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Vascularization of intravitreal injection of Conbercept in the treatment of retinopathy of prematurity

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玻璃体内注射康柏西普治疗早产儿视网膜病变的血管化过程

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摘要

目的:评价玻璃体内注射康柏西普在治疗Ⅰ型(阈值期和阈值前期)和A-ROP(急进性ROP)的早产儿视网膜病变(ROP)的一系列病例中引起的视网膜血管化过程。

方法:回顾性研究 2017-07/2020-03 在厦门市儿童医院眼科通过玻璃体腔注射康柏西普(IVC)治疗的 ROP 患者 34 例 67 眼。再活化是指急性期特征的复发,发生在疾病的任何阶段,无论是否存在其他疾病。

结果:患儿 34 例的平均胎龄为 28.82±2.32wk。平均出生体质量为 1155.18±398.22g。19 例 37 眼的病变区域为Ⅰ区。10 例 20 眼的病变位于Ⅱ区,5 例 10 眼的病变位于Ⅱ区后部。一次 IVC 治疗的 ROP 患儿疾病控制总有效率为 73.1%(49/67),且Ⅱ区血管化均完成。患者在Ⅲ区的血管化完成率出现差异。在接受过一次治疗且未再复发的患者中,Ⅰ型 ROP 血管化时间平均为 9.11±2.49wk,A-ROP为13.40±4.04wk。A-ROP 的血管化完成时间明显比Ⅰ型 ROP 的时间长,且结果有统计学差异。

结论:IVC 治疗后的病变为Ⅱ区的患儿均具有较高的血管完成率。

关键词:康柏西普;早产儿视网膜病变;血管化

Abstract

• AIM: To evaluate retinal vascularization caused by the intravitreal injection of Conbercept in the treatment of a series of retinopathy of prematurity (ROP) cases in Type Ⅰ (threshold and pre-threshold period) and aggressive ROP (A-ROP).

• METHODS: The data of 34 ROP cases (67 eyes) treated by intravitreal injection of Conbercept (IVC) in the ophthalmology department of the Xiamen Children's Hospital from July 2017 to March 2020 were retrospectively analyzed. Reactivation, which refers to recurrence of acute phase features, occurred at any stage of the disease in the presence or absence of other diseases.

• RESULT: The average gestational age of the 34 children was 28.82±2.32wk. The average birth weight was 1155.18±398.22g. The lesion zone of 19 cases (37 eyes) was Zone Ⅰ. In 10 cases (20 eyes), the lesion was in Zone Ⅱ, and in 5 cases(10 eyes), the lesion was in the posterior Zone Ⅱ. The total effective rate of disease control in ROP children treated with once IVC was 73.1% (49/67), and the vascularization of Zone Ⅱ was completed. The patients showed variable changes in the vascularization in Zone Ⅲ. For the patients who received one treatment and did not reactivate, the average rate of Type Ⅰ vascularization of ROP was 9.11±2.49wk, and the A-ROP was 13.40±4.04wk.

The rate of A-ROP vascularization in Zone Ⅱ was significantly longer compared to Type Ⅰ.

• CONCLUSION: IVC effectively completes vascularization in Zone Ⅱ.

• KEYWORDS: Conbercept; retinopathy of prematurity; vascularization

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INTRODUCTION

The expert consensus from the American Journal of Pediatrics, published for the first time in 2013, proposed the use of anti-vascular endothelial growth factor (VEGF) treatments in Stage 2 and 3 retinopathy of prematurity (ROP) with additional lesions in Zones Ⅰ and Ⅱ[1]. Recent studies showed that the intravitreal injection of anti-VEGF effectively treats ROP[2-5]. However, compared to traditional laser treatments, the use of anti-VEGF drugs remains controversial, as they may inhibit the development of normal blood vessels during retinal vascularization. In 2017, Wu *et al*[6] found that the level of serum VEGF decreased for 2mo after intraocular injection of bevacizumab to prolong the process of retinal vascularization. Furthermore, Sukgen and Koçluk[7] reported that the average vascular reconstruction time in Zone Ⅱ was 45wk (41-56wk) after the operation in children with aggressive ROP (A-ROP) treated with ranibizumab. Conbercept is a new anti-VEGF drug that exhibits high efficacy and a prolonged action time. It has recently been used in the treatment of ROP. The purpose of this study is to evaluate retinal vascularization resulting from the intravitreal injection of Conbercept in the treatment of a series of ROP cases in Zones Ⅰ and Ⅱ.

