• Clinical Research •

Efficacy evaluation of intravitreal ranibizumab therapy for three types of retinopathy of prematurity

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Abstract

● **AIM:** To evaluate efficacy of intravitreal ranibizumab (IVR) therapy for aggressive posterior retinopathy of prematurity (ROP), threshold ROP disease and type 1 pre-threshold ROP.

● **METHODS:** A retrospective analysis was performed on 40 patients (76 eyes) who had IVR as the primary treatment for ROP from April 2017 to January 2018. According to disease pathogenic features, the 76 eyes were divided into three groups: aggressive posterior ROP (AP-ROP) group (16 eyes), threshold ROP group (28 eyes) and type 1 pre-threshold ROP group (32 eyes). The characteristics of patients and lesions situation before the first intravitreal injection, and posttreatment fundus outcomes determined by wide-angle RetCam fundus imaging were recorded.

● **RESULTS:** The birth weight and postmenstrual age of first IVR treatment in AP-ROP, threshold ROP, and type 1 pre-threshold ROP groups were significant difference (1087.50±246.78, 1103.75±168.30, 1257.03±210.82 g, P=0.005; 34.50±1.46, 36.89±2.97, 36.50±2.36wk, P=0.008), while the gestational age was not difference (28.00±2.00, 28.54±1.90, 28.59±1.43wk, P=0.510). The retina hemorrhage ratio (with/without: 14/2, 8/20, 5/27), iris neovascularization or vascular engorgement ratio (with/without: 12/4, 11/17, 6/26), and the zone I (inside/outside: 16/0, 2/26, 5/27) in AP-ROP, threshold ROP, and type 1 pre-threshold ROP group were difference significantly (all P<0.05). The regression rates were 37.5%, 92.86%, and 100%, and the recurrence rates were 62.5%, 7.14%, and 0 in AP-ROP, threshold ROP, and type 1 pre-threshold ROP group, respectively (both P<0.05). The recurrence eyes were cured by secondary IVR or retinal laser photocoagulation.

● **CONCLUSION:** IVR is an effective treatment for all types of ROP. The regression of AP-ROP is significantly lower than type 1 pre-threshold and threshold disease. Birth weight, retinal hemorrhage, iris neovascularization or vascular engorgement and lesions located in zone I may be associated with AP-ROP recurrence and retreatment, which should be noted in follow-up.

● **KEYWORDS:** retinopathy of prematurity; ranibizumab; intravitreal injection

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INTRODUCTION

Retinopathy of prematurity (ROP) is a childhood blindness disease that is one of the most extensively visual impairment reasons after premature delivery. It relates to the abnormal retinal vascular development in vascular and avascular peripheral retinal boundary[1]. According to the Chinese Guidelines for the Screening of Retinopathy of Premature Infants (2014)[2] and with reference to disease pathogenic characteristics, it is not difficult to find that ROP can be mainly divided into threshold diseases, pre-threshold diseases (type 1 and type 2) and acute progressive posterior pole ROP. The guidelines clearly suggest that intervention should be carried out within 72h as soon as possible when diagnosis of threshold disease or type 1 pre-threshold disease. The acute type of posterior pole ROP usually occurs in the posterior pole most commonly in zone I but may also sometime in zone II, which is progressing rapidly, often accumulated in four quadrants and lesions can quickly and directly progress to stage 4 or 5 but no classic generally ROP features. As a kind of uncommon, rapidly progressing, severe ROP emergency, aggressive posterior-ROP (AP-ROP) need immediate treatment once diagnosis[3].

In the past, cryotherapy and retinal laser photocoagulation were the major treatments of ROP to seal the avascular zone retina. However, due to the involvement of all layers in ocular (conjunctiva, sclera, choroid and retina), which induced severe

postoperative reactions and more complications, cryotherapy was gradually replaced by retinal laser photocoagulation that had the advantages of accurate positioning and less postoperative complications[4]. In recent years, lots of studies have shown that vascular endothelial growth factor (VEGF) plays an important role in the development of ROP and anti-VEGF therapy has been a good choice in ROP treatment[5-6]. Intravitreal ranibizumab (IVR) in ROP could be the 1-month duration (half-life of ranibizumab is about 4.75d) of action in preterm infants' vitreous cavity and the systemic half-life of ranibizumab (6h) to avoid the severe systemic effects and induce effective results in ocular[7-8]. Therefore, in this study we chose intravitreal injection of anti-VEGF drug ranibizumab as the treatment of AP-ROP, threshold ROP and type 1 pre-threshold ROP, evaluated its efficacy and investigated the characteristics among three ROP subtypes. However, to our knowledge, ranibizumab has not been directly compared in the treatment of ROP subtypes. In this retrospective study, we focused on the effect and treatment outcomes evaluations in three types of ROP with ranibizumab, namely disease regression, recurrence rates and other characteristics, including gender, gestational age (GA), postmenstrual age (PMA), birth weight (BW), retina hemorrhage, iris neovascularization or vascular engorgement (INVE), and lesion locations.

