The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

The role of anti-vascular endothelial growth factor in treatment of retinopathy of prematurity—a current review

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The review aims to evaluate the uses of conventional laser therapy and intravitreal injection of various anti-VEGF in terms of efficacy and side effects for the treatment of retinopathy of prematurity. A literature search of the publication, concerning conventional laser treatment and intravitreal injection of anti-VEGF for ROP. A total of 40 articles were reviewed after curation by the authors for relevance. Intravitreal anti-VEGF showed better ocular efficacy in zone I ROP while laser therapy had a lower recurrence rate in zone II. Comparing the two mainstay anti-VEGF agents, bevacizumab showed lower ROP recurrence rate than ranibizumab. Anti-VEGF has a higher chance in developing persistent peripheral avascularisation compared to conventional laser therapy, but a lower chance of developing high myopia. Ranibizumab has a lower systemic absorption than bevacizumab, despite having no difference in the incidence of persistent peripheral avascularisation. In conclusion, it is advised that intravitreal anti-VEGF should be used as the first-line treatment for zone I ROP while laser therapy should be the mainstay for zone II ROP owing to the different pathogenetic mechanisms. In patients with recurrence after initial anti-VEGF injection, that given ranibizumab may opt to repeat the injection while that given bevacizumab should consider supplement laser ablative treatment.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a disease of developing retina that can result in bilateral blindness in premature infants [1–4]. It is one of the major causes of childhood blindness worldwide [5–7]. The overall incidence of ROP (all stages of ROP) ranges from 4.4% to 47%, as quoted from various international studies [8–15]. Data from developed regions (including United States, United Kingdom, Netherlands, Switzerland, New Zealand, Hong Kong) tend to show a lower incidence of ROP (4.4–23.3%) [8, 10, 12–15], whereas developing regions (including India, Indonesia, Romania, Kenya) have a slightly higher incidence of 14–47% [9, 11]. The incidence varies for ROP requiring treatment from 1.2% to 16.7%, according to the localities [10–12, 14].

The strongest risk factors of ROP are low gestational age, low birth weight, and oxygen-use related (the use of supplemental and prolonged mechanical ventilation) [7, 16–18]. Other possible risk factors include maternal factors (hypertensive disorder of pregnancy, maternal diabetes mellitus, advanced maternal age, smoking) [7, 19–22], prenatal and perinatal factors (assisted conception, cesarean section, premature rupture of membrane) [7, 23–25], infant factors (male, twin/multiple births, low Apgar scores) [7, 16, 26, 27], early post-natal low serum insulin growth factor one concentration and neonatal sepsis [7, 28]. ROP is the result of aberrant retinal vascularization and an arrest of the development of vascular and retinal neuronal components [6]. Its pathogenesis involves a biphasic pathologic neovascularization [29]. Increasing ex-utero oxygen saturation in preterm infants during Phase 1 results in a decrease in growth factors in the retina, arresting the development of vascular components [30]. The arrest of vascular development leads to a hypoxic state in the retina with overexpression of vascular endothelial growth factor (VEGF) during Phase 2, resulting in aberrant retinal vascularization, which ultimately leads to blindness. ROP is classified into three zones according to its location while its severity is classified into five stages.

ROP is conventionally treated by laser ablation of the avascular retina [31]. It reduces the retinal oxygen demand by tissue destruction and inhibits the production of angiogenic factors [32]. Historically, ROP is treated by cryoablation, which permanently reduces the visual field and induce myopia [30, 31]. Today, an alternative option for the treatment of ROP is the use of anti-VEGF by reducing the VEGF level in the vitreous humor and therefore suppresses pathologic vasculogenesis. However, the physiologic vascular development in the retina is also driven mainly by VEGF [1]. Anti-VEGF was proven to be effective in the treatment of ROP, which is able to promote regression of ROP and allow normal retinal vascularization [33–35]. Agents used for intravitreal injection in ROP, include bevacizumab and ranibizumab, pegaptanib, and more recently aflibercept and conbercept [1, 36, 37].

This review aims to summarize and compare the latest evidence for the management of ROP, focusing on the efficacy, safety, and mechanisms of action of anti-VEGF and conventional laser therapy.

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METHOD OF LITERATURE SEARCH

Eligibility criteria for considering studies for this review

We searched for clinical studies or randomized controlled trials (RCTs) published between January 1, 1991 and January 1, 2021, human studies, which compared anti-VEGF agents with laser therapy in terms of ocular efficacy, ROP recurrence, safety, mechanisms of action. The stage and zone of ROP had to be specified in the studies, but there was not any particular restriction on these two baseline factors.

The primary outcome of this study focuses on the efficacy of anti-VEGF agents in terms of ocular efficacy in managing ROP. Secondary outcome focuses on side effects of anti-VEGF agents.

Search methods

A search was performed on January 20th, 2021 on Pubmed and Medline via OvidSP. Search terms "anti-VEGF", "anti-vascular endothelial growth factor therapy", "ranibizumab", "bevacizumab", "conbercept", "aflibercept", "ROP", "retinopathy of prematurity" and "treatment" were used.

Study selection

A total of 259 entries were found using this search strategy. These papers were then manually curated to include only those concerning ROP treatment outcomes. Furthermore, papers investigating the efficacy and side effects of treatments of ROP other than anti-VEGF and laser therapy were excluded. Literature which are not English were also excluded. For example, papers exploring prophylactic propranolol for the prevention of ROP or efficacy of propranolol in the treatment of ROP were excluded in this review. Keywords such as "therapy" or "management" were also tested instead of "treatment", but no extra result was generated. The references of individual papers from the curated results were checked to yield further articles.

RESULTS

The search strategy yielded a total of 40 original articles for analysis after manual curation from the period between January 1, 1991 and January 1, 2021 (Table 1). Out of the 40 articles, 15 were RCTs [1–4, 33, 34, 38–46]. A total of 17 studies investigated intravitreal bevacizumab (IVB) and laser therapy [33, 38–41, 43, 45–55], whereas two studies compared intravitreal ranibizumab (IVR) with laser [2, 42]. Four articles compared IVB and IVR injections [56–59]. One study compared IVB with aflibercept (IVA) [60], while another paper studied IVR and conbercept (IVC) [61]. There were six articles on IVB monotherapy [62–67], three articles on laser monotherapy [3, 68, 69], three articles on IVC monotherapy [36, 70, 71], two articles on cryotherapy [4, 44], one article on IVR monotherapy [1], and one article on IVA monotherapy [72].

EFFICACY

Ocular efficacy of anti-VEGF agents

Eight studies have investigated the ocular efficacy of anti-VEGF agents [2, 33, 34, 36, 39, 42, 43, 72]. Out of the six studies that compared intravitreal anti-VEGF and conventional laser therapy in treating ROP [2, 33, 34, 39, 42, 43], the superiority of IVB over laser therapy was reported in two studies [33, 34]. In the BEAT-ROP study, the recurrence rate for zone I and posterior zone II ROP combined was significantly higher with laser therapy (26%) than with IVB (6%) [33]. An odds ratio with IVB injection, 0.17 (95% confidence interval [CI], 0.05 to 0.53; $P = 0.002$) was reported. Regarding IVR injection, better ocular outcomes were also reported in one multicentre RCT study (RAINBOW study) [2]. Of infants with any plus or stage three disease in zone I or stage 3+ disease in zone II, treatment success occurred in 80% of the 0.2 mg IVR group and 75% of the 0.1 mg IVR group, outperforming the 66% of the laser therapy group. However, the ETROP trial showed a treatment success rate of 85.7% in infants with any plus or stage 3 disease in zone I or stage 2 or 3+ disease in zone II [3], which is significantly higher than that reported in the RAINBOW study.

