ORIGINAL RESEARCH PAPER

Volume-8 | Issue-8 | August - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ADVANCES IN TYPE 1 RETINOPATHY OF PREMATURITY MANAGEMENT, A LITERATURE REVIEW

Ophthalmology

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ABSTRACT

Purpose: To investigate recent advances in treatment and follow up of type 1 Retinopathy of Prematurity (ROP) using intravitreal anti-vascular endothelial growth factor (anti-VEGF) as monotherapy or in combination with laser photocoagulation (LPC).

Methods: Search was conducted in Medline/PubMed database using keywords "anti-VEGF for retinopathy of prematurity, laser photocoagulation for retinopathy of Prematurity, Retinopathy of prematurity". Full texts of 99 original articles directly related to the aim of the review were used.

Results: In recent years, there has been increased interest in the use of anti VEGF as monotherapy or in combination with laser photocoagulation. Fluorescein angiography (FA) findings are helpful during follow-up to reveal areas of avascular retina or signs of reactivation that necessitates further laser photocoagulation following intravitreal anti VEGF treatment. Ultra-low dose of intravitreal Bevacizumab as much as 2.5% of adult dose may be effective in treatment of zone I and posterior zone II ROP except for Aggressive Posterior Retinopathy of Prematurity (APROP) which needs higher doses as high as 50% of adult dose

Conclusion: Based on current evidence, combination of intravitreal anti-VEGF and prophylactic laser may minimize the risk of early or late recurrence and development of progressive retinal detachment (RD). Future prospective studies for defining lowest appropriate anti-VEGF intravitreal doses as well as refining retreatment guidelines using FA findings are needed.

KEYWORDS

anti-VEGF for retinopathy of prematurity; laser photocoagulation for retinopathy of Prematurity; Retinopathy of prematurity

INTRODUCTION

Globally, in 2010, an estimated 184,700 babies of 14.9 million preterm babies developed any stage of ROP; 20,000 of them became blind or severely visually impaired, and a further, 12,300 others developed mild or moderate visual impairment[1]

ROP is thought to be at least in part an oxygen-induced retinopathy, that develops over 2 phases:[2]

1) Hyperoxic phase I: when exposure to relative hyperoxia causes downregulation of growth factors, resulting in retinovascular growth vasocessation.[3]
2) Hypoxic phase II: when decrease in vessel density and increased oxidative demands makes retinal tissue hypoxic. The hypoxia induces angiogenic factors secretion that lead to abnormal neovascularization at the boundary between vascularized and non vascularized retina, as well as vascular abnormalities inside the edge of vascularized retina,[4,5]

Furthermore, sudden loss of maternal fetal interaction contributes to the dramatic reduction in serum **Insulin-like growth factor-1 (**IGF-I).[6] A minimal level of IGF-I is required for vascular growth, rationalizing the poor vascular growth seen in phase I and II in premature infants. As the infant grows the body slowly produces endogenous IGF-I and VEGF-induced neovascularization may ensue.[6]

Although many efforts were made to prevent ROP,[7] most current treatments target the second phase.[2]

We carried this review to reveal important aspects of recent developments in type 1 ROP treatment and post-treatment follow-up.

METHODS

We searched the Medline/PubMed database using keywords "anti-VEGF for retinopathy of prematurity, laser photocoagulation for retinopathy of Prematurity, Retinopathy of prematurity". 1160 results were obtained. Case reports and editorials were excluded. We concentrated on publications within the last ten years. The original articles abstracts were analyzed among which 112 articles were chosen. Full texts of the latter articles were studied and 99 of them were found to be directly related to the aim of the review and used.