METHODS

Ethical Approval All patients were recruited underwritten informed consent by their parents. All experiments were approved by the institutional review committee and carried out under the ethical standards of the Declaration of Helsinki (No.2020-24).

Data from 34 cases (67 eyes) of ROP treated by intravitreal injection of Conbercept (IVC) in the Department of Ophthalmology of Xiamen Children's Hospital from July 2017 to March 2020 were retrospectively analyzed. The parents of the children were informed of the effects and possible complications of the operation before treatment. The diagnoses were performed based on the ICROP3[8] criteria, and treatment indications were based on the consensus[9] criteria. Before the examinations, the pupils were dilated with Topicamide (Mydrin-p; Santen pharm, Japan) and the retina was examined using a RetCam Ⅲ wide-angle digital retinal imaging system (Clarity Medical Devices, USA). Images were acquired, and the diagnoses were confirmed with a binocular indirect ophthalmoscope (Keeler, UK).

The operation was performed in the operating room under sterile conditions, and patients were monitored during the entire procedure. After anesthesia (combined intravenous and inhalation anesthesia, CIIA), povidone iodine (Shanghai disinfection Likang High Tech Co., Ltd., Ioerkang) was used to wipe the periphery of the eyes. The surface of the eye was cleaned with povidone iodine and 0.09% normal saline. The operation area was 1.5 mm from the superior temporal limbus. A local massage was performed with a sponge before the intravitreal injection of 0.25 mg/0.025 mL Conbercept (Chengdu Kanghong Biotechnology Co., Ltd., Langmu, China). All injections were performed by the same surgeon. After the injection, Tobramycin eye ointment was applied four times a day for 1wk to prevent postoperative infections. The anterior chamber was examined on the first day after the operation, and the fundus was examined one week after the operation. The follow-up interval was 1-2wk according to the development of the lesion until the vascularization of Zone Ⅱ was complete. The patients were reassessed every month.

RetCam was performed at each follow-up to assess the regression and reactivation of disease and the degree of peripheral vascularization. Effective treatment was defined as the reduction of retinal arteriovenous curvature, regression of disease, and vascularization of the surrounding retina. Reactivation is defined as the reactivation of any stage of the disease with or without additional disease[8]. Statistical analysis was performed using SPSS 20.0 software. The qualitative indices were expressed as frequencies and percentages, and the differences between the groups were compared using a Chi-square or Fisher exact probability test. The normal distribution of the quantitative indices was expressed by the mean ± standard deviation. Differences between groups were quantified using a two independent sample t-test and a one-way variance (ANOVA). The comparison between the two groups was further analyzed using an LSD t-test. $\alpha=0.05$ was set as the threshold for statistical significance.

RESULTS

The pretreatment findings and demographic data of the 34 children (19 females and 15 males) recruited to the study are listed in Table 1. The average gestational age (GA) was 28.82±2.32wk (range 26-33wk), and the average birth weight (BW) was 1155.18±398.22g (range 780-2500)g. The lesion zone in 19 cases (37 eyes) was Zone Ⅰ, 10 cases (20 eyes) in Zone Ⅱ, and 5 cases (10 eyes) in the posterior Zone Ⅱ. The average GA was 36.48±1.99wk (range 34-41). The follow-up time was 3 to 10mo after the operation. All children showed evident ridge dilution and regression within 48h-72h after treatment. No serious complications were observed after the injection.