However, two studies which focused on zone II ROP [39, 42] observed higher rate of recurrence in ROP if IVB or IVR was used as monotherapy. Regression of ROP in these studies was mostly induced with retreatment by second IVB/IVR injection or laser therapy, but the duration between the initial injection and retreatment varied. In the study by Karkhaneh et al., IVB reinjection was administered at a mean of 5.07 ± 1.66 weeks after the initial treatment. For the study by Zhang et al., the duration between initial IVR to laser retreatment was 12.62 ± 7.93 weeks.

One study had investigated the efficacy of the use of intravitreal aflibercept in eyes with high risk prethreshold ROP or threshold ROP or aggressive posterior ROP [72]. Vedantham et al. had performed a retrospective case series of 46 ROP eyes treated with 1 mg intravitreal aflibercept (IVF). The result showed all eyes achieved regression of ROP 1 week after treatment.

A retrospective study by Bai et al. investigated the efficacy of intravitreal injection of conbercept (IVC) in eyes with Type 1 ROP or AP-ROP [36]. All of the eyes were followed for at least 6 months and all achieved regression of ROP. Eight out of 48 eyes had recurrence (four eyes recurred at 5 weeks, two eyes recurred at 6 weeks and two eyes recurred at 7 weeks).

Ocular efficacy of anti-VEGF agents in zone I ROP

For stage 3+ ROP in zone I, the efficacy of IVB was shown to be clinically significant by the BEAT-ROP study, with lower recurrence rate when compared to laser therapy [33]. Both standard (type 1) and aggressive posterior (type 2) retinopathy were responsive to IVB. Similar findings were also observed for IVR. In the RAINBOW study, treatment success occurred in 70% of infants with stage 3 or any plus disease in zone I receiving 0.1 mg IVR, when compared to 61% using laser therapy [2]. Similar effect of another agent, pegaptanib, on stage 3+ ROP showed combination therapy with laser improved ROP in 91.2% of infants when compared to 69.0% in laser alone [34] (Table 2).

Retinal detachment is one of the main reasons for visual loss in ROP infants [73, 74]. The BEAT-ROP study showed the reduction of its incidence in zone I ROP [33]. Retinal detachment occurred in two infants after laser therapy, but none in the IVB group. Moreover, in the same study, other complications such as macular dragging were also reduced after IVB treatment. The complication rate of IVB treatment (3%) was significantly lower than that of conventional laser therapy (54%). Moreover, when looking into the need of vitrectomy in the BEAT-ROP study, 13 infants (out of 33) in the laser group required surgery as a result of failed laser therapy. On the contrary, 0 out of 31 infants in the IVB group required any vitrectomy [33]. The reduction in complication rate or retinal detachment incidence was not demonstrated in zone II ROP.

The efficacy of newer agents such as conbercept was also discussed in one article. Cheng et al. had performed a retrospective study comparing eyes with zone I or aggressive posterior ROP (APROP), injected with 0.25 mg IVR or 0.25 mg conbercept (IVC) [61]. A significantly higher recurrence prevalence was reported in eyes treated with IVR when compared to IVC (49.09% vs 28.57%, $p = 0.006$). A significantly longer interval from initial treatment to recurrence was reported in IVC eyes when compared with IVR (10.6 ± 1.53 vs 7.87 ± 0.65).

Ocular efficacy of anti-VEGF agents in zone II ROP

In general, treatment success was higher in zone II ROP in all three treatment groups (laser therapy, 0.2 mg IVR, 0.1 mg IVR) when compared to zone I [2]. Similar to the findings in zone I ROP in the RAINBOW study, IVR showed a better treatment success rate (88%)

Table 1. Summary of original studies on anti-vascular endothelial growth factor in treatment of retinopathy of prematurity.

	Studies	Type of study	Participants	Country/ region	Interventions	Study arms	Duration	Significant findings zone 1	Ocular efficacy outcome	Significant findings zone 2	Ocular efficacy outcome	Significant findings overall	Ocular efficacy outcome	Limitation/ potential source of error
Bevacizumab, Ranibizumab	Alyamaç Sukgen, E. (2016)	retrospective study	45	Turkey	Intravitreal injection of anti-VEGF	i. 0.625 mg bevacizumab; ii. 0.25 mg ranibizumab.	From Oct 2013 to Jun 2015					Higher prevalence of recurrence in IVR group when compared to IVB group	$P = 0.023$	retrospective study and lacking in wide field fundus photography
	Chandra., P. et al. (2020)	retrospective study	9	India	Vitrectomy combined with intravitreal anti-VEGF therapy	i. Vitrectomy combined with intravitreal bevacizumab (0.625 mg) ii. Vitrectomy combined with ranibizumab (0.25 mg)	From Aug 2017 to Jul 2018					The usage of Anti-VEGF treatment together with vitrectomy was found to be able to regressadvanced stage 4 ROP withextensive neovascular proliferationrapidly	NA	Retrospective study
	Erol., M., K., et.al (2015)	retrospective study	20	Turkey	Anti-VEGF treatment as first-line monotherapy	i. 0.25 mg ranibizumab ii.0.625 bevacizumab	From Aug 2011 to Feb 2013					Higher percentage of relapse of type 1 ROP in IVR eyes than IVB eyes	NA	Retrospective study
	Wu et al. (2017)	Prospective study	10	Taiwan	Intravitreal injection of ranibizumab and bevacizumab	i: 0.25 mg ranibizumab ii. 0.625 mg bevacizumab	From Feb 2013 to Dec 2014					The suppression of systemic VEGF was more pronounced in IVB when compared to IVR	N/A	Small sample size
Bevacizumab, Laser therapy	Harder et al. (2013)	retrospective study	12	N/A	Intravitreal bevacizumab or laser therapy	i. 0.375 mg or 0.625 mg bevacizumab ii. argon laser therapy	NA					Less myopia was found in eyes received IVB when compared with argon laser	$P = 0.02$	retrospective study, relatively short follow up for refractive error outcome
	Chen, Y. C., et al. (2019)	retrospective study	25	Taiwan	Intravitreal bevacizumab injection or laser therapy	i. 0.625 mg bevacizumab ii. laser photocoagulation	From Jan 2010 to Dec 2012					A significantly higher myopia was found in eyes treated with laser when compared with intravitreal anti-VEGF	$P = 0.01$	Relatively small patient sample size and potential selection bias due to exclusion of eyes with poor image quality
	Geloneck, M. M. et al. (2014)	RCT	131	USA	Intravitreal bevacizumab monotherapy or laser therapy	i. 0.625 mg bevacizumab; ii. laser therapy	From Mar 13, 2008 to Aug 4, 2010	IVB eyes had less myopia when compared with eyes with laser treatment	$P < 0.001$	Eyes reviewed IVB had less myopia than eyes received laser treatment	$P < 0.001$			22 out of 131 infants did not follow up and potential observer bias
	Gunay, M., et al. (2016)	prospective study	30	N/A	Intravitreal bevacizumab injection or laser therapy	i. 0.625 mg bevacizumab ii. laser photocoagulation iii. Spontaneously regressed ROP	NA					The prevalence of myopia was found to be lower in eyes without treatment when compared with eyes treated either IVB or laser therapy	$P = 0.028$	Not randomized study and small sample size
	Hwang et al. (2015)	retrospective study	28	Georgia	laser therapy or bevacizumab	i: laser therapy ii: 0.625 mg bevacizumab	From Jan 2008 to Dec 2012	Zone I ROP was associated with high myopia in eyes regardless of the treatment group assigned	$P = 0.007$			Intravitreal bevacizumab and laser are effective treatment options for Type 1 ROP and have low complication rates	N/A	retrospective study
	Karkhaneh, R et al. (2016)	RCT	79	Iran	Conventional indirect laser therapy or	i. 0.625 mg bevacizumab; ii. laser therapy	From Sep 2012 to Sep 2013			A significantly larger	$P = 0.018$			NA