RESULTS:

- **Retinal vascular endothelial growth factor is an important target for treatment of retinopathy of prematurity:**

Young et al[8] investigated the association between VEGF and ROP in humans. They obtained histo-pathological specimens from both retinas of premature infant, born at 24 weeks gestation, who developed severe ROP and died due to prematurity-related complications at 38 weeks postmenstrual age (PMA). While alive LPC was used to treat one eye with the more severe ROP. Investigators found increased VEGF messenger RNA (mRNA) in the avascular and peripheral region of the retina in the untreated eye, while in the eye treated with laser, VEGF mRNA was elevated between laser scars, but undetectable in photocoagulated areas.[8]

Furthermore, kwinta et al[9] investigated the correlation between serum concentration of VEGF and soluble VEGF receptor 1 (sVEGFR-1) and the risk of ROP in the first month of postnatal life and found that there were no significant differences in serum VEGF and sVEGF-R1 concentrations between premature infants with and without ROP.

In another study by pieh et al[10] plasma levels of VEGF-A, sVEGFR-1, sVEGFR-2 and soluble membrane-bound tyrosine kinase receptor (sTie) were measured between 5 days and 15 weeks in the post-natal period. Investigators found that VEGF-A and sVEGFR-1 levels were similar in premature infants with and without ROP, while infants with ROP had raised plasma levels of sVEGFR-2 and sTie compared with infants without ROP. They concluded that pathogenesis of ROP is mainly driven by local VEGF-A synthesis; as there is no difference in serum VEGF between the two groups.[10]

Peirovifar et al[11] found similar findings in that blood VEGF levels were not significantly different between two groups.

Other studies also led to the conclusion that in premature infants with ROP, VEGF is elevated locally in the retina and is the primary pathologic growth factor mediating neovascularization and the development of ROP.[12-14]

Thus VEGF became the target for current treatment options using intravitreal anti-VEGF injection treatment.[15] In contrast to LPC, anti-VEGF treatment allows the development of further retinal vascularization while inducing regression of vascular prolifera tions.[16,17]

- **Retinopathy of prematurity treatment evolution:**

The CRYO-ROP trial starting Jan 1986, established the efficacy of cryotherapy (VS. observation) as a treatment for threshold ROP (defined as 5 contiguous or 8 interrupted clock hours of stage 3 plus (3+) ROP in zone I or II).[18] There was a 50% reduction in unfavorable structural outcomes compared with untreated eyes.[18]

Later, the Early Treatment for Retinopathy of Prematurity randomized trial (ETROP) started in October 2000. This study stratified eyes into high-risk (Type 1) or low risk (Type 2) prethreshold disease and used LPC for high risk prethreshold ROP.[19]

The ETROP clinical guidelines for the ROP severity at which treatment should be considered is defined as type 1 ROP, and it includes any ROP with plus disease or stage 3 without plus disease in zone I, and stage 2 or 3 with plus disease in zone II.[2]

However, the 6-year ETROP outcomes showed unfavorable visual acuity outcome (20/200) in 25.1% of eyes and unfavorable structural outcome (retinal fold or detachment involving the macula, retrolental mass, or vitrectomy or scleral buckling surgery) in 8.9% of eyes.[2]

In recent years, there has been increased interest in use of anti-VEGF therapy by intravitreal injection for treatment of ROP.[20] It assumes that structural, functional and refractive outcomes are superior to other alternatives particularly in zone I. However, concerns about systemic side effects of anti-VEGF agents are still a very important issue, as VEGF is essential for angiogenesis in the eye as well as angiogenesis in other vital organs such as lungs, kidneys and brain.[21]

- **Intravitreal bevacizumab and ranibizumab for retinopathy of prematurity:**

Many reports have demonstrated the efficacy of Intravitreal bevacizumab (IVB) and ranibizumab (IVR) in treatment of Type 1 ROP.[22-24]

Bevacizumab is a monoclonal antibody that weighs approximately 149 KDa. It is detectable in the bloodstream for up to 60 days, with peak levels at approximately 2 weeks post-injection.[25,26] The longer suppression of systemic serum VEGF after IVB should be considered in premature infants with rapidly developing systemic organs, where VEGF participate in the process of organogenesis and neurodev elopment.[27]

