshold, threshold, and aggressive posterior retinopathy of prematurity - 27 month follow-up results from Turkey. Graefes Arch. Clin. Exp. Ophthalmol. Albrecht Von Graefes Arch. Für Klin. Exp. Ophthalmol. 2015;253:1677-83.
15. Wu W-C, Kuo H-K, Yeh P-T, Yang C-M, Lai C-C, Chen S-N. An updated study of the use of bevacizumab in the treat-ment of patients with prethreshold retinopathy of pre-maturity in taiwan. Am J Ophthalmol. 2013;155:150-8.e1.
16. Henaine-Berra A, Garcia-Aguirre G, Quiroz-Mercado H, Martinez-Castellanos MA. Retinal fluorescein angiographic changes following intravitreal anti-VEGF therapy. J. AAPOS Off. Publ. Am. Assoc. Pediatr. Ophthalmol. Strabismus Am. Assoc Pediatr Ophthalmol Strabismus. 2014;18:120-3.
17. Connor AJ, Papastavrou VT, Hillier RJ, Shafiq A. Ultra-low dose of intravitreal bevacizumab in the treatment of retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2015;52:e20-1.
18. Wong RK, Hubschman S, Tsui I. Reactivation of retinopathy of prematurity after ranibizumab treatment. Retina Phila. 2015;35:675-80.
19. Kim R, Kim YC. Posterior pole sparing laser photocoagulation combined with intravitreal bevacizumab injection in posterior retinopathy of prematurity. J Ophthalmol. 2014;2014:257286.
20. Chen S-N, Lian I, Hwang Y-C, Chen Y-H, Chang Y-C, Lee K-H, *et al*. Intravitreal anti-vascular endothelial growth factor treatment for retinopathy of prematurity: comparison between Ranibizumab and Bevacizumab. Retina Phila. 2015;35:667-74.
21. Minami T, Kuniyoshi K, Kusaka S, Sugioka K, Sakuramoto H, Sakamoto M, *et al*. Intravitreal injection of bevacizumab for retinopathy of prematurity in an infant with peters anomaly. Case Rep Ophthalmol. 2014;5:318-24.
22. Yaz Y, Erol N, Gursoy H, Basmak H, Bilgec MD. A rare association of intravitreal bevacizumab injection with double ridge formation in retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2014;51:e66-8.
23. Chen Y-H, Chen S-N, Lien R-I, Shih C-P, Chao A-N, Chen K-J, *et al*. Refractive errors after the use of bevacizumab for the treatment of retinopathy of prematurity: 2-year outcomes. Eye. 2014;28:1080-6.
24. Chen W, Binenbaum G, Karp K, Baumritter A, Pearson DJ, Maguire AM, *et al*. Late recurrence of retinopathy of prematurity after treatment with both intravitreal bevacizumab and laser. J AAPOS. 2014;18:402-4.
25. Menke MN, Framme C, Nelle M, Berger MR, Sturm V, Wolf S. Intravitreal ranibizumab monotherapy to treat retinopathy of prematurity zone II, stage 3 with plus disease. BMC Ophthalmol. 2015;15:20.
26. Ehmann D, Greve M. Intravitreal bevacizumab for exudative retinal detachment post laser therapy for retinopathy of prematurity. Can J Ophthalmol J Can Ophtalmol. 2014;49:228-31.
27. Bancalari MA, Schade YR, Peña ZR, Pavez PN. Intravitreal bevacizumab as single drug therapy for retinopathy of prematurity in 12 patients. Arch. Argent. Pediatría. 2014;112:160-3.
28. Kuniyoshi K, Sugioka K, Sakuramoto H, Kusaka S, Wada N, Shimomura Y. Intravitreal injection of bevacizumab for retinopathy of prematurity. Jpn J Ophthalmol. 2014; 58:237-43.
29. Tahija SG, Hersetyati R, Lam GC, Kusaka S, McMenamin PG. Fluorescein angiographic observations of peripheral retinal vessel growth in infants after intravitreal injection of bevacizumab as sole therapy for zone I and posterior zone II retinopathy of prematurity. Br J Ophthalmol. 2014; 98:507-12.
30. Chhablani J, Rani PK, Balakrishnan D, Jalali S. Unusual adverse choroidal reaction to intravitreal bevacizumab in aggressive posterior retinopathy of prematurity: The Indian Twin Cities ROP screening (ITCROPS) data base report number 7. Semin Ophthalmol. 2014;29:222-5.
31. Harder BC, von Baltz S, Jonas JB, Schlichtenbrede FC. Intravitreal low-dosage bevacizumab for retinopathy of prematurity. Acta Ophthalmol. (Copenh.). 2014;92: 577-81.
32. Flavahan PW, Lavy TE, Wykes W. Intravitreal bevacizumab for the treatment of retinopathy of prematurity: a case report. Scott Med J. 2013;58:130-2.
33. de Klerk TA, Park DY, Biswas S. Prolonged follow-up period following intravitreal bevacizumab injection for stage 3+ retinopathy of prematurity. Eye Lond Engl. 2013;27:1218.
34. Mehta S, Hubbard GB. Delayed recurrent neovascularization and persistent avascular retina following intravitreal bevacizumab for retinopathy of prematurity. Retin Cases Brief Rep. 2013;7:206-9.
35. Karaca C, Oner AO, Mirza E, Polat OA, Sahiner M. Bilateral effect of unilateral bevacizumab injection in retinopathy of prematurity. JAMA Ophthalmol. 2013; 131:1099-101.
36. Goldman DR, Baumal CR. Dramatic regression of persistent tunica vasculosa lentis associated with retinopathy of prematurity following treatment with intravitreal bevacizumab. J Pediatr Ophthalmol Strabismus. 2013;50 Online:e27-9.
37. Sahin A, Sahin M, Cingü AK, Cinar Y, Türkcü FM, Yüksel H, *et al*. Intravitreal bevacizumab monotherapy for retinopathy of prematurity. Pediatr Int Off J Jpn. Pediatr