Table 1. continued

Studies	Type of study	Participants	Country/ region	Interventions	Study arms	Duration	Significant findings zone 1	Ocular efficacy outcome	Significant findings zone 2	Ocular efficacy outcome	Significant findings overall	Ocular efficacy outcome	Limitation/ potential source of error
				intravitreal bevacizumab injections					amount of eyes treated with IVB require retreatment when compared with laser group				
Kennedy, K. A. and H. A. Mintz-Hittner (2018)	RCT	150	USA	Conventional indirect laser therapy or Intravitreal bevacizumab injections	i. 0.625 mg bevacizumab; ii. laser therapy	From Mar 2008 to Apr 2010					No difference was found between infants treated with IVB or laser therapy in adverse neurodevelopmental outcomes	NA	NA
Kong, L., et al. (2015)	RCT	24	USA	Intravitreal bevacizumab or laser therapy for infants with type 1 ROP	i. 0.625 mg bevacizumab; ii.0.25 mg bevacizumab; iii. laser therapy	From Jul 2012 to Jan 2014					Both laser therapy and IVB reduce the serum IGF-1 level	NA	Small sample size
Lepore, D., et al. (2014)	RCT	13	Italy	Intravitreal bevacizumab or laser therapy	i. 0.5 mg bevacizumab on one eye; ii. laser therapy on the other eye	From Sep 2009 to Dec 2010	Macular abnormalities were more common to be found in eyes treated with IVB when compared with laser	$P < 0.05$					Small sample size
Lepore, D., et al. (2018)	RCT	21	Italy	Intravitreal injection of bevacizumab and conventional laser photoablation	i. 0.5 bevacizumab ii. conventional laser photoablation	From Sep 2009 to Mar 2012	Eyes treated with IVB continue to have extensive areas of non-vascularized peripheral retina	NA					Within-subject randomization due to leakage of IVB from the eye into systemic circulation
Mintz-Hittner, H. A. (2012)	RCT	(eye: 152)	USA	Pegaptanib with laser therapy or bevacizumab monotherapy	NA	NA					The use of anti-VEGF therapy for ROP has been shown to be effective and safe without any report of toxicity.	NA	NA
Mintz-Hittner, H. A., et al. (2011)	RCT	150	USA	Intravitreal bevacizumab or conventional laser therapy	i. 0.625 bevacizumab (injected 2.5 mm from the limbus) ii. conventional laser therapy	From Mar 2008 to Aug 2010					Rate of recurrence was found to be higher in eyes treated with laser therapy than with IVB	$P = 0.002$	NA
Moran, S., et al. (2014)	RCT	15	N/A	Intravitreal Bevacizumab or laser	i.1.25 mg of Bevacizumab ii. Treatment with diode laser	NA					Bevacizumab is less destructive and more convenient to use when compared to laser treatment.	NA	Small sample size
Morin et al. (2016)	Retrospective study	125	Canada	laser therapy or Intravitreal bevacizumab	i: laser therapy ii: Bevacizumab	From Jan 2010 to Sep 2011					Infants treated with IVB had higher odds of severe neurodevelopmental disabilities when to laser therapy.	N/A	retrospective study and limited by lost of infants for follow up
Kuo et al. (2015)	retrospective study	54	Taiwan	laser therapy or intravitreal bevacizumab	i. laser therapy; ii. 0.5 mg bevacizumab	From 2003 to 2012					The difference in the myopic status between laser and IVB treatment was	$p < 0.001$	Retrospective study and small sample size

Table 1. continued

	Studies	Type of study	Participants	Country/ region	Interventions	Study arms	Duration	Significant findings zone 1	Ocular efficacy outcome	Significant findings zone 2	Ocular efficacy outcome	Significant findings overall	Ocular efficacy outcome	Limitation/ potential source of error
												not statistically significant.		
	Lien et al. (2016)	Retrospective observational case series	61	Taiwan	laser therapy or Intravitreal bevacizumab or combination of both	i: laser only ii: 0.625 mg Bevacizumab only iii: a combination of 0.625 mg Bevacizumab and laser treatment	From Dec 2007 to Dec 2010					There was no difference in neurodevelopmental outcome between 0.625 mg IVB group and laser group, but the combination group showed a higher incidence of psychomotor and mental impairment of infants at the 24 months of age.	N/A	Retrospective study and small number of enrolled patients
	Rodriguez et al. (2019)	Retrospective study	86	N/A	laser therapy or Intravitreal bevacizumab	i: laser therapy ii: Bevacizumab	From 2006 to 2016					There were no significant differences in primary outcome measures between the two groups except laser therapy had a higher adjusted odds of causing bilateral visual impairment. IVB was not found to be associated with severe neurodevelopmental disabilities.	$P = 0.038$	Retrospective study
Bevacizumab	Chang et al. (2019)	Retrospective study	114	Taiwan	Intravitreous bevacizumab injections	i: 0.625 mg Bevacizumab ii: control (no treatment)	From 2008 to 2014					No significant differences in body weight and neurodevelopmental outcomes were observed between the IVB and control groups up to 2 years of age	$P = 0.389$	Retrospective design, small sample size, lack of serum VEGF data
	Fan et al. (2019)	Prospective study	148	Taiwan	Intravitreous bevacizumab injections	i: 0.625 mg Bevacizumab	From Jun 2014 to Jan 2019					At 1.5-year mean age, ROP children with prior history of IVB use and those without the need of treatment showed similar refractive and neurodevelopmental outcomes.	N/A	Non-randomized design, limited number of patients
	Crouch et al. (2020)	Prospective study	61	N/A	Intravitreous bevacizumab injections of 0.625 mg to 0.031 mg	i: 0.25 mg Bevacizumab ii: 0.125 mg Bevacizumab iii: 0.063 mg Bevacizumab iv: 0.031 mg Bevaizumab	From Apr 2016 to Oct 2017					The rate of high myopia of low dose bevacizumab was consistent with rates reported in higher dosages	N/A	Small sample size
	Wallace, D. K., et al. (2018)	prospective study	61	N/A	Intravitreal bevacizumab injection	i. 0.25 mg bevacizumab ii. 0.125 mg bevacizumab iii. 0.063 bevacizumab, iv.0.031 mg bevacizumab	NA					Retinal structural outcomes are good after reducing the bevacizumab dose to as low as 0.031 mg.	NA	small sample size
	Wallace, D. K., et al. (2017)	prospective study	58	N/A	Intravitreal bevacizumab	i. 25 mg bevacizumab	From May 2015 to Sep 2016					Intravitreal bevacizumab therapy as low as 0.031 mg, or 5% of the previously mentioned dose, was	NA	Small sample size