Ranibizumab is an antibody fragment weighing approximately 49KDa, that has been noted to cause decreased plasma VEGF levels as bevacizumab, but to a lesser extend with VEGF levels returning to baseline by 1 week.[28] This theoretically limits systemic exposure and decreases the risk of neurological development defects compare with bevacizumab.[29]

The selection of anti-VEGF agent with less systemic VEGF interference, and/or reducing its dose, as well as using single injection in ROP patients, seems to be safer.[13]

The advantages of using intravitreal anti VEGF agents compared to LPC include: less time to administer treatment, no need for general anesthesia, less treatment-related destruction of peripheral retina, faster improvement in plus disease and regression of ROP and a lower likelihood of myopia, high myopia and astigmatism.[2]

The disadvantages of anti-VEGF therapy include: a longer follow-up period as a result of delayed or incomplete vascularization, significant rates of recurrence, the potential need for later retreatment and the possible development of abnormal or atypical retinal vascular patterns.[2]

Many infants treated with intravitreal anti-VEGF agents have vascular abnormalities and/or persistent avascular peripheral retina even after years of follow-up.[5,16,30] These peripheral retinal abnormalities are risk factors for recurrences and progressive tractional retinal detachments (TRDs).[31] Furthermore, peripheral avascular retina is prone to lattice like changes, and retinal breaks predisposing to rhegmatogenous retinal detachments (RRD) in teenage years.[32] Because of the reasons above, it is preferable to treat persistent avascular retina with LPC to help control the disease, avoid reactivations and minimize late ROP associated RRDs.[33]

Anti-VEGF injections cause elevation of transforming growth factor beta (TGF-β), a potent profibrotic agent.[34,35] In addition to this iatrogenic rise in TGF-β, premature infants experience an endogenous rise of TGF-β as they approach term age.[36,37] This elevation of TGF-β can cause rapid contraction of fibrovascular membranes with consequent progressive retinal detachment (RD).[36,37]

- **Intravitreal bevacizumab for type 1 retinopathy of prematurity:**

The Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) clinical trial started in 2008 to investigate outcomes in infants with zone I or posterior zone II stage 3 ROP who received intravitreal 0.625mg bevacizumab monotherapy versus LPC.[22,26]

Results from the BEAT-ROP trial found that IVB showed significant efficacy for zone I stage 3 ROP, with evidence for continued retinal vascularization into the peripheral retina, along with decreased myopia for both zone I and zone II eyes.[22] It reported a 42% recurrence rate (defined as neovascularization requiring retreatment by 54 weeks PMA) in zone I disease eyes treated with LPC versus 6% in eyes treated with IVB.[22] For zone II recurrence rates were 12% for LPC versus 5% for IVB.[26]

Mueller et al[17] found that IVB led to faster regression of type 1 ROP in eyes with posterior ROP compared with LPC. Recurrences after IVB treatment may occur in about 12% of cases 12-15 weeks after treatment, requiring prolonged follow up. In majority of cases, the retina will not be fully vascularized after 12-15 months. They also found[17] that infants treated with IVB had more myopic refractive error if they had posterior ROP compared with peripheral zone II ROP. This suggests that retinal immaturity has a prominent effect on refractive error in infants with ROP.[17]

- **Intravitreal bevacizumab and laser photocoagulation combination for retinopathy of prematurity:**

To overcome the disadvantages of both conventional laser treatment and IVB monotherapy, combined treatments were evaluated. This was based on previous studies which showed that the area of peripheral retinal vascularization increased over several months after IVB.[22,38,39]

Therefore, if LPC is deferred for a period of time and is performed on the peripheral avascular retina after IVB, fewer retinal areas may be subjected to LPC, which may result in larger functional areas in the retina. In addition, IVB combined with laser may lessen the concerns regarding follow-up schedule and late reactivation.[39]