SUBJECTS AND METHODS

Ethical Approval This study was approved by Ethics Committee of Eye Hospital Affiliated to Nanchang University and carried out according to the principles of the Helsinki Declaration in 1995 (revised in Edinburgh in 2000) and all guardians of children knew and signed informed consent.

General Information A retrospective analysis was made on 40 ROP patients (76 eyes) who received IVR as a first treatment in the Affiliated Eye Hospital of Nanchang University from April 2017 to January 2018. The 76 eyes were divided into three groups: AP-ROP group (16 eyes), threshold ROP group (28 eyes) and type 1 pre-threshold ROP group (32 eyes). According to the Guidelines for Screening Retinopathy of Prematurity in China (2014), the inclusion criteria included: 1) threshold ROP: stage 3+ in zone II or I that adjacent lesions lasting for at least 5h or accumulated for up to 8h. 2) type 1 pre-threshold ROP: ROP lesions were obviously present but not reached threshold ROP such as any stage lesion with plus disease in zone I, stage 3 lesion without plus disease in zone I, and stage 2+ or stage 3+ lesion in zone II. 3) AP-ROP: it usually located at zone I and posterior pole, progresses rapidly and often involves four quadrants. The ridge is not obvious. The vascular shunting can occur not only at the junction between vascular and avascular retina, but also within retina. It suggested that threshold ROP, type 1 pre-threshold ROP and AP-ROP are recommended as treatment indications. In this study, the general medical information such as the gender, GA, PMA of first IVR treatment, BW, retina hemorrhage, INVE, and lesion locations were reviewed. All patients received IVR whose regression and recurrence rates of ROP were in follow-up time postoperatively.

Intravitreal Ranibizumab All patients performed IVR under topical anesthesia in sterile laminar flow operating room. Preoperative rinse conjunctival sac twice using polyvidone iodine solution. Ranibizumab 0.25 mg/0.025 mL was injected into the vitreous cavity using a 29-gauge needle (insulin syringe, 1 mL) through the pars plicata 1.0 mm behind limbus cornea parallel to the visual axis. Tobramycin dexamethasone eye ointment was used at the end of operation.

Postoperative Follow-up and Evaluation The wide-angle RetCam III (Clarity Medical Systems, Pleasanton, USA) was used to record ocular examinations in follow-up. All fundus images were independently diagnosed by two of the authors (Zou Q and Liu QP). If there was a discrepancy, the images were reviewed again with another senior ROP specialist present to render a consensus. Examinations were performed at 1, 2wk, 1, 2, 3, 6, 9, and 12mo postoperatively, recording lesion regression and retina vascular development. And then all patients were followed every 3mo. The examinations were repeated from the beginning if recurrence appear. Efficacy evaluation standard: plus disease and ridge are complete regressed, no neovascularization and new ridge appear, the peripheral retina vessel (Zone III) is reached and keep stable condition, they were identified as cure besides need to retreatment. Disease progress and aggravate indicate fibrous proliferation membrane continuous stretch retina, neovascularization or ridge appear again even reach ROP stage 4.

Statistical Analysis Statistical SPSS 20.0 (IBM SPSS Statistics for mac, version 26.0, Armonk, NY IBM Corp, USA) was used to perform all statistical analyses. One-way ANOVA analysis and Bonferroni test was used for continuous variables. Fisher's exact test was used for categorical variables. $P<0.05$ was considered statistical significance.

RESULTS

The characteristics of patients in the three groups were shown in Table 1. There were more eyes with retina hemorrhage and INVE ($P<0.001$) and more lesions located at zone I ($P<0.001$) in AP-ROP group. They have lower PMA ($P=0.008$) and BW ($P=0.005$).