Table 1. continued

	Studies	Type of study	Participants	Country/ region	Interventions	Study arms	Duration	Significant findings zone 1	Ocular efficacy outcome	Significant findings zone 2	Ocular efficacy outcome	Significant findings overall	Ocular efficacy outcome	Limitation/ potential source of error
												found to be efficacious.		
Ranibizumab	Stahl, A., et al. (2018)	RCT	19	Germany	Baseline ranibizumab injection per eye	i.0.12 mg ranibizumab ii. 0.2 mg ranibizumab	From Sep 2014 to Jul 2016					Ranibizumab is effective in treating ROP. Physiologic intraretinal vascularization to the ora serrata was found to be more favorable in the 0.12-mg than the 0.20-mg group. Systemic level of VEGF was not suppressed in either group.	NA	Small sample size and a early primary endpoint
Ranibizumab, Laser therapy	Stahl, A., et al. (2019)	RCT	214	multiple countries: USA, Austria, Belgium, Croatia, Czechia, Denmark, Egypt, Estonia, France, Germany, Greece, Hungary, India, Italy, Japan, Lithuania, Malaysia, Mexico, Poland, Romania, Russian Federation, Saudi Arabia, Slovakia, Taiwan, Turkey, United Kingdom	Intravitreal ranibizumab or laser therapy	i. 0.2 mg ranibizumab ii. 0.1 mg ranibizumab iii. Laser therapy at baseline	From Dec 2015 to Jun 2017	68% of eyes treated with 0.2 mg IVR achieved primary outcome (survival without achieve retinopathy). 70% of eyes treated with 0.1 mg IVR achieved primary outcome	NA	88% eyes treated with 0.2 mg IVR achieved primary outcome. 78% eyes treated with 0.1 mg IVR achieved primary outcome.	NA	Infants received 0.1 mg IVR had a higher treatment success odd ratio when compared with laser therapy	$P = 0.051$	Clinicians providing care were from a wide range of settings and no training in the use of fundoscopy were provided to clinicians.
	Zhang, G., et al. (2017)	RCT	50	China	Conventional laser therapy or single dose intravitreal injection of ranibizumab	i. Conventional laser therapy (indirect infrared diode laser 810 nm) ii. 0.3 mg single dose ranibizumab	From Jan 2014–Dec 2014 (12 m)			Eyes treated with IVR was found to have a greater recurrence rate of ROP when compared to eyes treated with laser	$P = 0.001$			Relatively small sample size, short follow-up of patients
Aflibercept	Vedantham, V. et al. (2019)	retrospective study	23	India	Intravitreal Aflibercept	i.1 mg aflibercept	NA					All ROP Eyes treated with IVF was found to be able to achieve regression of ROP	NA	Retrospective study
Aflibercept, Bevacizumab	Huang et al. (2018)	Prospective study	14	Taiwan	Intravitreal injection of aflibercept and bevacizumab	i: 1 mg aflibercept ii. 0.625 mg bevacizumab	From Sep 2014 to Aug 2016					Despite a lower concentration of IVB used when compared to IVA, systemic VEGF was more suppressed in the IVB group than the IVA patients	$P = 0.273$	Small cohort study and unequal distribution of two study arm group
Conbercept	Bai, Y., et al. (2018)	retrospective study	24	China	Intravitreal conbercept	i. 0.25 mg conbercept	From Jun 2015 to Jul 2016					All eyes injected with IVC achieved ROP regression	NA	Small sample size and

Table 1. continued

	Studies	Type of study	Participants	Country/ region	Interventions	Study arms	Duration	Significant findings zone 1	Ocular efficacy outcome	Significant findings zone 2	Ocular efficacy outcome	Significant findings overall	Ocular efficacy outcome	Limitation/ potential source of error
														retrospective study
	Cheng et al. (2020)	case series	70	China	Intravitreal conbercept injections or no treatment	i: 0.25 mg Conbercept ii: control (no treatment)	From Nov 2017 to Sep 2018					The plasma levels of VEGF-A and VEGF-D were suppressed at 1 week after injection of 0.25 mg IVC, but their levels returned to baseline at 4 weeks.	$P = 0.021$	case series
	Cheng, Y., et al. (2018)	retrospective study	20	China	Intravitreal conbercept	i. 0.15 mg conbercept	From Aug 2016 to Nov 2016					84.2% of eyes was able to achieve primary effectiveness with IVC 0.15 mg alone	NA	Retrospective study
Conbercept, Ranibizumab	Cheng, Y., et al. (2020)	retrospective study	145	China	Intravitreal conbercept or Intravitreal ranibizumab	i. 0.25 mg conbercept ii. 0.25 mg ranibizumab	From Jul 2012 to Mar 2018					The prevalence of recurrence was found to be significantly higher in IVR when compared with IVC	$P = 0.006$	Retrospective study
Cryotherapy	Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years. (2001)	RCT	291	Multiple countries: United Kingdom, USA	cryotherapy or no cryotherapy	i. cryotherapy in one eye ii. no cryotherapy in another eye	NA					Visual field reduction is an expected finding after cryotherapy even if retinal detachment is prevented	N/A	N/A
	Quinn et al. (1996)	RCT	78	USA	cryotherapy	i. cryotherapy in one eye ii. no cryotherapy in another eye	NA					In 5.5-year, an average visual field reduction of 6.4° in treated eyes was observed when compared to untreated control eyes of the same patient.	N/A	N/A
Laser therapy	Fallaha et al. (2001)	Retrospective study	47	Georgia	Conventional laser therapy	i: confluent diode laser photoablation	From Aug 1997 to Jul 2000					Anterior segment ischemia after laser ablation for APROP is rare	N/A	retrospective study
	Good et al. (2004)	RCT	317	USA	Early retinal ablative treatment or conventional treatment	i. early retinal ablative treatment in one eye ii: conventional treatment in another eye	From Oct 2000 to Sep 2002					Early laser ablation resulted in a reduction in unfavorable visual acuity outcomes from 19.8% to 14.3%.	$P < .005$	N/A
	Gunay et al. (2015)	Retrospective study	175	Turkey	Conventional laser therapy	i. Laser ablations with a head-mounted 810 nm diode laser	From Nov 2010 to Dec 2013					Anterior segment ischemia after laser ablation for APROP is rare	N/A	Retrospective study

when compared to that of laser therapy (70%) for stage 3+ zone II disease (Table 2).

Three studies compared the ocular outcome (in terms of the need for vitrectomy and the incidence of disease complications) of intravitreal anti-VEGF with that of laser therapy on zone II ROP [33, 39, 42], with the BEAT-ROP study specifically treating infants with posterior zone II ROP. In the BEAT-ROP study, IVB had more infants (2 of 39 infants) requiring vitrectomy, when compared to laser therapy (0 of 40 infants) in treating posterior zone II ROP. An adverse visual outcome such as retinal detachment also occurred in two infants in the IVB group but not in the laser group [33]. The need for vitrectomy was also mentioned in the study by Karkhaneh et al. [39]. One eye in the IVR group required vitrectomy due to dense preretinal haemorrhage, when compared to no eye in the laser treatment arm requiring vitrectomy ($P = 0.54$). Zhang et al. also compared the ocular outcome between anti-VEGF and laser therapy [42]. Within 1 week after IVR injection, all infants showed regression of neovascularization and plus disease. In the laser treatment group, disease regression occurred in all infants within 1 week except in one infant. Aggravated plus disease and worst neovascularization with vitreous and retinal hemorrhage around the ridge were observed in both eyes of this infant. This infant required IVR as additional treatment and the vitreous haemorrhage eventually resolved.

Regarding the recurrence rate, the BEAT-ROP study showed that 5% of the IVB group (2 of 39 infants) and 12% of the laser group (5 of 40 infants) had a recurrence of their stage 3+ posterior zone II ROP [33]. However, the difference in the recurrence rate was not statistically significant to conclude that IVB is better for posterior zone II ROP. Karkhaneh et al. and Zhang et al. even observed more recurrence and greater need for retreatment after IVB in stage 2 to stage 3+ zone II ROP [39, 42]. In the study by Karkhaneh et al., 9 of the 86 eyes (10.5%) in the IVB group and 1 of the 72 eyes (1.39%) in the laser group eventually required retreatment. (p value = 0.018). Out of the nine eyes in IVB group which required retreatment, the ROP of eight eyes regressed after a second injection, but one eye needed vitrectomy. A similar trend was observed by Zhang et al., and the difference in the ROP recurrence rate between IVR and laser group was shown to be statistically significant ($p = 0.001$) [42].

Evidence regarding the ocular outcome and the disease recurrence between anti-VEGF and laser therapy in zone II ROP remains inconclusive; it is difficult to decide which of the two treatments is better for zone II ROP. However, studies on newer agents like aflibercept and conbercept may shed light on this issue. The retrospective study of Cheng et al. compared the use of IVR and IVC in zone II ROP eyes, suggested the prevalence of recurrence was significantly lower in eyes treated with IVC when compared with IVR (13.31% vs 23.56%, $p < 0.001$) [61]. A significantly shorter time interval from first treatment to recurrence was reported in eyes treated with IVR when compared to IVC (8.40 ± 0.88 vs 11.4 ± 1.35 weeks, $P < 0.001$).