Je Moon Yoon et al[39] compared the anatomical and refractive outcomes in consecutive patients with Type 1 ROP in zone I who were treated with the following 3 different strategies: conventional LPC, combined IVB and zone I sparing laser, and IVB with deferred laser. They concluded that IVB with concomitant or deferred laser might result in more favorable anatomic outcomes than laser alone. Moreover, IVB with deferred laser resulted in less myopic refractive error. Thus, the advantages of combination treatment may include more favorable anatomic outcomes, lower possibility of reactivation, less frequent examinations after treatment, preservation of larger non-lasered retinal area and less myopia.[39]

- **Systemic side effects of intravitreal bevacizumab:**

Morin et al[40] documented a 3.1 times higher risk of severe neurodevelopmental disabilities at 18 months in their IVB infant versus the laser treated infants.

In addition, lien et al[41] reported that infants treated with IVB and laser had a 5.3 times higher risk of severe psychomotor delays than the laser alone group.

Other studies did not identify clear differences in neurodevelopmental outcomes between infants treated with laser versus those treated with anti VEGF agents.[42]

- **Intravitreal ranibizumab for type 1 retinopathy of prematurity:**

The **RA**nibizumab compared with laser therapy for the treatment of **IN**fants **BO**rn Prematurely **W**ith retinopathy of prematurity study (RAINBOW study) is a randomized, multicenter, prospective clinical trial started in December 30/2015 and was designed to investigate the efficacy and safety of both 0.2mg and 0.1mg doses of IVR in infants with type 1 ROP and APROP compared with LPC.[43]

The highest treatment success rate was observed in the 0.2mg IVR dose group (80%) compared to 75% with 0.1mg IVR dose and 66.2% following LPC.[43]

Huang Q et al[44] reported the results of their experience in using

0.25mg/0.025ml IVR as primary treatment for type 1 ROP. The positive response was defined as regression without reactivation or regression with reactivation, whereas negative/no response was defined as follows: ROP worsened after IVR and progressed into stage 4A, 4B, 5, or if plus disease and ridge did not show any change 1 week after IVR. Laser was chosen as re-treatment for patients in the regression with reactivation group. In spite of that positive response was noticed in 94% of eyes, still 5.7% of eyes progressed to stage 4 or 5 requiring further treatment. No systemic adverse events were noticed.[44]

As zone I ROP and APROP require more time to achieve full vascularization after IVR than zone II, (the fact that makes the retina more susceptible to increased VEGF levels in zone I cases), reactivation rate was higher in zone I ROP 57.8% compared to that in zone II (35.4%). Incomplete vascularization and vascular abnormalities without reactivation were observed in 3% of eyes.[44]

- **Comparison of intravitreal ranibizumab versus laser for zone II treatment requiring retinopathy of prematurity:**

Zhang G et al[45] compared the efficacy and recurrence rates after IVR monotherapy and laser therapy for zone II stage 2 or 3 ROP with plus disease. They found a higher recurrence rate after treatment with IVR monotherapy compared to laser therapy. They explained their results by the two distinct mechanisms and pathophysiologic processes that underline zone I and zone II ROP disease: vasculogenesis and angiogenesis. Zone I and APROP are more related with the vasculogenesis stage, causing treatment with laser photocoagulation to be less effective. As zone II ROP is more related to angiogenesis, laser treatment might be a more effective option compared with anti-VEGF monotherapy.[45]

Kang HG et al[29] compared the efficacy, anatomical outcomes and complications of IVR with those of LPC in Type 1 ROP. 13.7% of laser treated eyes and 9.8% of IVR treated eyes had recurrences that required further intervention. The mean interval to retreatment was 2.3 weeks for the laser group and 5.7 weeks for the IVR group. RD was noted in 5% of laser treated eyes and 0.7% of IVR treated eyes. There were no reported deaths or major systemic complications for both groups. In IVR group, fully vascularized peripheral retinas were observed in 95.6%. Authors[29] concluded that IVR appears to achieve better anatomical outcomes than LPC for ROP.