Soc. 2013;55:599-603.
38. Ittiara S, Blair MP, Shapiro MJ, Lichtenstein SJ. Exudative retinopathy and detachment: a late reactivation of retinopathy of prematurity after intravitreal bevacizumab. J AAPOS. 2013;17:323-5.
39. Jalali S, Balakrishnan D, Zeynalova Z, Padhi TR, Rani PK. Serious adverse events and visual outcomes of rescue therapy using adjunct bevacizumab to laser and surgery for retinopathy of prematurity. The Indian Twin Cities Retinopathy of Prematurity Screening database Report number 5. Arch Dis Child Fetal Neonatal Ed. 2013; 98:F327-33.
40. Martínez-Castellanos MA, Schwartz S, Hernández-Rojas ML, Kon-Jara VA, García-Aguirre G, Guerrero-Naranjo JL, *et al*. Long-term effect of antiangiogenic therapy for retinopathy of prematurity up to 5 years of follow-up. Retina Phila. 2013;33:329-38.
41. Tseng C-C, Chen S-N, Hwang J-F, Lin C-J. Different refractive errors in triplets with retinopathy of prematurity treated with bevacizumab. J Pediatr Ophthalmol Strabismus. 2012;49:e41-3.
42. Sun HJ, Choi KS, Lee SJ. Adjunctive effect of intravitreal bevacizumab prior to lens-sparing vitrectomy in aggressive posterior retinopathy of prematurity: a case report. Jpn J Ophthalmol. 2012;56:476-80.
43. Patel RD, Blair MP, Shapiro MJ, Lichtenstein SJ. Significant treatment failure with intravitreous bevacizumab for retinopathy of prematurity. Arch Ophthalmol 1960. 2012;130:801-2.
44. Lee BJ, Kim JH, Heo H, Yu YS. Delayed onset atypical vitreoretinal traction band formation after an intravitreal injection of bevacizumab in stage 3 retinopathy of prematurity. Eye. 2012;26:903-9.
45. Choovuthayakorn J, Ubonrat K. Intravitreal bevacizumab injection in advanced retinopathy of prematurity. J Med Assoc Thail. 2012;95 Suppl 4:S70-5.
46. Dani C, Frosini S, Fortunato P, Bertini G, Pratesi S, Pollazzi L, *et al*. Intravitreal bevacizumab for retinopathy of prematurity as first line or rescue therapy with focal laser treatment. A case series. J. Matern. Fetal Neonatal Med. 2012;25:2194-7.
47. Hu J, Blair MP, Shapiro MJ, Lichtenstein SJ, Galasso JM, Kapur R. Reactivation of retinopathy of prematurity after bevacizumab injection. Arch Ophthalmol Chic 1960. 2012;130:1000-6.
48. Wutthiworawong B, Thitiratsanont U, Saovaprut C, Subhangkasen I, Geyuraphun B, Ampornprut A, *et al*. Combine intravitreal bevacizumab injection with laser treatment for aggressive posterior retinopathy of prematurity (AP-ROP). J Med Assoc Thail. 2011;94 Suppl 3:S15-21.
49. Harder BC, von Baltz S, Jonas JB, Schlichtenbrede FC. Intravitreal bevacizumab for retinopathy of prematurity. J Ocul Pharmacol Ther. 2011;27:623-7.
50. Axer-Siegel R, Snir M, Ron Y, Friling R, Sirota L, Weinberger D. Intravitreal bevacizumab as supplemental treatment or monotherapy for severe retinopathy of prematurity. Retina Phila. 2011;31:1239-47.