The relative effectiveness of various anti-VEGF agents

Bevacizumab and ranibizumab are currently the two most commonly used anti-VEGF for intravitreal injection in ROP. Three retrospective studies were reviewed in regards to the recurrence rate of ROP in patients treated with IVR and IVB, all showing IVR has a higher portion of eyes with recurrence [56–58]. The study by Alyamac Sukgen, Comez, Kocluk, and Cevher demonstrated that eyes treated with IVR has a significantly higher ROP recurrence rate than patients treated with IVB with stage 1 to stage 3+ ROP [56]. Patients with zone I or posterior zone II were reviewed and divided into two groups, either injected with 0.625 mg IVB or 0.25 mg IVR. IVR was found to have a significantly higher prevalence of recurrence of ROP than IVB ($P = 0.023$), though no difference was found between the two groups in terms of need for additional treatment of recurrence (i.e., diode laser photocoagulation to control ROP progression) ($P = 0.963$). Another retrospective study conducted by Chandra, included patients with Stage 4 ROP in zone I or II ROP treated with vitrectomy combined with either 0.25 mg IVR or 0.625 mg IVB, which demonstrated recurrence in one out of three eyes in the IVR group. No recurrence of ROP was reported in 12 eyes with combined vitrectomy and 0.625 mg IVB injection [57]. Furthermore, Erol et al. demonstrated a higher percentage of relapse in IVR injection (0.25 mg) than IVB (0.625 mg) treatment for type 1 ROP [58]. However, due to the small sample size and retrospective nature of these three studies, the actual differences between the two anti-VEGF remains inconclusive [56–58].

Effective dosage of anti-VEGF

The effective dosage of anti-VEGF is an important topic regarding ROP treatment. Various studies have been exploring the lowest possible dosage of anti-VEGF that can control ROP progression but minimize the systemic effects of ROP on patients. As indicated by Kong et al., the serum concentration of bevacizumab correlated well with the dosage of IVB injection, and this phenomenon lasted for at least 60 days (the study only followed up the patients up to 60 days) [40]. The group with 0.625 mg IVB injection showed persistently higher serum bevacizumab concentration at the four time points (days 2, 14, 42, and 60 postinjection) when compared to the 0.25 mg IVB group.

The therapeutic range of intravitreal anti-VEGF was explored in three articles [33, 65, 66]. In the phase 1 dosing study by Wallace et al. [65, 66], patients with stage 3 zone I ROP were divided into four groups, being injected with 0.25 mg, 0.125 mg, 0.063 mg, and 0.031 mg of IVB, respectively. Retreatment due to early failure or late recurrence was required in 18% of eyes treated with 0.25 mg, 25% of eyes treated with 0.125 mg, 33% of eyes treated with 0.063 mg, and 0% of eyes treated with 0.031 mg [65]. In terms of the need for retreatment, this study showed low dose IVB (0.031 mg, 5% of the dose used in the BEAT-ROP trial [33] was not inferior to higher-dose IVB regularly used by various studies [33, 38–41, 45, 46, 56]. Wallace et al. also conducted another phase 1 dosing study to further deescalate the dose of IVB [67]. A total of 4 week persistent regression of ROP was achieved in 13 of 13 eyes (100%) in 0.016 mg IVB, 9 of 9 eyes (100%) in 0.008 mg IVB, 9 of 10 eyes (90%) in 0.004 mg IVB, but only 17 of 23 eyes (74%) in 0.002 mg IVB. It was suggested that 0.004 mg may be the lowest effective dose of IVB for ROP. However, given the small number of dosing studies for anti-VEGF in ROP, larger studies would confirm whether a reduction in the dose of IVB to level as low as 0.004 mg could produce the same efficacy, given the potential benefit that a lower dose can minimize the systemic side effects to the infants.

Similar dosing study was also conducted on IVR [1]. Stahl et al. demonstrated that 0.12 mg IVR was equally effective as 0.2 mg IVR in controlling acute zone I and II, stage 3+ ROP. This study further supported the hypothesis that we could possibly reduce our current dosage of intravitreal anti-VEGF for side effect reduction.

There was one dosing study for conbercept by Cheng et al. [71]. In this study, Cheng et al. used a lower dose of conbercept (0.15 mg) than the conventional dose of 0.25 mg for treating zone II Stage 2/3+ ROP. Treatment success occurred in 84.2% of eyes (32 of 38 eyes) while the ROP of the remaining eyes regressed after a second injection, showing that 0.15 mg conbercept was also an effective dosage for zone II Stage 2/3+ ROP treatment.

Delay in ROP recurrence after anti-VEGF therapy and its implication in post-operative management

Three studies have shown that anti-VEGF therapy can delay the mean time to ROP recurrence [33, 42, 73]. In the BEAT-ROP study, IVB took a longer time than laser therapy, with a mean of 16.0 ± 4.6 weeks with ROP recurrence, when compared to 6.2 ± 5.7 weeks for the recurred stage 3+ ROP after conventional laser therapy [33]. Squandau et al. and Zhang et al. also made similar comments

of IVB recurring later compared to laser [42, 73], with time to recurrence reported to be 12.62 ± 7.93 weeks in Zhang et al. The delay in ROP recurrence with intravitreal anti-VEGF was a disadvantage as suggested by various studies [33, 73]. It would take ophthalmologists a longer time to ensure that the infants are free from ROP. Therefore, longer follow-up is advised for infants who choose intravitreal anti-VEGF for the treatment of their ROP.

MECHANISM OF ACTION

The pathogenesis of ROP has to be discussed before looking into the mechanism of action of anti-VEGF therapy. ROP involves a biphasic pathologic neovascularization [29]. Phase I occurs at the time of premature birth. The cessation of normal retinal vessel growth is associated with the loss of in-utero growth factors and the increased oxygen level in the extrauterine environment. The relative hyperoxia is aggravated by supplemental oxygen given to premature infants. As a result, the peripheral retina becomes avascular in phase I. The lack of vascularization in the peripheral retina will lead to hypoxia and, therefore, enters phase II of ROP pathogenesis. Hypoxia in phase II will stimulate the production of VEGF and pathological neovascularization. Anti-VEGF therapy mainly targets phase II of ROP. It has been shown that IVB injection can effectively reduce the level of VEGF in the vitreous humor. Similar degree of reduction on VEGF was not observed after conventional laser therapy [51].

The previous section on ocular efficacy suggested that intravitreal anti-VEGF can reduce the ROP recurrence in zone I but not zone II. This can be explained by the two distinct mechanisms involved in the pathogenesis of zone I and II ROP. In the inner retina, both vasculogenesis and angiogenesis take place. Vasculogenesis is the formation of the primitive vascular network [75]. Angiogenesis is the development of new capillaries from preexisting vessels by intussusception or sprouting [75]. The formation of primordial vessels is mediated by vasculogenesis, while angiogenesis further increases vascular density in the inner retina. In contrast, the vessels in the outer retina are formed by angiogenesis only [76]. Thus, zone I ROP is more associated with vasculogenesis and less sensitive to conventional laser therapy, as observed in various studies [77–79]. On the other hand, zone II ROP is more related to angiogenesis. Therefore, laser treatment might be a more effective option compared with anti-VEGF monotherapy, as suggested by Zhang et al. [42].

SIDE EFFECTS

Peripheral avascularisation of retina

Various studies demonstrated peripheral avascularisation of the retina after the administration of intravitreal anti-VEGF in eyes with ROP [1, 28, 33, 39, 41, 45, 56, 80, 81]. A total of 55% of eyes were found to have peripheral avascularisation in a study by Tahija et al., who retrospectively reviewed 20 infants with zone I or zone II using RetCam fundus photos of ROP treated with a single injection of IVB (32-28 weeks of gestation) [28]. The BEAT-ROP study also showed that peripheral retinal vessels delayed or did not fully vascularized after IVB administrated at the gestation age of 32–38 weeks in eyes with zone I or II stage 3+ ROP (0.625 mg in 0.025 ml of solution) [33]. However, JY Lee et al. offered contrasting view where IVB did not inhibit peripheral retinal vasculogenesis in stage 3 ROP if administrated after gestational age of 32 weeks. The study suggested that anti-VEGF should be administrated during phase II of ROP neovascularization [82].