- **Efficacy of intravitreal Conbercept in retinopathy of prematurity:**

Conbercept, a relatively novel anti-VEGF agent. It has 50 fold higher binding affinity for VEGF than does bevacizumab and a long half-life in the vitreous. It is designed to bind all VEGF isoforms and placental growth factor with high affinity,[46] thus exerting strong antiangiogenic effects.[47]

Bai Y et al[48] found that using intravitreal conbercept (IVC) 0.25mg/0.025ml as monotherapy in type 1 ROP and APROP is effective and resulted in regression of plus disease without recurrence in 83.7% of eyes.

Jin E et al[46] also studied outcomes of IVC for treatment of type 1 ROP and APROP and found that 75% of eyes obtained regression of plus disease with one injection and had stable control of ROP without recurrence during observation period of 6 months. The other 25% of eyes obtained same results after second injection. 20% of all treated eyes acquired full retinal vascularization while 80% had avascular retina in zone III of peripheral retina.

According to the above two studies, IVC appeared to be effective for ROP treatment. In case of recurrence, retreatment with another injection can effectively control the disease.[46,48]

- **Spectrum of spontaneous regression and regression following intravitreal bevacizumab for retinopathy of prematurity:**

Spontaneous ROP regression classically follows a stepwise pattern starting with reversal of plus disease, waning of disease stage, vascular growth beyond the previous avascular demarcation and finally, full vascular maturation (perfusion to within 2DD of the ora serrata).[49]

In spite of that the optimal outcome following IVB for type 1 ROP is complete vascular maturation,[50-52] it is common to encounter vascular arrest which may be either vascular arrest alone (VAA) with peripheral non perfusion>2DD from the ora serrata, or vascular arrest with persistent tortuosity (VAT). Reactivated ROP may also be encountered. VAT seems to be a unique regression pattern following IVB but not laser therapy.[49]

Chen TA et al,[49] found 3.3% complete vascular maturity among their IVB treated eyes with type 1 ROP or APROP, 43.8% had VAA, 38.2% had VAT, and 18% had reactivated ROP. 89/92 of studied eyes underwent LPC for reactivation or peripheral nonperfusion at 60 weeks gestational age (GA). It appeared that combination of IVB and prophylactic laser minimizes the risk of early and late RD, in comparison to LPC or IVB alone.[49,53,54]

- **Foveal development in infants treated with intravitreal bevacizumab or laser for retinopathy of prematurity:**

Maldonado et al[55] performed hand held spectral domain ocular coherence tomography imaging (SD OCT) on preterm infants from 31 to 41 weeks PMA, which helped to establish a timeline of human foveal development during this dynamic period. This was later expanded by imaging infants beyond 41 weeks PMA.[56-58]

Before full term birth, the fovea has an immature appearance characterized by shallow foveal pit, persistent inner retinal layers at foveal center, thin outer retinal layers, and absent photoreceptor elements, such as ellipsoid zone (EZ) and interdigitation zone (IZ). Inner and outer foveal layers develop along different time frames, with the inner layers maturing around the time of full term birth and the outer layers reaching maturity within the first few years after birth [56]

The inner retinal layers extruded from the foveal center sequentially with the ganglion cell layer (GCL) disappearing first, followed by the inner nuclear layer (INL).[56] The EZ initially was seen peripherally at approximately 33 weeks PMA, and developed centripetally over time, reaching the foveal center by 41 to 52 weeks PMA.[56] The IZ always developed after the EZ reached the foveal center.[56,59] Persistent inner retinal layers at the foveal center are a hallmark of retinal immaturity, and this can be seen in adults with a history of ROP.[60]

The development of EZ at foveal center was delayed in LPC treated eyes compared with untreated eyes after adjusting for age.[56] This suggests that outer retina or photoreceptor maturation is delayed in LPC treated eyes. Furthermore, foveal development outcomes were different for bevacizumab-treated and LPC-treated eyes.[56] Bevacizumab treatment was associated with more rapid outer retinal thickening, whereas LPC was associated with earlier inner retinal layer extrusion and delayed EZ development.[56]