51. Roohipoor R, Ghasemi H, Ghassemi F, Karkhaneh R, Riazi-Esfahani M, Nili-Ahmadabadi M. Intravitreal bevacizumab in retinopathy of prematurity: an interventional case series. Graefes Arch Clin Exp Ophthalmol. Albrecht Von Graefes Arch. Für Klin Exp. Ophthalmol. 2011;249:1295-301.
52. Erol N, Gürsoy H, Sahin A, Basmak H. Intravitreal bevacizumab following laser therapy for severe retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2010; 47:e1-4.
53. Shah PK, Morris RJ, Narendran V, Kalpana N. Visual acuity and electroretinography findings 3½ years after the first intravitreal injection of bevacizumab (Avastin) in aggressive posterior retinopathy of prematurity. Indian J Ophthalmol. 2011;59:73-4.
54. Jang SY, Choi KS, Lee SJ. Delayed-onset retinal detachment after an intravitreal injection of ranibizumab for zone 1 plus retinopathy of prematurity. J AAPOS. 2010;14:457-9.
55. Ahmed AE, Channa R, Durrani J, Ali A, Ahmad K. Early experience with intravitreal bevacizumab combined with laser treatment for retinopathy of prematurity. Middle East Afr J Ophthalmol. 2010;17:264-7.
56. Hoang QV, Kiernan DF, Chau FY, Shapiro MJ, Blair MP. Fluorescein angiography of recurrent retinopathy of prematurity after initial intravitreous bevacizumab treatment. Arch Ophthalmol 1960. 2010;128:1080-1.
57. Wu W-C, Yeh P-T, Chen S-N, Yang C-M, Lai C-C, Kuo H-K. Effects and complications of bevacizumab use in patients with retinopathy of prematurity: A multicenter study in taiwan. Ophthalmology. 2011;118:176-83.
58. Atchaneeyasakul L-O, Trinavarat A. Choroidal ruptures after adjuvant intravitreal injection of bevacizumab for aggressive posterior retinopathy of prematurity. J. Perinatol. 2010;30:497-9.
59. Nazari H, Modarres M, Parvaresh MM, Ghasemi Falavarjani K. Intravitreal bevacizumab in combination with laser therapy for the treatment of severe retinopathy of prematurity (ROP) associated with vitreous or retinal hemorrhage. Graefes Arch. Clin. Exp. Ophthalmol. Albrecht Von Graefes Arch. Für Klin Exp Ophthalmol. 2010;248:1713-8.
60. Altinsoy HI, Mutlu FM, Güngör R, Sarici SÜ. Combination of Laser Photocoagulation and Intravitreal Bevacizumab in Aggressive Posterior Retinopathy of Prematurity. Ophthalmic Surg. Lasers Imaging. 2010;1-5.
61. Law JC, Recchia FM, Morrison DG, Donahue SP, Estes RL. Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. J AAPOS 2010;14:6-10.
62. Dorta P, Kychenthal A. Treatment of type 1 retinopathy of prematurity with intravitreal bevacizumab (Avastin). Retina Phila. 2010;30:S24-31.
63. Kychenthal A, Dorta P. Vitrectomy after intravitreal bevacizumab (Avastin) for retinal detachment in retinopathy of prematurity. Retina Phila. 2010;30:S32-6.
64. Quiroz-Mercado H, Martinez-Castellanos MA, Hernandez-Rojas ML, Salazar-Teran N, Chan RVP. Antiangiogenic therapy with intravitreal bevacizumab for retinopathy of prematurity. Retina Phila. 2008;28:S19-25.
65. Lalwani GA, Berrocal AM, Murray TG, Buch M, Cardone S, Hess D, *et al*. Off-label use of intravitreal bevacizumab