Table 1 Summary of patient demographic data and pretreatment findings

Patients	GA (weeks+days)	BW(g)	Eye	Diagnosis	Zone	Plus	Postmenstrual age at treatment (weeks+days)	Postmenstrual weight at treatment (g)	Zone Ⅱ vascularization (weeks+days)
1	26+0	840	ou	Type Ⅰ	Ⅰ	−	36+0	1490	43+0
2	27+2	780	ou	Type Ⅰ	Ⅱ	+	40+3	1980	43+3
3	33+3	2340	ou	Type Ⅰ	Ⅱ	+	37+1	2750	46+2
4	28+6	1030	ou	Type Ⅰ	Ⅱ	+	34+5	1880	42+0
5	27+0	1100	ou	A-ROP	Ⅰ	+	39+0	1800	48+0
6	29+0	1000	OU/OD	Type Ⅰ	Ⅱ/Posterior Zone Ⅱ	+/+	34+5/44+0	1320/1600	56+0
7	28+0	800	ou	A-ROP	Ⅰ	+	34+1	1350	51+0
8	28+0	1400	ou	A-ROP	Ⅰ	+	41+0	3000	58+0
9	33+1	1380	ou	A-ROP	Ⅰ	+	34+6	1800	44+0
10	29+3	1300	ou	Type Ⅰ	Ⅱ	+	36+3	1480	44+0
11	27+1	800	ou	A-ROP	Ⅰ	+	35+1	1450	43+0
12	27+5	800	OU/OD	A-ROP/ Type Ⅰ	Ⅰ/Posterior Zone Ⅱ	+/+	35+0/43+1	1320/1560	44+6/57+2
13	32+5	1400	ou	Type Ⅰ	Posterior Zone Ⅱ	+	34+6	2150	45+1
14	30+5	1350	ou	A-ROP	Ⅰ	+	37+5	2500	58+4
15	26+6	1010	ou	A-ROP	Ⅰ	+	33+0	1810	41+6
16	30+0	1376	OU/OS	Type Ⅰ	Ⅰ/Posterior Zone Ⅱ	−/+	35+1/37+2	2300/2500	46+5
17	27+2	960	ou	Type Ⅰ	Ⅱ	+	36+3	1530	46+0
18	27+3	1300	ou	Type Ⅰ	Posterior Zone Ⅱ	+	38+5	1780	45+0
19	30+0	1400	ou	Type Ⅰ	Posterior Zone Ⅱ	+	37+1	2850	48+5
20	26+3	880	ou	Type Ⅰ	Ⅰ	−	36+2	1510	47+1
21	27+2	1180	ou	A-ROP	Ⅰ	+	39+2	1800	52+0
22	32+1	1380	ou	A-ROP	Ⅰ	+	34+6	1810	44+0
23	28+6	800	ou	Type Ⅰ	Ⅰ	−	38+6	1350	48+6
24	26+1	800	ou	A-ROP	Ⅰ	+	35+1	1500	44+0
25	26+6	1010	ou	Type Ⅰ	Ⅱ	+	36+0	1810	51+6
26	31+6	1380	ou	Type Ⅰ	Posterior Zone Ⅱ	+	35+6	2320	46+5
27	26+3	870	ou	Type Ⅰ	Ⅱ	+	36+3	1500	48+0
28	26+0	810	ou	A-ROP	Ⅰ	+	34+1	1320	52+0
29	31+0	1400	ou	A-ROP	Ⅰ	+	41+0	3050	56+0
30	29+5	900	ou	Type Ⅰ	Ⅱ	+	36+4	1360	45+1
31	27+5	780	OS	A-ROP	Ⅰ	+	35+0	1320	46+3
32	28+4	1210	ou	Type Ⅰ	Posterior Zone Ⅱ	+	36+3	1880	44+6
33	26+6	1010	ou	A-ROP	Ⅰ	+	35+0	1810	52+3
34	33+6	2500	ou	Type Ⅰ	Ⅱ	+	36+6	2500	41+2

GA: Gestational age; BW: Birth weight; A-ROP: Aggressive retinopathy of prematurity; OD: Oculus dexter; OS: Oculus sinister; OU: Oculi unitas.

The mean corrected GA of complete vascularization of the Zone Ⅱ after treatment was 47.09±4.47 wk (range 41-58; Table 2). Fifteen cases (29 eyes) were reactivated after the first treatment, which occurred at a median of 42wk after the operation (range 40.5-44; Table 3). A total of 43.3% (29/67) cases reactivated, among which 9 cases (17 eyes) occurred in Zone Ⅰ, 4 cases (8 eyes) occurred in Zone Ⅱ, and 2 cases (4 eyes) occurred in posterior Zone Ⅱ. Four cases (8 eyes) received repeated IVC treatment, and 5 cases (10 eyes) received laser treatment. Spontaneous regression of the disease was observed in 6 cases (11 eyes), and these patients were not retreated.