For the use of IVR dosage, Stahl et al. demonstrated that in infants with zone 1 or posterior zone II, stage 3+ ROP, IVR (0.12 mg) a higher number of eyes achieved full vascularization of the peripheral retina than IVR (0.2 mg), with 16.7 % achieved full vascularization. This suggests that a lower dose may have a better chance to achieve full vascularization, though this study is limited by the small sample size [1].

In eyes with Type 1 ROP or AP-ROP treated with IVC, Bia et al. showed that out of 48 eyes, only 12 eyes achieved full retinal vascularization [36]. And, 32 eyes retained avascularization in zone III while four eyes were found to have scarring in zone II.

The effect of ranibizumab and bevacizumab on peripheral retinal avascularisation were compared in the study by Alyamac Sukgen et al. retrospectively [56]. Four out of 22 infants treated with IVB and 6 out of 23 infants treated with IVR presented with peripheral avascular retinal areas. No significant difference ($P = 0.42$) was found between IVR (0.25 mg) and IVB (0.625 mg). The mean time for completion of vascularization for IVB was 55.93 ± 4.13 weeks, while the mean time for completion of vascularization for IVR was 56.3 ± 4.3.

Peripheral avascularisation of retina in anti-VEGF treated Zone I ROP

Two studies showed persistent peripheral avascularisation of retina in IVB infants in the treatment of zone I ROP [33, 41, 45]. Lepore et al. showed that eyes with stage 3 ROP treated with IVB (0.5 mg in 0.02 ml balanced salt solution) had avascular retina peripheral to the location of acute-phase retinopathy 9 months after the injection, which is uncommon in eyes treated with conventional laser photoablation [41]. Eyes in 27.3% of laser treated demonstrated capillary bed loss in either central or peripheral, when compared to 91.6% of eyes in the IVB group. Lepore et al. demonstrated that after 4 years of intervention, IVB eyes continue to have extensive areas of non-vascularized peripheral retina (75% of eyes for IVR and 10.5% for laser treatment in terms of central or peripheral capillary bed loss) 65% of the IVB eyes showed leakage at the junction between vascular and avascular retina while lasered eyes showed typical chorioretinal atrophy [45].

The BEAT-ROP study concluded that although eyes with stage 3 + after IVB did not fully vascularization at far peripheral retinal, the peripheral retinal vessels continued developed after injection. However, for conventional ablative laser therapy, infants with zone I ROP was complicated with significant loss of visual field [33]. This shows that eyes treated with IVB is more common than laser to be complicated with persistent peripheral avascularisation.

Peripheral avascularisation of retina in anti-VEGF treated Zone II ROP

About half of the eyes treated with anti-VEGF in eyes with zone II ROP was complicated with delayed peripheral avascularisation of retina. Karkhaneh et al. compared infants with zone II ROP, stage 2–3+. 79% of eyes had avascular areas at 54 weeks postmenstrual age, and 45 % of eyes with avascular areas at 90 weeks [39]. Long lasting peripheral retinal avascularity after IVB was reported; therefore, bevacizumab monotherapy should be followed up until the retina is fully vascularized (the process can be up to 2 years).

Myopia

A total of six studies compared eyes with ROP treated with laser therapy and anti-VEGF in refractive error, demonstrating different conclusions [38, 47–50, 53], and one study has investigated the spherical equivalent in ROP eyes treated with different doses of IVB [64].

Two studies demonstrated no significant difference in myopic status between eyes treated with anti-VEGF or laser therapy [49, 53]. The retrospective study by Kuo HK et al. demonstrated eyes with type 1 stage 3 ROP, which required treatment are more susceptible to severe myopia compared with eyes without ROP at the age of 3 years old [53]. The mean spherical equivalent at 3 years old for eyes without ROP was 0.41 ± 1.95 diopters (D), which is less severe than eyes treated with laser therapy (−1.71 ± 1.27 D) and IVB (−1.53 ± 2.20 D) [53]. No significant difference in myopic

Table 2. Recurrence rate and time to recurrence of anti-vascular endothelial growth factor injection in zone 1 and 2 retinopathy of prematurity.

	Zone 1		Zone 2	
	Recurrence rate	**Time to recurrence (weeks)**	**Recurrence rate**	**Time to recurrence (weeks)**
Bevacizumab	6% [33]	NA	5% [33] to 10.5% [39]	5.07 [39]
Ranibizumab	49.09% [61]	7.87 [61]	23.56% to [61] to 26% [42]	8.40 [61] to 12.62 [42]
Aflibercept	0% [60] to 81.8% [72]	6 [72]	0% [60] to 54.2% [72]	6 [72]
Conbercept	0% [36] to 28.57% [61]	10.6 [61]	13.31% [61] to 22.9% [36]	5 [36] to 11.4 [61]

status was observed between eyes with type I ROP treated with laser or IVB (0.5 mg in 0.02 mL). However, this study is limited by its small sample size and not a RCT. Another prospective study by Gunay et al., showed that the median spherical equivalent of eyes with zone I or zone II ROP treated with 0.625 mg IVB monotherapy and ROP eyes treated with laser therapy had no significant difference (0.25 D vs 0.75 D). The incidence of myopia of IVB monotherapy eyes was 40.7%, while the incidence of laser treated eyes was 32.7% [49]. The study was limited by its short duration follow up, with the infant's refraction measured at 1-year adjusted age.

Another four studies had demonstrated that eyes treated with anti-VEGF had less myopia when compared with eyes treated with laser therapy [38, 47, 48, 50]. Geloneck et al. demonstrated a different conclusion in a randomized control trial, investigating infants at the age of 2.5 years, showing that stage 3 ROP eyes treated with laser treatment in posterior zone II had a higher percentage of eyes with very high myopia (≥−8.00 D) when compared with eyes treated with IVB (36.4% vs 1.7%). Such difference is related to the difference of anterior segment development, which is present with IVB but absent following laser therapy [38], as only IVB allows the continued development of retinal vessels beyond the neovascular ridges and the local growth factor expression for a more normal anterior segment development with minimal myopia The mean spherical equivalent refraction for eyes with zone I ROP received IVB 0.625 mg (0.025 mL) was found to be −1.51 (SD 3.42) diopters (D) which is significantly higher than eyes received laser therapy −8.44 (SD 7.57) D ($P < 0.001$). For zone II ROP, the mean spherical equivalent refraction for IVB was −0.58 (SD 2.53) D, which is significantly lower than eyes received laser treatment, −5.83 (SD 5.87) D ($P < 0.001$). The study also demonstrated no difference between zone I and posterior zone II ROP in terms of severity of myopia.

Three other retrospective studies also demonstrated similar results [47, 48, 50]. Chen et al. performed a retrospective and comparative case series, comparing the refractive error and optical biometry of children with previous type 1 ROP who were treated with intravitreal injection of 0.625 mg bevacizumab (25 eyes, mean age 8.77 ± 0.93) or laser photocoagulation with 810 nm wavelength (22 eyes, mean age 8.83 ± 2.41). The study result showed that children treated with the laser group had a significant myopia when compared to the IVB injection group (−3.49 ± 4.39 and −0.16 ± 2.00) ($P < 0.01$) [48]. The study performed by Harder et al. compared zone 1 or zone 2 ROP infants received monotherapy IVB (0.375 mg or 0.625 mg) injection and infants received laser. A total of 23 eyes received IVB while 26 eyes received laser therapy. After 11.4 ± 2.3 months of followup after birth, significantly less myopia was found in eyes received IVB when compared with laser therapy eyes (−1.04 ± 4.24 D vs −12.5 ± 4.63 D) [47]. Hwang et al. compared outcomes after IVB (0.0625 mg) (28 eyes) and laser photocoagulation (32 eyes) with either zone 1 or zone 2 ROP. In eyes with zone 1 ROP, the mean spherical equivalent was found to be −3.7 D and −10.1 D (IVB and laser therapy). For zone 2 ROP, the results were 0.6D and −4.7 D, respectively, showing a significant difference between the two groups. The refractive error was measured at 22.4 months of mean post-gestational age for IVB eyes and 37.1 months of laser treated eyes [50].