(Avastin) for salvage treatment in progressive threshold retinopathy of prematurity. Retina Phila. 2008;28:S13-8.
66. Kong L, Mintz-Hittner HA, Penland RL, Kretzer FL, Chévez-Barrios P. Intravitreous bevacizumab as anti-vascular endothelial growth factor therapy for retinopathy of prematurity: a morphologic study. Arch Ophthalmol. 1960. 2008;126:1161-3.
67. Kusaka S, Shima C, Wada K, Arahori H, Shimojyo H, Sato T, *et al*. Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: A pilot study. Br J Ophthalmol. 2008;92:1450-5.
68. Mintz-Hittner HA, Kuffel RR. Intravitreal injection of bevacizumab (avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. Retina Phila. Pa. 2008;28:831-8.
69. Honda S, Hirabayashi H, Tsukahara Y, Negi A. Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch. Für Klin Exp Ophthalmol. 2008;246:1061-3.
70. Chung EJ, Kim JH, Ahn HS, Koh HJ. Combination of laser photocoagulation and intravitreal bevacizumab (Avastin) for aggressive zone I retinopathy of prematurity. Graefes Arch. Clin. Exp. Ophthalmol. Albrecht Von Graefes Arch Für Klin Exp Ophthalmol. 2007;245:1727-30.
71. Travassos A, Teixeira S, Ferreira P, Regadas I, Travassos AS, Esperancinha FE, *et al*. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthalmic Surg. Lasers Imaging. 2007;38:233-7.
72. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603-15.
73. Geloneck MM, Chuang AZ, Clark WL, Hunt MG, Norman AA, Packwood EA, *et al*. Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial. JAMA Ophthalmol. 2014;132:1327-33.
74. Moshfeghi DM, Berrocal AM. Retinopathy of prematurity in the time of bevacizumab: Incorporating the BEAT-ROP results into clinical practice. Ophthalmology. 2011; 118:1227-8.
75. Good WV, Palmer EA. Bevacizumab for retinopathy of prematurity. N Engl J Med. 2011;364:2359.
76. Darlow BA, Ells AL, Gilbert CE, Gole GA, Quinn GE. Are we there yet? Bevacizumab therapy for retinopathy of prematurity. Arch Dis Child Fetal Neonatal Ed. 2013; 98:F170-4.
77. Gilbert CE, Zin A, Darlow B. Bevacizumab for retinopathy of prematurity. N Engl J Med. 2011;364:2359-60.
78. Lim LS, Mitchell P, Wong TY. Bevacizumab for retinopathy of prematurity. N Engl J Med. 2011;364:2360; author reply 2361-2.
79. Autrata R, Senková K, Holousová M, Krejcírová I, Dolezel Z, Borek I. Effects of intravitreal pegaptanib or bevacizumab and laser in treatment of threshold retinopathy of prematurity in zone I and posterior zone II-four years results. Ceská Slov. Oftalmol. Cas. Ceské Oftalmol. Spolecnosti Slov. Oftalmol. Spolecnosti. 2012;68:29-36.
80. Lepore D, Quinn GE, Molle F, Baldascino A, Orazi L, Sammartino M, *et al*. Intravitreal bevacizumab versus laser treatment in type 1 retinopathy of prematurity: report on fluorescein angiographic findings. Ophthal. 2014; 121:2212-9.
81. Moran S, O'Keefe M, Hartnett C, Lanigan B, Murphy J, Donoghue V. Bevacizumab versus diode laser in stage 3 posterior retinopathy of prematurity. Acta Ophthalmol (Copenh). 2014;92:e496-7.
82. Araz-Ersan B, Kir N, Tuncer S, Aydinoglu-Candan O, Yildiz-Inec D, Akdogan B, *et al*. Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. Curr Eye Res. 2015;40:585-91.
83. Hwang CK, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after Intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: A 5-Year Retrospective Analysis. Ophthalmol. 2015;122:1008-15.
84. Morin J, Luu TM, Superstein R, Ospina LH, Lefebvre F, Simand M-N, *et al*. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics. 2016;137:e20153218.
85. Isaac M, Mireskandari K, Tehrani N. Treatment of type 1 retinopathy of prematurity with bevacizumab versus laser. J AAPOS 2015;19:140-4.
86. Harder BC, Schlichtenbrede FC, von Baltz S, Jendritza W, Jendritza B, Jonas JB. Intravitreal bevacizumab for retinopathy of prematurity: refractive error results. Am J Ophthalmol. 2013;155:1119-24.e1.
87. Lee JY, Chae JB, Yang SJ, Yoon YH, Kim J-G. Effects of intravitreal bevacizumab and laser in retinopathy of prematurity therapy on the development of peripheral retinal vessels. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Für Klin Exp Ophthalmol. 2010;248:1257-62.
88. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, *et al*. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health. 2013;1:e26-36.