There are 10 eyes in AP-ROP group, 2 eyes in threshold ROP group were recurrence after the first treatment with IVR ($P<0.001$; Table 2). Recurrences occurred in bilateral eyes of six patients (5 females and 1 male) and all eyes appeared retina hemorrhage, the lesions locating at zone I, and only one case (two eyes) in AP-ROP group without INVE. Six of 41 infants (14.6%) developed recurrence within 8-12wk after the first

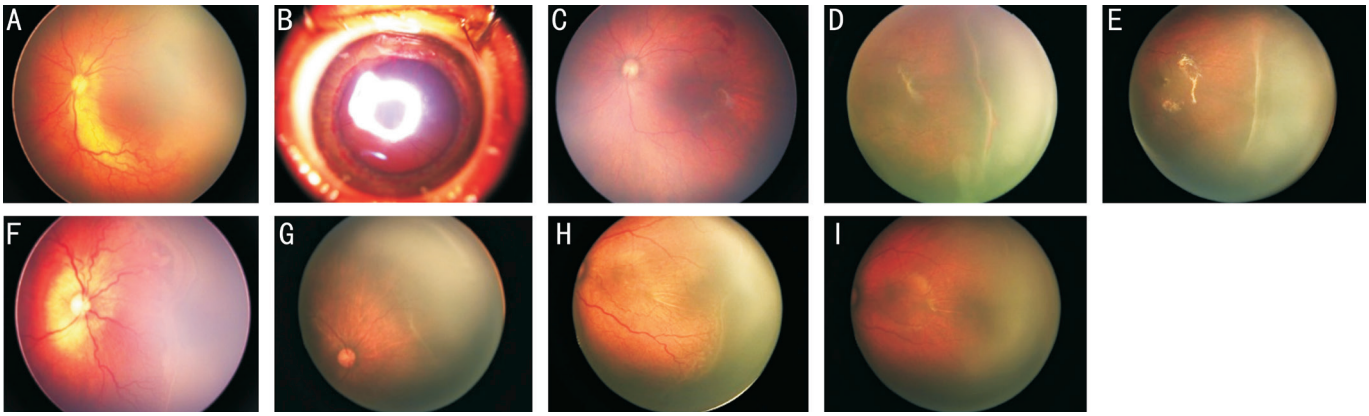

Figure 1 Fundus photos of AP-ROP group (A-E), threshold ROP group (F-G) and type 1 pre-threshold ROP group (H-I) A: Before the first intravitreal injection of AP-ROP with retinal hemorrhage and massive arteriovenous circulation; B: Iris neovascularization or vascular engorgement; C: 1mo after the first intravitreal injection of AP-ROP with retinal hemorrhage absorbed; D: 2mo after the first intravitreal injection of AP-ROP with high ridges in another zone; E: 3.5mo after the second vitreous injection of AP-ROP with scar leave; F: Before the first injection of threshold ROP with the high and wide ridge and extraretinal fibrovascular proliferation; G: 3mo after the first vitreous injection of threshold ROP with scar like membrane adhesion to the retina and the vessel developing to Zone III of peripheral retina; H: Before the first vitreous injection of type 1 pre-threshold disease with the obvious ridge; I: 1wk after the first vitreous injection of type 1 pre-threshold disease with ridge disappeared. AP-ROP: Aggressive posterior retinopathy of prematurity; ROP: Retinopathy of prematurity.

Table 1 Characteristics of patients in the three types of ROP

Parameters	AP-ROP group	Threshold ROP group	Type 1 pre-threshold ROP group	*P*
Eyes	16	28	32	-
Male/female	6/10	17/11	23/9	0.078
Retina hemorrhage	14	8	5	<0.001
INVE	12	11	6	<0.001
Zone I	16	2	5	<0.001
GA (wk)	28.00±2.00	28.54±1.90	28.59±1.43	0.510
PMA (wk)	34.50±1.46	36.89±2.97	36.50±2.36	0.008
BW (g)	1087.50±246.78	1103.75±168.30	1257.03±210.82	0.005

AP-ROP: Aggressive posterior retinopathy of prematurity; ROP: Retinopathy of prematurity; INVE: Iris neovascularization or vascular engorgement; GA: Gestational age; PMA: Postmenstrual age; BW: Birth weight.