Intravitreal anti-VEGF therapy has been shown to result in decreased VEGF expression in both the vascular and avascular retina, although some VEGF expression remains.[61] LPC has been shown to result in no VEGF expression within areas of laser scars, but increased VEGF expression in areas between scars.[7] These differences in VEGF expression between eyes treated with anti VEGF and LPC could explain the differences seen in foveal development.[56]

Hand held SD-OCT also led to the discovery of cystoid macular changes (CMC) in premature neonates, which tend to resolve spontaneously.[62-64]Reported incidence of CMCs in preterm eyes varies based on the population studied and ranges from 16% to 72%.[55,63-70] Cystoid macular changes have been associated with lower gestational age and ROP severity,[63,64,70]although Dubis et al[66]found that CMCs do not correlate with ROP stage.

CMC have been found in healthy full-term infants as well.[71] Cabrera MT et al[72] examined 20 full-term Hispanic newborns median gestational age: 39 weeks; (range: 36 to 40 weeks),and found that two (10%) had bilateral subfoveal fluid. Three eyes of two infants (10%) had retinal macular cystoid structures.[72]

- **Fluorescein angiography findings in retinopathy of prema turity:**

Peripheral vascular abnormalities after primary IVB and IVR treatment for ROP includes incomplete vascularization,[52,73] disease reactivation[31,50,74,75]and other vascular abnormalities such as branching, shunt vessels and leakage.[4]

The potential for avascularity to induce ischemia and fibrovascular changes is concerning, especially given a number of reports of late

disease recurrence and RD after anti-VEGF treatment for type 1 ROP.[50,59,76-78] Thus if anti-VEGF treatment is to be given, it is imperative that the treating clinician be aware of the vascular changes that can follow.[78]

The use of Fluorescein angiography (FA) in recent years appeared to be more sensitive for detecting vascular abnormalities in ROP compared with direct observation.[53] These abnormalities were more frequent with IVB and IVR than with LPC.[4,53,78,79]

Garcia Gonzalez JM et al[53] reported results of their preferred regimen for IVB treatment, which included prophylactic LPC after 60 weeks PMA for treating persistent avascular retina based on FA of the periphery, including the ora serrata region.

Eyes that had vascular termini within 1.5 disc diameter (DD) of the ora serrata temporally and 0.5DD of the ora serrata nasally were considered to have normal vascularization, based on a previous study of peripheral FA of normal eyes.[80] These eyes do not require treatment.[80]

Lepore et al[5] described the following characteristics of fluorescein angiograms in ROP: I) Abnormalities at the junction of vascular and avascular retina were considered present if irregular arteriolar branching or naked arteriovenous shunts were noticed in at least 1 quadrant of the fundus. The same criteria was used to assess capillary loss within the vascularized retina and the posterior pole. II) The macula was considered abnormal if any or all of the following were present: 1) absence of Foveal Avascular Zone (FAZ), 2) presence of hyperfluorescent lesions, and 3) presence of pigment epithelium abnormalities. III) If only large linear choroidal vessels without choriocapillaris were observed in early FA phases, a linear choroidal filling pattern was recorded.[5]

In their study to compare FA findings in two groups of eyes with type 1 ROP treated with IVB: first group with APROP and second group with classical ROP (CROP), Garcia Gonzalez JM et al[53] found that the areas of temporal and nasal peripheral nonperfusion were significantly larger both temporally and nasally in APROP eyes than in CROP eyes (4.4, 2.6 DD in APROP and 2.6, 1.2 DD in CROP respectively). Authors did not report any RDs in any eye that received IVB and prophylactic treatment completion with laser.[53]