Web Box 1 LITERATURE SEARCH

PubMed and Cochrane Register of Clinical Trials were searched for studies evaluating role of anti-VEGF in ROP. No study design or language restriction was used. Search term used was ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonate"[All Fields]) AND ("retinopathy of prematurity"[MeSH Terms] OR ("retinopathy"[All Fields] AND "prematurity"[All Fields]) OR "retinopathy of prematurity"[All Fields]) AND (("bevacizumab"[Supplementary Concept] OR "bevacizumab"[All Fields]) OR ("ranibizumab"[Supplementary Concept] OR "ranibizumab"[All Fields]) OR ("ranibizumab"[Supplementary Concept] OR "ranibizumab"[All Fields])). One hundred and forty-three studies were retrieved. Of these 107 were found relevant and further screened. Seventy-three studies reporting original research were selected. Review articles, editorial and comments on published articles or letters not providing original reports were excluded. These were divided into three categories: pharmacokinetics studies (n=5), observational studies without control group (n=59) and clinical trials with a control group (*n*=9).

WEB TABLE I PHARMACOKINETIC STUDIES ON USE OF ANTI-VEGF ANTIBODIES IN NEONATES

Author (Year)	*Study design*	*Subjects*	*Intervention group*	*Control group*	*Outcome*
Hong, *et al*. [10] (2015)	Case series	11 eyes of 6 patients with threshold ROP with plus disease in Zone 1 or 2	0.6 mg (0.025 mL) of IVB	-	Significant reduction in plasma VEGF persisting at 8 weeks after IVB
Kong, *et al*. [9] (2015)	Randomized controlled trial	24 neonates with Type 1 ROP	IVB at 0.625 mg or 0.25 mg per eye per dose	Laser ablation	Dose-dependent reduction in serum VEGF 60 days post-treatment
Wu, *et al.* [11]. (2015)	Case series	8 neonates with type 1 ROP	IVB	-	Negative correlation between serum levels of bevacizumab and VEGF 8 weeks after IVB
Sato, *et al.* [12] (2012)	Case series	11 neonates with "vascularly-active" ROP	0.25 or 0.5 mg of IVB	-	Negative correlation between serum levels of bevacizumab and VEGF 2 weeks after IVB
Nonobe, *et al.* [13] (2009)	Case series	8 neonates with stage 4 or 5 ROP	0.75 mg/0.03 mL/eye of IVB	4 patients with congenital cataract	IVB led to reduction of VEGF concentration in aqueous humor

IVB: Intravitreal bevacizumab; ROP: Retinopathy of prematurity; VEGF: Vascular endothelial growth factor

WEB TABLE II CASE REPORTS AND CASE SERIES ON USE OF INTRAVITREAL ANTI-VEGF ANTIBODIES IN RETINOPATHY OF PREMATURITY

Author (Year)	*Study design*	*Subjects*	*Intervention group*	*Outcome*
Connor, *et al.* [17] (2015)	Case report	2 eyes of 1 neonate with Stage 2 ROP with plus disease in zone 1-2	IVB 0.16 mg in one and 0.32 mg in second eye	Response in 2 days Complete resolution in 12 days
Wong, *et al.* [18] (2015)	Case series	10 eyes in 6 neonates with ROP	Bevacizumab or ranibizumab	ROP reactivation occurred in 5/6 (83%) eyes treated with ranibizumab. None with bevacizumab
Kim, *et al.* [19] (2014)	Case series	16 eyes of 10 neonates with zone 1 ROP or aggressive posterior zone 2 ROP	0.5 mg of IVB with laser. If ROP within 2 disc diameter of fovea this area spared of laser	Complete regression of the ROP without recurrence or complications
Yetik, *et al.* [14] (2014)	Case series	Pre-threshold ROP (type 1) in 152 eyes of 79 neonates Threshold ROP in 24 eyes of 12 neonates Aggressive posterior in 62 eyes of 31 neonates	A total of 253 IVB injections in 122 subjects	Total regression in 227/238 eyes (95.4 %) after the first dose. Regression in 98.2% after 2 and 100% with 3 doses No complications
Chen, *et al.* [20] (2015)	Case series	72 eyes of 37 patients type 1 ROP	Bevacizumab or ranibizumab as primary treatment	Similar and complete response, higher chances of myopia in IVB group
Minami, et al. (2014)[21]	Case report	2 eyes of 1 neonate with corneal opacity and stage 3 ROP	IVB	Retinal detachment in one eye after IVB. Other eye ROP regressed
Yaz, *et al.* [22] (2014)	Case report	1 neonate with zone 2 stage 3 ROP	IVB	Formation of second ridge anterior to previous ridge
Chen, *et al.* [23] (2014)	Case series	64 eyes of 34 neonates with type 1 ROP	Three kinds of therapies: IVB, combined IVB and laser treatment or IVB and lens-sparing vitrectomy	At 2 years prevalence of myopia lower in IVB alone group
Chen, *et al.* [24] (2014)	Case report	2 eyes of a neonate with type 1 ROP	IVB followed by laser ablation	Despite combine treatment recurrence of plus disease at 51 weeks PMA
Menke, *et al.* [25] (2015)	Case series	6 eyes of 4 neonates with ROP stage 3 plus disease	Ranibizumab	Postoperative URI in one neonates. Three eyes required paracentesis to reduce the intraocular pressure after injection and to restore central artery perfusion. After six months, all eyes showed complete retinal vascularization without any signs of disease recurrence