Table 2 Outcome of three types ROP after treatment *n* (%)

Groups	Total	Regression	Recurrence
AP-ROP group	16	6 (37.5)	10 (62.5)
Threshold ROP group	28	26 (92.86)	2 (7.14)
Type 1 pre-threshold ROP group	32	32 (100)	0

AP-ROP: Aggressive posterior retinopathy of prematurity; ROP: Retinopathy of prematurity.

injection. The mean recurrence period was 10±1.53wk and the PMA was from 41 to 48wk. Recurrent cases were treated by repeat IVR or retinal laser photocoagulation. Until final follow-up, only one eye in AP-ROP group was blind because of delay treatment of recurrence.

In AP-ROP group, the retinal vascular tortuosity, retina hemorrhage and INVE were obviously reduced in one week. After two months, the peripheral vascular developed in 7 eyes but plus disease increased in the other 9 eyes which were progress and aggravate with wide and high ridges, retinal venous dilatation and arteriolar tortuosity in the posterior retinal, reappearance of retinal neovascularization or hemorrhage. In follow-up, 8 recurrent eyes were cured in which 6 eyes performed with second IVR and 2 eyes with laser photocoagulation. In threshold ROP group, tortuosity of retinal blood vessels of 2 eyes increased after 3mo, and new wider and higher ridges emerge, which were treated with the second IVR. In type 1 pre-threshold group, there were no obvious ridges appear and most peripheral retina vessel (Zone III) was achieved after 2mo. No recurrence of ROP and complete vascularization of the retina (Figure 1).

DISCUSSION

Anti-VEGF treatment was effective for ROP that had been reported in recent studies[9-12]. Intravitreal injections of anti-VEGF agents may have advantages over retinal laser photocoagulation, including rapid action as well as safety

outcomes. Comparing with the side effects of extensive retinal laser photocoagulation like peripheral field loss and high myopia[13-14], it has been increasingly employed in curing ROP ever since ranibizumab received approval for ROP in the EU from the European Commission (European Medicines Agency)[15]. However, its efficacy especially at various types of ROP and potential relating characteristics in ocular need to be further evaluated and established. In our study, IVR was an effective treatment for ROP, yet the regression of AP-ROP was significantly lower than type 1 pre-threshold and threshold disease. Retinal hemorrhage, INVE and lesions insides zone I may be related with AP-ROP recurrence and retreatment, which should be paid attention to and follow-up examination closely.

After IVR, the regression rate in our study was 37.5%, 92.86%, and 100%, and the recurrence rate was 62.5%, 6.90% and 0. We found that the cure rate in AP-ROP group was significantly lower than threshold group and type 1 pre-threshold group, while the recurrence rate was significantly higher than threshold group and type 1 pre-threshold group. The recurrence eyes would be treated by secondary IVR or retinal laser photocoagulation. Similar situation was in accordance with other studies[9,16-18]. Tong *et al*[9] showed that following initial treatment with IVR, only 43 (26.9%) of the 160 eyes diagnosed with AP-ROP regressed after one injection, and 82 eyes (51.3%) retreated with good anatomic outcomes, however, the addition progressed to retinal detachment. Chen *et al*[16] reported that none of the eyes had recurrence after an initial good response in type 1 ROP who had intravitreal injections of either bevacizumab or ranibizumab as the primary treatment. Sukgen and Koçluk[17] noticed that seven of thirteen patients with AP-ROP reactivate after the first IVR and they should be retreated according to ETROP criteria, in which only one developed threshold disease without retreatment. Autrata *et al*[18] showed that 90.2% threshold ROP in zone I and posterior zone II attain to favorable anatomic outcome and stable regression of ROP after intravitreal pegaptanib or bevacizumab combining laser in treatment.

Comparing the three groups, low BW may contribute to ROP recurrence in our study, which is in keeping with Mintz-Hittner *et al*'s[19] research that lower BW infants should be more vigilant, examination be more possible and longer. There was a significant difference in BW comparing type 1 pre-threshold with threshold ROP group, and AP-ROP with type 1 pre-threshold ROP, yet no significance between AP-ROP and threshold ROP group, which indicates that the average weight of patients in AP-ROP and threshold ROP were significantly lighter than type 1 pre-threshold patients, and AP-ROP group was not significantly different from threshold ROP. ROP pathogenesis is multifactorial and known to be associated with lower GA, BW and further uncontrolled use of oxygen therapy. Most studies[20-21] have showed that lower GA and BW were independently associated with the occurrence or severity of ROP. Walz *et al*[20] reported infants born at lower GA developed more severe stages AP-ROP, stage 4 and zone I disease. Ahn *et al*[21] reported that comparing with infants with non AP-ROP, infants with AP-ROP exhibited significantly lower GA and BW. A recent report showed that in North America premature infants were significant difference in BW (617 g) and GA (24.3wk) and reached peak severity at postmenstrual age (34.7wk) between infants with AP-ROP and without AP-ROP. AP-ROP infants tended to occur in younger premature babies and presented earlier, more aggressively than other severe treatment-requiring ROP disease[22]. The GA and BW in severe ROP were much higher than those in developed countries, which were approximately 25wk and 750 g[23]. It may be associated with the wider screening criteria being used in China that more older infants included.