Crouch et al. has compared the 12-month outcome in terms of spherical equivalent in type 1 ROP eyes receiving a different dosage of IVB (0.625 mg, 0.25 mg, 0.125 mg, 0.063 mg, 0.031 mg), demonstrating that the rate of high myopia of low dose bevacizumab was similar with rates reported in higher dosages [64].

There are no clinical studies comparing different types of anti-VEGF in terms of myopia; further studies are needed to conclude differences between different types of anti-VEGF therapy.

Visual field reduction

It is believed that conventional treatments such as cryotherapy or laser ablation would cause visual field reduction due to the ablative techniques [3, 4, 44, 83, 84]. Fulton et al. pointed out that the visual fields of cryotherapy or laser treated eyes were slightly more constricted than untreated eyes, though the field reduction was thought to be of little functional significance [84]. The CRYO-ROP study mentioned that visual field reduction is an expected finding after cryotherapy even if the retinal detachment is prevented [4]. Cryotherapy would cause late chorioretinal scars at the periphery of the visual field, which would then lead to visual field defects. From the perimetry result of a subset of the CRYO-ROP study population in 5.5-year, an average visual field reduction of 6.4° in treated eyes was observed when compared to untreated control eyes of the same patient [44]. However, the effect of visual field loss after cryotherapy is limited as no children complained of any subjective visual field derangements 10–14 years after treatment [83]. Similar visual field reduction was also reported in the ETROP trial as laser therapy also involves the peripheral retinal ablation. It was also suggested that zone I ablation would result in a greater field loss than zone II ablation [3]. Regarding anti-VEGF use in ROP, there is no evidence on reduction in visual field yet since the therapy is relatively new. However, it is likely that anti-VEGF injection may also result in slight visual field loss as the vision in the peripheral avascularised retina would be presumably worse.

Systemic absorption of the anti-VEGF

In general, three out of four studies showed that IVR has a lower systemic absorption when compared with IVB [1, 2, 40, 42]. VEGF is important for angiogenesis and tissue development in preterm infants [1, 2]. Stahl et al. (2018) indicated that systemic VEGF levels remained unchanged for IVR (0.12 mg or 0.2 mg), without significant difference between dosage, while a single dose of IVB can suppress VEGF below the limit of detection for weeks [1]. Stahl et al. (2019) demonstrated that ranibizumab level in serum fell slowly and reduced significantly at day 29, which is shorter than bevacizumab, with a serum half-life of 21 days after intravitreal injection [2]. These suggest that in terms of systemic absorption, IVR is less than IVB.

The decrease in serum free VEGF levels was found to be more significant in IVB treated groups (0.625 mg or 0.25 mg) when compared with laser therapy [40]. There was no difference in serum free VEGF level between the different dosages of IVB. By comparing serum free VEGF levels between the 0.652 mg and 0.25 mg IVB treated groups over time, no significant difference was found ($P = 0.6$) both of them showed similar changes in serum free VEGF levels over time [40].

The serum VEGF levels after IVB, IVR, intravitreal aflibercept (IVA) treatments were measured by Huang et al. and Wu et al. [59, 60] and were found to be significantly lower from baseline lasting up to 12 weeks post treatment. In the study comparing serum VEGF levels of IVB and IVR, the suppression of systemic VEGF was more pronounced in the IVB treatment arm [59]. Similar findings were observed in the study by Huang et al. Despite a lower concentration of IVB used (0.625 mg, 0.025 mL) when compared to IVA (1 mg, 0.025 mL), systemic VEGF was more suppressed in the IVB group than the IVA patients. Nevertheless, at 12 weeks after intravitreal injection, the reduction of systemic VEGF levels between the two groups was not significantly different ($P = 0.273$) [60].

Cheng et al. had investigated the changes in serum VEGF concentrations in infants injected with 0.25 mg IVC. Infants had their blood samples collected before and after the injection of IVC (1 week and 4 week) [70]. The serum level of VEGF-A and VEGF-D were found to be significantly lower at 1 week after injection and returned to normal at 4 weeks.

Serum IGF-1 level

Kong et al. also suggested that both laser therapy and IVB reduced the serum IGF-1 level [40]. The decrease in serum IGF-1 level is not related to dosage as no difference is found between 0.625 mg and 0.25 mg of IVB. However, infants treated with IVB have a lower serum IGF-1 than laser treated groups. IGF-1 serum level was also found to be correlated with infant body weight. A study has also reported that IGF-1 was involved in promoting hypoxia-inducible factor -1a expression through MAPK and P13K/Akt pathways, which promotes VEGF activity and hence involved in the ROP development [40].

NEURODEVELOPMENTAL OUTCOMES

Several recent studies have investigated the possible adverse effects of neurodevelopment with the use of anti-VEGF in the treatment of ROP [46, 52, 54, 55, 62, 63]. However, the results of the studies varied, and most studies only investigated the short term neurodevelopmental adverse effects for not more than 2 years of age [46, 52, 54, 55, 62], except for the study by Fan et al., which assessed the neurodevelopmental outcome of infants at 1 to 3 years old [63]. Further studies are needed to investigate the long-term neurodevelopmental outcome of the use of anti-VEGF in infants with ROP.

All of the included studies used Bayley Scales of Infant and Toddler Development for the assessment of the neurodevelopment of the infants. Five out of the studies used the Bayley Scales of Infant and Toddler Development III [46, 52, 62, 63], while one study used the second edition [54]. Fan et al. performed a prospective case-control study, which had compared three groups of infants [63]. The first group was premature children with ROP, the second group was premature children with type I ROP but regressed spontaneously without any treatment. The last group was premature children with type I ROP treated with single 0.625 mg bevacizumab. The developmental outcomes were assessed at 1 to 3 years of age, showing no significant difference in neurodevelopmental outcome when comparing group 2 and group 3 [63]. The remaining studies were retrospective studies [46, 52, 54, 55, 62]. Cheng et al. and Kennedy et al. demonstrated similar results as Fan et al., no significant difference was demonstrated between infants receiving anti-VEGF and infants receiving laser therapy [46, 62].

Rodriguez et al. found that infants treated with IVB had a higher chance of having bilateral visual impairment (BCVA less than 0.1, absent visual fixation, bilateral nystagmus), when compared with laser therapy ($P = 0.038$) [55]. No significant differences were found in terms of motor, language, or cognitive Bayley II domain scores, cerebral palsy, hearing loss. Morin et al. also showed no significant difference in language composition score, cognitive score [52]. However, a significant difference was detected on motor score (IVB group median score 81 vs laser group median score 88). The result also suggested that the chances of severe neurodevelopmental disabilities were 3.1 times higher in the IVB group when compared with laser group. The severe neurodevelopmental disabilities include (Bayley scores less than 70, need of hearing aids, bilateral blindness, and severe cerebral palsy [52].

Lien et al. measured the neurodevelopmental outcomes of infants with type 1 ROP treated by IVB or laser or IVB and laser therapy. The result showed that there was no difference between 0.625 mg IVB group and laser group. Interestingly, a significant difference was demonstrated in the IVB + laser group when compared with the laser group, with a higher incidence of psychomotor and mental impairment of infants at 24 months of age [54].

Up till now, there are no studies comparing the effect on neurodevelopmental outcomes between the different anti-VEGF in the treatment of ROP. Further studies are needed to explore the topic.