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Ehmann, *et al.* [26] (2014)	Case series	2 neonates with exudative retinal detachment after laser therapy for pre-threshold and threshold ROP	IVB 0.625 mg X 3 times weekly+ intravenous dexamethasone	Complete resolution of the sub-retinal fluid
Henaine-Berra, *et al.* [16](2014)	Case series	47 eyes of 26 neonates stage 3 threshold or pre-threshold ROP	0.75 mg IVB	Fluorescein angiography showed improvement in neovascularization. However, avascular area later shows large areas devoid of micro-vessels, formation of vascular loops and non-development of retinal vessels in far periphery. Perivascular leakage present in majority
Bancalari, *et al.* [27] (2014)	Case series	12 neonates with threshold ROP in whom laser ablation was contraindicated	IVB	Good response in 8/12. Laser needed in 4/12
Kuniyoshi, *et al.* [28] (2014)	Case series	8 eyes of 4 neonates with type 1 ROP	0.25 mg IVB	IVB effective in all eyes with ROP in zone 2. Vitreous hemorrhage and cataract at 19 weeks and 5 months after the initial IVB in the two eyes with ROP in zone I.
Tahija, *et al*. [29] (2014)	Case series	20 eyes of 10 neonates who received IVB for zone I and posterior zone II ROP and had initial resolution of posterior disease.	IVB	Follow up for up to 259 weeks PMA. 11 of 20 eyes did not achieved normal retinal vascularization
Chhablani, *et al.* [30] (2014)	Case report	1 neonate with severe zone 1 APROP	IVB	After 16 hours, hypotony and exudative retinal detachment with patches of choroidal whitening suggestive of choroidal ischemia
Harder, *et al.* [31] (2014)	Case series	57 eyes of 29 neonates with ROP in zone 1 or zone 2	0.375 mg IVB	Regression of ROP in all. Only one needed additional dose of IVB
Flavahan, *et al.* [32] (2013)	Case report	2 eyes of 1 neonate with stage 3+ disease in zone 1	IVB	Complete resolution
de Klerk, *et al*. [33] (2013)	Case report	2 eyes of 1 neonate with type 1 ROP	0.625?mg IVB	Regression by 2 weeks. Retinal vascularization completed at 52 weeks CA
Mehta, *et al*. [34] (2013)	Case report	2 eyes of 1 neonate with zone 1 stage 3 ROP with plus disease	IVB	Regression followed by recurrent neovascularization and plus disease of both eyes requiring treatment with laser photocoagulation at 53 weeks PMA.

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Kim, *et al.* [19] (2014)	Case series	18 eyes of 10 neonates with type 1 ROP	Combined IVB (0.25 mg) and zone 1 sparing laser ablation	Regression without recurrence in all
Karaca, *et al*. [35] (2013)	Case series	4 neonates with stage 3 ROP	Unilateral laser and IVB	Regression in both eyes
Goldman, *et al*. [36] (2013)	Case report	1 neonate with ROP and tunica vasculosa lentis	IVB	Regression of tunica vasculosa lentis
Sahin, *et al.* [37] (2013)	Case series	30 eyes of 17 neonates with type 1 ROP	IVB	Regression all except one eye. Mean full retinal vascularization time 136.6 ± 26.6 days
Ittiara, *et al*. [38] (2013)	Case report	2 eyes of 1 neonate with ROP	IVB	Bilateral exudative retinal detachment 1 year after IVB
Jalali, *et al.* [39] (2013)	Case series	24 eyes in 13 neonates for type 1 or more severe ROP	IVB	New vessels regressed in all eyes. Complications reported include macular hole and retinal breaks causing rhegmatogenous retinal detachment in 1 eye; Bilateral progressive vascular attenuation, perivascular exudation and optic atrophy in 1 neonate; progression of detachment bilaterally to stage 5 in 1 neonate. A neonate who received injection into the anterior chamber later developed hepatic dysfunction and large choroidal rupture in 1 eye.
Martínez-Castellanos, *et al.* [40] (2013)	Case series	18 eyes in 13 neonates with threshold ROP	IVB	Follow up for 5 years. Regression in all. Recurrence in one.12 eyes developed low myopia mean value of 3.2 D. median vision 20/25
Wu, *et al.* [15] (2013)	Case series	162 eyes from 85 neonates with ROP	IVB	Regression in 143 eyes (88%). Fourteen eyes (9%) needed additional laser treatment. Three eyes (2%) progressed to stage 4 ROP. Complications: vitreous or pre-retinal hemorrhage in 2 eyes; cataract in 1 eye and exotropia in 1 eye
Tseng, *et al.* (2012)[41]	Case series	3 triplets	IVB	Regression of ROP in all three triplets. High myopia with increased axial length of both eyes in one triplet
Sun, *et al*. (2012)[42]	Case report	A neonate with APROP	Laser and IVB 0.75 mg. Repeated once	Resolution in both eyes. Post retinal detachment in 1 eye
Patel, *et al.* (2012)[43]	Case report	2 eyes of 1 neonate with zone 1 stage 3 ROP	0.625 mg IVB	Complete retinal detachment in both eyes