Although no significant difference of GA, this study showed that AP-ROP occurred lower PMA, which was different from type 1 pre-threshold ROP and threshold ROP group (P=0.008, 0.029). The reason for earlier treatment than other groups may be associated with the pathophysiology of AP-ROP group. When the disease develops, the delayed growth of blood vessels and capillaries were converted to abnormal growth of extraretinal blood vessels because oxygen-induced vascular and capillary delay can induce excessive expression of VEGF, resulting in the formation of extraretinal vessels. No matter what subtype of ROP, elevating VEGF levels can cause ROP attack in a specific period. We would not perform IVR until the ROP develop to the threshold disease and take action in pre-threshold, which would bring better and more ideal outcomes. At the same time the infusion of anti-VEGF drugs, the normal blood vessels development was originally slow[17]. However, complete understanding which role earlier anti-VEGF treatment plays in the progression patterns of ROP and what role it plays was not clear and these required further investigations. What cannot be blamed was that systemic pregnancy file management, image analysis and other technical developments contributed to a deeper awareness and alertness of disease, which in reward mutual progress and achieve win-win.

There was no significant gender difference among groups in our study, but male more than female in threshold ROP and type 1 pre-threshold ROP group, which is contrary to the outcomes in the USA[24] yet female constitute in AP-ROP group similarly. One important factor leading to this invert maybe regional differences like more male employed in an examination, and clear identity in classical type rather critical boundaries in AP-ROP. The hemorrhage and INVE rate

among three groups were significant difference. In our study, comparing with type 1 pre-threshold ROP and threshold ROP group, AP-ROP group most happened and was more likely to have retinal hemorrhage required additional treatment, although least patients diagnosed as AP-ROP, which was consistent with the results of previous studies[9,25-26]. Fukushima *et al*'s[26] research and e-ROP study reported that progression of AP-ROP was more homogeneous than type 1 ROP appearing in clinical. Blot retinal hemorrhage was a strongly predictive factor of ROP that need treatment, which maybe a risk factor of developing severe ROP. Tong *et al*[9] showed that 83 AP-ROP preterm infants (160 eyes) primarily treated with IVR and retinal hemorrhage was significantly related with recurrence and retreatment in non-retinal detachment AP-ROP, which means retinal hemorrhage maybe an independent risk factor for AP-ROP recurrence. In the progression of ROP, the avascular area of the retina induces VEGF production in the next VEGF induces endothelial cell proliferation, a key trigger contributing to uncontrolled retinal neovascularization[27], thus IVR was more effective than retinal laser photocoagulation, which can rapidly reduce the level of VEGF in the vitreous cavity, yet timely and appropriate treatment are critical[28-29]. Although there was not significant difference in the GA, we found that the PMA in AP-ROP was more younger than the other two groups, which means the PMA in AP-ROP maybe earlier acquired treatment because of severe and aggressive ROP pathological progression, which is similar to the report of Bellsmith *et al*[22]. There is no doubt that VEGF signal transduction makes an effort in arteriolar tortuosity just like human plus disease and inhibiting it would achieve for orderly retinal vascularization[30-31]. In our study, AP-ROP almost appeared INVE, which may be due to higher VEGF level compared with other two groups. Higher level of VEGF may cause more retina hemorrhage and neovascularization so that more possible need to ROP retreatment, which was consistent with previous studies[9,32-33]. The ROP severity not only preferred to occur lower BW and GA, but also directly related to the presence of hemorrhage[32]. Retreatment were required in many retinal hemorrhage infants following initial treatment with IVR[9]. Recurrence of ROP was associated with persistence of anterior vascularization after anti-VEGF therapy progressing extraretinal fibrovascular proliferation. These were found to be tended to ROP recurrence in type 1 ROP with extensive retinal neovascularization after IVR treatment at earlier PMA as well as recurrence risk period was from 2.5 to 12.0wk after first injection with its risk peak at 8wk[33]. Our study showed that whether INVE occurred in ROP infants, a later sign of plus disease, it may be an increasing trend consistent with ROP recurrence and severe. Both eyes of the six recurrent cases all appeared retina hemorrhage and INVE except only one case without INVE. The 6 of 41 infants (14.63%) developed recurrence, whose mean time receiving second treatment was 10wk in this study occurring from 8.0 to 12.0wk after first IVR. It is similar to recurrence time in previous reporting[34-37] at 4 to 8wk or PMA about at 41 to 42wk and has to do with clearance period and half-life of ranibizumab, suggesting that this time rage was particularly important in follow-up examinations. ROP infants should be closely monitored to ensure timely retreatment when needed and knowledge of the recurrence period enables targeted clinical management[19,38].