OTHER OCULAR SIDE EFFECTS

In general, less unfavorable structural outcomes (i.e., retrolental membrane obscuring the view of the posterior pole, retinal detachment involving the macula, posterior retinal fold involving the macula, or substantial temporal retinal vessel dragging causing abnormal structural features or macular ectopia) were reported in anti-VEGF therapy. In the RAINBOW study, 0.2 mg IVR had the lowest rate of unfavorable structural outcomes (one case), when compared to five cases after 0.1 mg IVR and seven cases after laser therapy [2]. The rate of unfavorable structural outcomes was only 1.43% after 0.2 mg IVR, a marked reduction in contrast to rate of 10% in the same study and rate of 9.1% reported in the ETROP study [3]. The study performed by Lepore D et al. suggested that the IVB group of patients had a significantly higher frequency of persistent macular abnormalities when compared with laser (75% vs 36.4% after 9 months of intervention, 55% vs 16 % after 4 years of intervention) ($p < 0.05$) [41, 45].

Anterior segment ischemia was reported to be a complication of laser treatment of eyes with ROP [68, 69, 85] and was reported to be a rarely encountered clinical entity by Gunay et al. [69]. For the use of anti-VEGF, a very limited number of studies had reported about the finding of anterior segment ischemia [42]. Zhang et al. has reported that no infants had developed anterior segment ischemia in 25 eyes treated with single dose 0.3 mg IVR injection [42].

Cataract and endophthalmitis were reported in two eyes with IVR therapy in the RAINBOW study [2]. In the study by Bai et al., out of 48 eyes treated with IVC, none had developed corneal and lens opacity, endophthalmitis or vitreous hemorrhage or retinal detachment [36]. Despite the low incidence of these complications, ophthalmologists should be aware of the existence of these complications and avoid intravitreal injection if the patient has any periocular infection right before the injection.

DISCUSSION

In this review, two types of treatment for ROP were discussed, that is, the conventional laser therapy and intravitreal injection of anti-VEGF. For different zone of ROP, different treatment approaches should be used. Gotz-Wieckowska et al. suggested that zone I ROP should be treated with IVR while zone II ROP should be treated with laser therapy [86]. For zone I ROP, some studies also suggested the combined administration of anti-VEGF and laser therapy at the same time [87] or using laser as the rescue therapy only when the intravitreal anti-VEGF failed [73, 88].

The superiority of IVB or IVR over laser therapy, in terms of higher treatment success and reduced recurrence, were demonstrated in studies mainly concerning zone I ROP. In contrast, the results in zone II ROP were more bipolar. The RAINBOW study showed better treatment success of IVR over laser therapy in stage 3+ ROP [2], whereas three other studies (BEAT-ROP, Karkhaneh et al., and Zhang et al.) [33, 39, 42] showed no additional benefit in efficacy with anti-VEGF over laser therapy. The studies by Karkhaneh et al. and Zhang et al. even showed that a single intravitreal anti-VEGF injection would lead to more frequent zone II ROP recurrence. Regarding the differences in the results of various studies, it is important to look at the primary outcomes measured in these studies. The RAINBOW study primarily measured treatment success including those who resolved after retreatments; the latter three studies measured the rate of recurrence of neovascularization after initial treatment. Therefore, this may imply that single dose anti-VEGF monotherapy is less effective for zone II ROP. However, the recurred ROP will mostly resolve after retreatment by additional injection as demonstrated in the RAINBOW study.

Bevacizumab and ranibizumab are the two anti-VEGF commonly used for intravitreal injection in ROP. Bevacizumab is the whole anti-VEGF antibody, whereas ranibizumab is an antibody fragment. Comparing the pharmacological properties of the two, ranibizumab has a higher binding affinity to VEGF and a shorter half-life [89, 90]. Theoretically, greater binding affinity means better treatment efficacy, while a shorter half-life implies that the drug stays in patients' body shorter with less side effects. Thus, ranibizumab is thought to be a better treatment option than bevacizumab. Nevertheless, our review showed higher recurrence rate in IVR therapy. The results were demonstrated consistently in multiple studies. However, these studies didn't offer any explanation for the superiority of IVB over IVR. Further studies need to be done on the retinal pharmacodynamics of anti-VEGF to offer an explanation on this interesting phenomenon. Although bevacizumab being an off label drug, future head-to-head comparative studies will likely focus on the newer drugs like aflibercept and conbercept against ranibizumab.

In view of side effects, anti-VEGF was found to have a higher chance of developing avascularisation when compared with laser therapy. Studies suggested that lowering the dosage of anti-VEGF administered after the gestational age of 32 weeks can lower the chances of developing persistent peripheral avascularisation [82, 91]. On the contrary, in terms of myopia, eyes treated with anti-VEGF therapy were found to have less myopia than eyes treated with laser therapy [38, 47, 48, 50], which include a randomized control trial and three retrospective studies. Although two studies had opposite outcomes, the two of them were limited by their study methods [49, 53]. Kuo HK et al. was a retrospective study while Gunay et al. was limited by its short duration of followup, and the refractive error of the infants were measured at 1-year adjusted age. It should be concluded that eyes treated with anti-VEGF therapy had a better myopia outcome when compared with laser therapy as the results of Geloneck et al. is more convincing, given that it is a randomized control trial. However, up till now, there are no clinical studies comparing different types of anti-VEGF in terms of myopia. Further studies should be conducted to explore the differences between different types of anti-VEGF therapy. For the systemic absorption, IVR is a better option as IVR has a shorter half-life than IVB. For neurodevelopmental outcomes, results of the studies varied, and most were limited by the short duration of follow up. Further studies are needed to investigate the long-term neurodevelopmental outcome in infants treated with anti-VEGF.

From the current evidence, it is found that anti-VEGF would be a more preferred choice of therapy in managing zone I ROP. On the other hand, laser therapy is still considered a better choice in zone II ROP given the inconclusive evidence of anti-VEGF use in zone II disease. Regarding the choice of anti-VEGF, our review discusses four agents, namely bevacizumab, ranibizumab, aflibercept, and conbercept. The efficacy of the former two agents (bevacizumab and ranibizumab) was evaluated in multiple prospective studies or RCTs and should be the mainstay option for ROP treatment. Despite the emergence of new studies on the latter two agents (aflibercept and conbercept), current publications on IVA and IVC were only retrospective series and await major trials to support their use.

Recurrence was another concern in ROP treatment, and there is yet to be an agreement on which therapy (an extra anti-VEGF injection or switch to laser therapy) should be used to treat the recurrence after anti-VEGF therapy. We propose that the choice of treatment for recurrence should depend on the initial agent used. If the initial agent is IVR, we would suggest to use an additional IVR injection to treat the recurrence in view of the relatively short half-life of IVR. However, if IVB is used in the initial treatment, laser therapy would be a more suitable option as the repeated use of IVB may expose the patients to more systemic side effects given the longer half-life of the agent.

CONCLUSION

This review analyzed 40 articles concerning the application of anti-VEGF for the treatment of ROP, with 15 of them being RCTs. Although both anti-VEGF and laser ablative therapy are accepted forms of treatment for ROP, it is advised that intravitreal anti-VEGF be used as the first-line treatment for zone I ROP while laser therapy should be the mainstay in zone II ROP. Based on our review, bevacizumab shows lower systemic absorption and may be the preferred anti-VEGF for ROP; however, it is off label for ophthalmic use and further studies are needed to verify the overall safety and long-term effects of anti-VEGF in ROP patients. The practice of anti-VEGF usage in adults for various retinal diseases has been extensively studied; however, basic guidelines in treating ROP are still lacking. As the management of premature infants improve, the severity and frequency of ROP are reducing; however, it is beneficial to have more data on the role of Anti-VEGF. Future studies may include direct head-to-head comparison of the ROP regression efficacy and stability of different anti-VEGFs, the safety and long-term effects of various dosages in the eyes of premature infants, as well as the optimal anti-VEGF dosages.

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AUTHOR CONTRIBUTIONS

SCC and PYL were responsible for determining the review search parameters, reviewing, screening, and curating the selected papers, updating the reference list, creating the table, extracting the data, and drafting and editing the manuscript. In addition to the previous responsibilities, NSKF was also responsible for designing the review and finalization of the report. WCL provided feedback of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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