Lepore D et al[4] compared FA findings in IVB versus LPC treatment in eyes with type 1 ROP. They described the following FA features at 9 months after treatment:[4] 1) IVB eyes had extensive areas of avascular retina, whereas all lasered eyes showed the typical retinochoroidal atrophy expected from the treatment, 2) A massive loss of retinal capillary bed at posterior pole or in the periphery within the vascularized retina was found in most of IVB eyes, whereas only very few eyes treated with LPC showed hypofluorescent lesions within the vascularized retina, 3) Absence of FAZ or hyperfluorescent lesions in posterior pole persists in eyes treated with IVB more frequently than in eyes treated with laser (75% vs. 36.4%), 4) A linear choroidal filling pattern was visible in 50% of IVB treated eyes, while a lobular pattern was observed in 72.73% of eyes treated with laser. Authors[4] concluded that in the conventional management of severe ROP using LPC, the peripheral avascular retina is ablated, and there is a low further risk for abnormal angiogenesis. On the other hand, after IVB treatment, there were large peripheral avascular areas. The abnormal arteriolar branching noted in IVB eyes likely indicates abnormal angiogenesis.[4]

Armitage Harper III C et al[78] evaluated peripheral vascular changes on FA after primary IVR for type 1 ROP They found vascular abnormalities which persisted up to 150 weeks PMA, that were similar to previous reports of vascular abnormalities persisting in the peripheral retina years after IVB therapy for type 1 ROP.[31,59]

- **Retinal vascular development with lower doses of intravitreal bevacizumab:**

Intravitreal anti-VEGF became the treatment of choice for eyes with type 1 ROP.[20,81] Dosage of bevacizumab is particularly important in premature infants who are extremely fragile and display rapid growth of all organs.[82]

Although elevated VEGF drives pathological vasoproliferation in stage 3 ROP, lower levels of VEGF are crucial for normal retinal vascular development.[83] Thus, it may be that a lesser degree of VEGF suppression might offer the optimal compromise between suppression of severe retinopathy while allowing normal ocular vascular development to proceed.[84]

In addition it is also desirable to reduce the dosage as much as possible while maintaining efficacy, because bevacizumab enters the blood stream after intravitreal injection.[25,27,85] This is particularly important because ROP treatment is bilateral in more than 90% of cases. Bilateral injections of bevacizumab cause its increased accumulation of the drug in the systemic circulation leading to potential off-target effects on the developing organs of the premature infant.[81]

Lorenz B et al[82] described the effect of intravitreal 0.312mg/0.025ml IVB monotherapy in eyes with posterior zone II or zone I stage 3+ ROP, or APROP. They found that the use of 0.312mg dose of bevacizumab, that is a quarter of the adult dose very likely shows similar results of disease silencing in posterior zone II and zone I disease compared with the use of half the adult dose used in the BEAT-ROP study. In contrast, 0.312mg bevacizumab did not seem to be the treatment of choice for APROP.[82]

Similar results for posterior zone II and zone I ROP were found with IVB doses of 0.375mg[86] and 0.25mg.[87]

Wallace DK et al[88] used a dose escalation for IVB from 20% of the adult dose to merely 2.5%. Recurrence rates were found to increase with decreasing dose from 18% retreatments in the 20% adult dose group to 33% in the 5% adult dose group. However, the lowest dose investigated (2.5% adult dose) surprisingly required no re-treatment.[81]

Hillier RJ et al[84] reported the efficacy of ultra-low dose IVB by using a dose of 0.16mg/0.025ml bevacizumab for type 1 ROP. They noted some important differences between the clinical response to standard versus ultra-low dose IVB. Improvement of ROP and plus disease was observed within the early days following 0.16mg IVB. However the response was notably slower and less brisk compared with standard dose. In addition the retreatment rate was 20.7% in ultra-low dose, which was higher than that in standard dose.[84]

APROP treatment remains challenging. Better results are achieved with high dose of 0.75mg[89-91] or 0.625mg[92,93] IVB combined with simultaneous or deferred laser.