In addition, one of the reasons for the high relapse of AP-ROP in our study may be that the positions of AP-ROP patients were more serious, and the fundus diseases were located in the more posterior area (zone I). The location of ROP disease in different zones relates with different risk levels, more inner zone and more risk. If without intervention, ROP in zone I would rapidly develop to retinal detachment and correlates with poorer outcome[39-41]. In Tahija *et al*'s[42] study containing AP-ROP almost in zone I, approximately 55% of the treated eyes remained avascular areas, which was consistent with the situation in our study. Zone II responded well to cryopexy or laser therapy, a particular area with ROP development which has unique clinical characteristics like popcorn and double track signs hampering angiogenesis[43]. The RAINBOW trial[38] included ROP in all zones and their results reported that the efficacy of ranibizumab was similar (or better) to laser in zone I and zone II, while the success rate of zone II was higher than that of zone I, generally speaking, zone I ROP would get a good outcome if screening is done early and timely, adequate intervention attained and frequent follow-up until regression.

There were several limitations in our study. First, all the identified characteristics could not be included. ROP is a multistage disease different phase with numerous features. Therefore, a selection bias of risk factors was possible during the selection of potential characteristics. Second, this study had no matched laser-treated group because of the anti-VEGF therapy had been suggested to be the primary choice. Undoubtedly, the fluorescein angiography to diagnosis or observation would be helpful. The total number was small, more samples are needed for further confirmation. This study reported the observation of short-term outcomes after IVR and it was a retrospective study. The long-term safety cannot be acquired in current study. The appropriate time of treatment is still confused and follow-up period is required.

In summary, IVR was a very effective treatment for ROP subtypes, however about half AP-ROP need the second treatment. Rapid identification was very important for recurrence. We hope that the report will enable clinicians to be advantageous to the use of IVR and get more information

about patients after relapse: a lower recurrence rate (14.6% infants namely 15.79% eyes in this study, 62.5% in AP-ROP, 7.14% in threshold ROP and 0 in type 1 pre-threshold ROP); Some characteristics in three types of ROP with high risk of recurrence infants may be identified (AP-ROP, lower BW, INVE, retinal hemorrhage, lesions located in zone I); The risk period for recurrence was limited in our study (about 8 to 12wk after initial IVR treatment), so that ROP infants should be closely monitored at critical periods until exceed the crucial time and ensured timely retreatment; and with the progress of ROP in premature infants, three specific signs (INVE and retinal hemorrhage, lesions located in zone I) needed to be reexamined more carefully and more frequently possibly.

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REFERENCES

1 Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Quintos M, Tung B, Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. *Pediatrics* 2005;116(1):15-23.

2 Ophthalmology Group Chinese Medical Association Ophthalmology Branch. Guidelines for Screening Retinopathy of Premature Infants in China (2014). *Chinese Journal of Ophthalmology* 2014;50(12):933-935.

3 International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. *Arch Ophthalmol* 2005;123(7):991-999.

4 Autrata R, Holousová M, Rehůrek J. Cryotherapy and photocoagulation in the treatment of retinopathy of prematurity. *Cesk Slov Oftalmol* 2002;58(1):30-35.

5 Eldweik L, Mantagos IS. Role of VEGF inhibition in the treatment of retinopathy of prematurity. *Semin Ophthalmol* 2016;31(1-2):163-168.

6 Kong L, Mintz-Hittner HA, Penland RL, Kretzer FL, Chévez-Barrios P. Intravitreous bevacizumab as anti-vascular endothelial growth factor therapy for retinopathy of prematurity: a morphologic study. *Arch Ophthalmol* 2008;126(8):1161-1163.