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Lee, *et al.* (2012)[44]	Case series	5 eyes of 3 neonates with stage 3 ROP	IVB with or without laser ablation	Regression of ROP in all. Atypical fibrous traction membrane along the major vascular arcades with 2.5 to 4 months of latency, which progressed into retinal detachment in 3/5 eyes
Choovuthayakorn, *et al*. (2012)[45]	Case series	34 eyes of 19 patients with 'advanced' ROP	In 2 patients IVB followed by laser ablation. Reverse sequence in 17 patients	Regression in all. Retinal detachment in 1.
Dani, *et al.* (2012)[46]	Case series	7 neonates with complicated ROP or APROP	IVB as first line monotherapy (n=2) or rescue therapy combined with laser treatment	Regression in all neonates
Hu, *et al*. (2012)[47]	Cases series	17 eyes of 9 patients with recurrence of ROP after initial treatment with IVB	IVB	Mean age at treatment-requiring recurrence was 49.3 weeks (SD, 9.1 weeks; minimum, 37 weeks; maximum, 69 weeks) postmenstrual age (PMA). Fives eyes progressed to retinal detachment. No eye that received laser treatment for recurrence progressed to retinal detachment.
Wutthiworawong, *et al*. (2011)[48]	Case series	12 neonates with APROP	Laser ablation followed by IVB	Complete regression in all
Harder, *et al.* (2011)[49]	Case series	23 eyes in 12 neonates with threshold ROP in zone 1 or zone 2	0.375 mg IVB	Complete regression in all
Axer-Siegel, *et al.* (2011)[50]	Case series	18 eyes of 9 neonates in which laser ablation was not possible because of advanced disease	IVB	Subsidence of the active vascular component in all eyes.
Roohipoor, *et al.* (2011)[51]	Case series	10 eyes of 12 neonates no response to laser ablation (group 1) with APROP (group 2)	IVB	All responded in group 1. 2 eyes of group 2 needed laser
Erol, *et al*. (2010)[52]	Case series	7 eyes of 4 infants who had continued ROP progression despite laser therapy	IVB	Regression in 6/7 eyes
Shah, *et al.* (2011)[53]	Case report	1 eye of 1 neonate in whom APROP despite laser ablation	0.75 mg of IVB in 1 eye. Other eye managed conservatively	ROP regressed in both. Adverse visual outcome in eye which received IVB

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Jang, *et al.* (2010)[54]	Case report	2 eyes of 1 neonate with bilateral, zone 1, stage 3 plus	Combined laser ablation and intravitreal ranibizumab	Regression at 3 months after injection but bilateral retinal detachments after 1 month.
Ahmed, *et al.* (2010)[55]	Case series	15 eyes of 8 neonates with stage 3-4 ROP	IVB and laser ablation	Regression in all. No side effects
Hoang QV, *et al.* (2010)[56]	Case report	2 eyes of a neonate with type 1 pre-threshold ROP	IVB	Initial regression followed by recurrence in the form of more anterior stage 3 ROP
Wu, *et al.* (2011)[57]	Case series	49 eyes of 27 patients with ROP stage 3 or more	0.625 mg IVB	90% response in stage 3. Lower response rate in higher stages. Complications noted were vitreous or pre-retinal hemorrhage in 4 eyes (8%) and transient vascular sheathing in 2 eyes (4%)
Atchaneeyasakul, *et al*. (2010)[58]	Case report	2 eyes of a neonate with APROP	Laser followed by 0.75 mg IVB	Choroidal ruptures at the site of laser scar
Nazari, *et al.* (2010)[59]	Case series	14 eyes of 8 neonates with severe ROP associated with vitreous or retinal hemorrhage	0.625 mg IVB	Complete regression. Hemorrhage disappeared.
Altinsoy, *et al.* (2010)[60]	Case series	2 patients with ROP with APROP	Laser and 0.75 mg IVB	Response in 1 neonate
Law, *et al.* (2010)[61]	Case series	13 eyes of 7 neonates in which Laser not possible or failed	0.75 mg IVB followed by laser/vitrectomy	Ability to do successful laser/vitrectomy within 72 h
Dorta, *et al.* (2010)[62]	Case series	12 eyes in 7 neonates with type 1 ROP	0.625 mg IVB	Regression in all
Kychenthal A, *et al*. (2010)[63]	Case series	11 eyes of 8 neonates with poor response to laser and posted for vitrectomy	IVB 1 week before vitrectomy	Good structural outcome
Quiroz-Mercado H, *et al*. (2008)[64]	Case series	18 eyes of 13 neonates with severe ROP but no response to laser or laser not possible	IVB	Regression in 17/18 eyes
Lalwani, *et al.* (2008)[65]	Case series	5 eyes of 3 neonates who had progressive ROP despite laser	IVB. Some neonates received multiple doses.	Vascular component stabilized ROP stabilized after VEGF allowing laser. However some neonates had retinal detachment
Kong, *et al*. (2008)[66]	Case report	2 eyes of 1 neonate with zone 1 stage 2 plus ROP	0.5 mg IVB	Initial regression followed by development of zone 2 Stage 3+ ROP needing second injection of IVB