DISCUSSION

Increased interest in use of intravitreal anti VEGF injection for treatment of high risk (type 1) ROP[20] in recent years, can be related to the fact that locally elevated retinal VEGF is thought to be the primary pathologic growth factor mediating neovascularization and abnormal angiogenesis in ROP.[11]

However the issue about systemic side effects of anti-VEGF agents is still open, as VEGF is essential for normal angiogenesis in the eye as well as angiogenesis in other vital organs such as lungs, kidney and brain. This made the selection of anti-VEGF agent with less systemic VEGF interference and/or reducing its dose, as well as using it only once, to be essential for safety.[21,40,41]

In spite of advantages of intravitreal anti-VEGF over laser (less treatment time, no need for anesthesia, faster improvement and regression of type 1 ROP, less destruction to peripheral retina and less induced myopia), there were important disadvantages including: longer needed follow-up because of delayed or incomplete peripheral vascularization, significant rates of recurrence and the potential need for later retreatment and occurrence of progressive TRD.[2]

The rates of recurrence or incomplete response requiring further treatment varied from 0% to 46% after IVB[24,94-97] and from 0% to 83% after IVR.[24,75]

To overcome the disadvantages of both conventional laser treatment and intravitreal anti-VEGF monotherapy, combined anti-VEGF and laser treatments were evaluated.[39]

Combination therapy has the advantages of fast regression of ROP after anti-VEGF injection and delaying LPC treatment by giving the chance for further development of normal retinal vessels toward the periphery, thus subjecting less retinal area to later LPC, which results

in larger functional retinal areas.[39] Performing laser treatment also lessens the concern about longer follow up schedule and late reactivation.[39] Many reports found that IVB with concomitant LPC results in more favorable outcomes than laser alone or IVB monotherapy.[22,38,39,48]

Few reports were published revealing the efficacy of intravitreal conbercept (IVC) in type 1 ROP and APROP. Regression rate following one injection of IVC without recurrence ranged from 75% to 83%.[46,48]

Following IVB for type 1 ROP, it was common to encounter two types of vascular arrest: vascular arrest alone VAA, or vascular arrest with persistent tortuosity VAT. Other types of regression after IVB were reactivated ROP or complete vascular maturation.[50-52]

Hand held SD-OCT studies described different time frames for inner and outer foveal layers development, with inner layers maturing around the time of full term birth and the outer layers reaching maturity after birth.[56] The development of EZ on OCT is a marker of photoreceptor development. EZ forms peripherally at approximately 33 weeks PMA and reaches the foveal center by 43-48 weeks PMA.[59] Bevacizumab was associated with more rapid outer retinal thickening, whereas LPC was associated with earlier inner retinal layers extrusion and delayed EZ development.[56]

Peripheral vascular abnormalities after primary IVB and IVR treatment for ROP including incomplete vascularization,[52,73] disease reactivation[31,50,74,75] and other vascular abnormalities such as branching, shunt vessels and leakage were studied using FA.[4]

Lepore et al[5] described characteristics of FA angiograms in ROP as well as Lorenz B et al.[82] Decision for further laser treatment after anti-VEGF treatment was recommended to be based on FA findings.[31,50,78,98,99]

There is still a serious unanswered question regarding ideal anti-VEGF dosing. There is a great need to reduce the anti-VEGF dosage as much as possible, while maintaining efficacy, as this will help in lessening the effect of systemic VEGF suppression on development of other organs of premature infants, as well as giving better chance for normal retinal vascular development while suppressing abnormal angiogenesis.[81,82,84,86-88] It appeared that ultra-low dose as much as 2.5% of adult dose[81,88]may be effective in zone I and posterior zone II ROP except for APROP which needs higher doses as high as 50% of adult dose.[89-93]

In conclusion, further prospective studies for defining the lower anti-VEGF dose with maximal effect and lower ocular and systemic complications, as well as refining retreatment guidelines using FA findings are still needed.

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