7 Vedantham V. Intravitreal aflibercept injection in Indian eyes with retinopathy of prematurity. *Indian J Ophthalmol* 2019;67(6):884-888.

8 Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina* 2012;32(3):434-457.

9 Tong Q, Yin H, Zhao M, Li X, Yu W. Outcomes and prognostic factors for aggressive posterior retinopathy of prematurity following initial treatment with intravitreal ranibizumab. *BMC Ophthalmol* 2018;18(1):150.

10 Castellanos MA, Schwartz S, García-Aguirre G, Quiroz-Mercado H. Short-term outcome after intravitreal ranibizumab injections for the treatment of retinopathy of prematurity. *Br J Ophthalmol* 2012;97:816-819.

11 Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahashi-Shima C, Kusaka S. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. *Am J Ophthalmol* 2012;153(2):327-333.e1.

12 Jin E, Yin H, Li X, Zhao M. Short-term outcomes after intravitreal injections of conbercept versus ranibizumab for the treatment of retinopathy of prematurity. *Retina* 2018;38(8):1595-1604.

13 Mori Y, Arima M, Ueda E, Fujiwara K, Seki E, Nakama T, Tsukamoto S, Akiyama M, Sonoda KH. Risk factors for myopia at 1-year corrected age following laser photocoagulation for retinopathy of prematurity. *Eye* (*Lond*) 2021;35(10):2820-2825.

14 Li Z, Zhang Y, Liao Y, Zeng R, Zeng P, Lan Y. Comparison of efficacy between anti-vascular endothelial growth factor (VEGF) and laser treatment in Type-1 and threshold retinopathy of prematurity (ROP). *BMC Ophthalmol* 2018;18(1):19.

15 Patel JR, Ranjan SS, Wasserman BN. Antivascular endothelial growth factor in the treatment of retinopathy of prematurity. *Curr Opin Ophthalmol* 2016;27(5):387-392.

16 Chen SN, Lian I, Hwang YC, Chen YH, Chang YC, Lee KH, Chuang CC, Wu WC. Intravitreal anti-vascular endothelial growth factor treatment for retinopathy of prematurity. *Retina* 2015;35(4):667-674.

17 Sukgen EA, Koçluk Y. The vascularization process after intravitreal ranibizumab injections for aggressive posterior retinopathy of prematurity. *Arq Bras Oftalmol* 2017;80(1):30-34.

18 Autrata R, Senková K, Holousová M, Krejcírová I, Dolezel Z, Borek I. Effects of intravitreal pegaptanib or bevacizumab and laser in treatment of threshold retinopathy of prematurity in zone I and posterior zone II—four years results. *Cesk Slov Oftalmol* 2012;68(1):29-36.

19 Mintz-Hittner HA, Geloneck MM, Chuang AZ. Clinical management of recurrent retinopathy of prematurity after intravitreal bevacizumab monotherapy. *Ophthalmology* 2016;123(9):1845-1855.

20 Walz JM, Bemme S, Pielen A, Aisenbrey S, Breuß H, Alex AF, Wagenfeld L, Schiedel S, Krohne TU, Stahl A; Retina.net ROP Registry. The German ROP Registry: data from 90 infants treated for retinopathy of prematurity. *Acta Ophthalmol* 2016;94(8):e744-e752.

21 Ahn YJ, Hong KE, Yum HR, Lee JH, Kim KS, Youn YA, Park SH. Characteristic clinical features associated with aggressive posterior retinopathy of prematurity. *Eye* (*Lond*) 2017;31(6):924-930.

22 Bellsmith KN, Brown J, Kim SJ, Goldstein IH, Coyner A, Ostmo S, Gupta K, Chan RVP, Kalpathy-Cramer J, Chiang MF, Campbell JP. Aggressive posterior retinopathy of prematurity: clinical and quantitative imaging features in a large North American cohort. *Ophthalmology* 2020;127(8):1105-1112.

23 Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P, Zin A, International NO-ROP Group. Characteristics of infants with severe

retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. *Pediatrics* 2005;115(5):e518-e525.

24 Ludwig CA, Chen TA, Hernandez-Boussard T, Moshfeghi AA, Moshfeghi DM. The epidemiology of retinopathy of prematurity in the United States. *Ophthalmic Surg Lasers Imaging Retina* 2017;48(7):553-562.