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Kusaka, *et al.* (2008)[67]	Case series	23 eyes of 14 neonates with stage 3 or more	IVB 0.5 mg alone or with vitrectomy	Regression on fluorescein angiography in 14/15 eyes. Retinal detachment in 3 eyes
Mintz-Hittner, *et al.* (2008)[68]	Case series	22 eyes of 11 neonates with stage 3 in zone 1-2	IVB	Regression in all
Honda, *et al.* (2008)[69]	Case report	1 eye with stage 4A with plus disease after laser	0.4 mg IVB	Regression of vascular component followed by fibrosis and deterioration of retinal detachment
Chung, *et al.* (2007)[70]	Case report	2 eyes of 1 neonate with APROP	Laser + 0.75 mg IVB	Regression
Travassos, *et al.* (2007)[71]	Case series	3 eyes of 3 neonates with APROP	IVB with or without laser	Regression in all

IVB: Intravitreal bevacizumab; ROP: Retinopathy of prematurity; VEGF: Vascular endothelial growth factor.

WEB TABLE III: CLINICAL TRIALS WITH A COMPARISON GROUP ON USE OF ANTI-VEGF ANTIBODIES N NEONATES

Author (Year)	*Study design*	*Subjects*	*Intervention group*	*Control group*	*Outcome*
Isaac, *et al*. (2015)[85]	Retrospective cohort	Type 1 ROP in zone 2 or zone 2 posterior	23 eyes of 13 neonates received 0.625 mg IVB	22 eyes of 12 neonates Who underwent laser ablation	Similar structural outcomes, visual acuity and incidence of myopia in two groups. IVB group needed more frequent hospital visits.
Lepore, *et al*.(2014) [80]	Randomized controlled trial	Type 1 zone 1 ROP in both eyes	13 eyes received 0.5 mg IVB	13 contralateral eyes received laser ablation	Fluorescein angiography before and 9 months after treatment: persistence of avascular area, serious vascular abnormalities in IVB group even at 9 months
Hwang, *et al*. (2015) [83]	Retrospective cohort	Type 1 ROP	22 eyes of 11 neonates received IVB	32 eyes of 17 neonates received	ROP recurred in 14% of IVB-treated eyes and in 3% of laser eyes. IVB associated with less myopia.
Mintz-Hittner, *et al*. (2011) [72] and Geloneck, *et al*. (2014) [73]	Randomized controlled trial (BEAT-ROP)	300 eyes of 150 neonates with zone 1 or zone 2 posterior stage 3+ ROP	140 eyes IVB	146 eyes laser ablation	Recurrence of ROP: 4% versus 22%. At 2.5 years, severity of myopia and incidence of severe myopia lower in IVB group
Araz-Ersan, *et al*. (2015) [82]	Retrospective cohort	Type 1 ROP	18 eyes of 13 neonates received 0.625 mg IVB in addition to laser ablation	13 neonates who received only laser ablation	Anatomical success in 78% eyes and retinal detachment in 22% eyes. No significant difference in refractive errors
Moran, *et al*. (2014)[81]	Randomized controlled trial	14 infants with symmetrical zone 1 or posterior zone 2 Stage 3 + ROP	1.25 mg IVB in one eye	Laser ablation in contralateral eye	Rapid regression of in all eyes. Recurrence of ROP: 21.4% in IVB and 7.1% in laser therapy group. Mean age of recurrence 51 weeks PMA in IVB and 37 weeks PMA in laser group.

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Harder, *et al*. (2013) [86]	Retrospective cohort	Threshold ROP in zone 1 or 2	23 eyes of 12 neonates received 0.375 mg or 0.625 mg single dose IVB	26 eyes of 13 neonates received laser ablation	Less myopic eyes in IVB group. Prevalence of moderate and severe myopia lower in IVB group. Refractive astigmatism lower in IVB
Autrata, *et al*. (2012) [79]	Randomized controlled trial	Stage 3+ ROP for zone 1 or posterior zone 2	92 eyes of 46 neonates intravitreal pegaptanib or bevacizumab of with laser ablation	82 eyes of 41 neonates received laser ablation combined with cryotherapy	Favorable anatomic outcome and stable regression of ROP: 90.2% vs. 62%. No retinal detachment
Lee, *et al*. (2010)[87]	Retrospective cohort	Stage 3 ROP 30 eyes of 15 neonates	IVB and laser ablation	Only laser ablation	Regression of plus disease and peripheral retinal vessel development more rapidly in neonates who received both IVB and laser

IVB: Intravitreal bevacizumab; ROP: Retinopathy of prematurity; VEGF: Vascular endothelial growth factor.