25 Ying GS, VanderVeen D, Daniel E, Quinn GE, Baumritter A, Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity Cooperative Group. Risk score for predicting treatment-requiring retinopathy of prematurity (ROP) in the telemedicine approaches to evaluating acute-phase ROP study. *Ophthalmology* 2016;123(10):2176-2182.

26 Fukushima Y, Kawasaki R, Sakaguchi H, Winegarner A, Ineyama H, Imanishi Y, Hirano S, Wada K, Hatsukawa Y, Nishida K. Characterization of the progression pattern in retinopathy of prematurity subtypes. *Ophthalmol Retina* 2020;4(3):231-237.

27 Bressler SB. Introduction: Understanding the role of angiogenesis and antiangiogenic agents in age-related macular degeneration. *Ophthalmology* 2009;116(10 Suppl):S1-S7.

28 Smith LE. Through the eyes of a child: understanding retinopathy through ROP the Friedenwald lecture. *Invest Ophthalmol Vis Sci* 2008;49(12):5177-5182.

29 Zhou Y, Jiang Y, Bai Y, Wen J, Chen L. Vascular endothelial growth factor plasma levels before and after treatment of retinopathy of prematurity with ranibizumab. *Graefes Arch Clin Exp Ophthalmol* 2016;254(1):31-36.

30 Hartnett ME. Pathophysiology and mechanisms of severe retinopathy of prematurity. *Ophthalmology* 2015;122(1):200-210.

31 Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011;364(7):603-615.

32 Daniel E, Ying GS, Siatkowski RM, Pan W, Smith E, Quinn GE; e-ROP Cooperative Group. Intraocular hemorrhages and retinopathy of prematurity in the telemedicine approaches to evaluating acute-phase retinopathy of prematurity (e-ROP) study. *Ophthalmology* 2017;124(3):374-381.

33 Lyu J, Zhang Q, Chen CL, Xu Y, Ji XD, Li JK, Huang QJ, Zhao PQ. Recurrence of retinopathy of prematurity after intravitreal ranibizumab monotherapy: timing and risk factors. *Invest Ophthalmol Vis Sci* 2017;58(3):1719.

34 Chan JJT, Lam CPS, Kwok MKM, Wong RLM, Lee GKY, Lau WWY, Yam JCS. Risk of recurrence of retinopathy of prematurity after initial intravitreal ranibizumab therapy. *Sci Rep* 2016;6:27082.

35 Feng J, Qian J, Jiang Y, Zhao M, Liang J, Yin H, Chen Y, Yu W, Li X. Efficacy of primary intravitreal ranibizumab for retinopathy of prematurity in China. *Ophthalmology* 2017;124(3):408-409.

36 Huang Q, Zhang Q, Fei P, Xu Y, Lyu J, Ji X, Peng J, Li YA, Zhao P. Ranibizumab injection as primary treatment in patients with retinopathy of prematurity: anatomic outcomes and influencing factors. *Ophthalmology* 2017;124(8):1156-1164.

37 Cheng Y, Zhu X, Linghu D, Liang J. Comparison of the effectiveness of conbercept and ranibizumab treatment for retinopathy of prematurity. *Acta Ophthalmol* 2020;98(8):e1004-e1008.

38 Stahl A, Lepore D, Fielder A, Fleck B, Reynolds JD, Chiang MF, Li J, Liew M, Maier R, Zhu Q, Marlow N. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet* 2019;394(10208):1551-1559.

39 Katoch D, Dogra MR, Aggarwal K, Sanghi G, Samanta R, Handa S, Dogra M. Posterior zone I retinopathy of prematurity: spectrum of disease and outcome after laser treatment. *Can J Ophthalmol* 2019;54(1):87-93.

40 Sun Y, Smith LEH. Retinal vasculature in development and diseases. *Annu Rev Vis Sci* 2018;4:101-122.

41 Selvam S, Kumar T, Fruttiger M. Retinal vasculature development in health and disease. *Prog Retin Eye Res* 2018;63:1-19.

42 Tahija SG, Hersetyati R, Lam GC, Kusaka S, McMenamin PG. Fluorescein angiographic observations of peripheral retinal vessel growth in infants after intravitreal injection of bevacizumab as sole therapy for zone I and posterior zone II retinopathy of prematurity. *Br J Ophthalmol* 2014;98(4):507-512.

43 Ni YQ, Xu SS, Zhang T, Huang X. Clinical features and changes of disease spectrum of zone II retinopathy of prematurity: a 10-year review. *Int J Ophthalmol* 2020;13(11):1753-1757.