Table 2 Vascularization rate in Zone Ⅱ of patients who received only one treatment ($\bar{x}\pm s$, wk)

Group (diagnosis)	No. of eyes	First treatment gestational age	Gestational age of complete vascularization in Zone Ⅱ	Completion rate of vascularization in Zone Ⅱ
Type Ⅰ	28	36.86±1.54	45.01±2.17	9.11±2.49
A-ROP	21	36.44±2.48	49.74±5.30	13.40±4.04
t		-0.528	3.042	4.031
P		0.603	0.006[a]	0.001[a]

9 cases (18 eyes) of recurrent retreatment were excluded. [a]$P<0.05$; A-ROP: Aggressive retinopathy of prematurity.

Table 3 General information on reactivated cases $\bar{x}\pm s$

Group	Eyes	GA (wk)	BW(g)
Reactivated cases	29	27.90±1.68	986.4±259.12
Non-reactivated cases	38	29.53±2.54	1288.42±442.75
t		2.138	2.340
P		0.040[a]	0.026[a]

[a]$P<0.05$. GA: Gestational age; BW: Birth weight.

The average rate of vascularization in Zone Ⅱ was compared between cases that received one treatment and were not reactivated (from the GA of the first treatment to the GA of complete vascularization in Zone Ⅱ): Type Ⅰ was 9.11±2.49wk, A-ROP was 13.40±4.04wk. These two groups yielded significantly different results ($P=0.001$; Table 2). An LSD t-test showed that the rate of A-ROP vascularization in Zone Ⅱ was significantly longer compared to Type Ⅰ ($P=0.001$, 0.045).

During the follow-up period, 25 cases(49 eyes) degenerated and were completely vascularized (Figure 1). A total of 15 cases (29 eyes) achieved complete vascularization in Zone Ⅲ. A total of 4 cases (8 eyes) left showed white lesions in the peripheral retina (Figure 3). Only 5 cases (10 eyes) were not completely vascularized (Figure 2), among which 2 cases (4 eyes) still contained cristae. The original popcorn features disappeared, and the cristae regressed in 3 cases (6 eyes). With the exception of the 6 cases (11 eyes) that were reactivated and did not receive retreatment, the incomplete vascularization rate of Zone Ⅰ lesion group was significantly higher than that of Zone Ⅱ and the posterior Zone Ⅱ lesion group ($\chi^2=3.419$a, $P<0.10$; Table 4).

DISCUSSION

ROP is a proliferative retinal disease that most commonly occurs in preterm infants with low BW and small GA. More than 50,000 premature infants are diagnosed with ROP every year. Mild ROP can spontaneously resolve, however, severe cases of ROP can progress to retinal detachment, visual impairment, and ultimately lead to blindness[8]. The main pathological development in ROP is vascular occlusion caused by high levels of hypoxia, which results in the release of VEGF to drive abnormal angiogenesis in the retina. The use of anti-VEGF drugs can reduce the level of neovascularization in the ridge of the retina, which is therefore an effective treatment for ROP. Conbercept is a novel anti-VEGF drug that has a high affinity for the VEGF receptor, a long half-life and a bioavailability of 44%, which partially reduces systemic adverse reactions[10]. Conbercept has recently been used in the treatment of ROP, and in June 2021, the State Drug Administration issued the notice of approval for clinical trials of Conbercept with ophthalmic injection. Furthermore, Conbercept has been officially approved for clinical trials for ROP in Zones Ⅰ and Ⅱ or A-ROP in China (No. 2021LP00814).

In this study, we found that the single total effective rate of the Conbercept injection in children with ROP was 73.1% (49/67) for Zone Ⅰ, Ⅱ and posterior Zone Ⅱ lesions. After injection, additional lesions subsided, and the diameter of the vessels was reduced. Previous reports reported the single treatment effectiveness of IVC at 84.2 % to 90.0%[5,11-13]. Our results are slightly lower than the previously reported data. The recurrence rate after the first treatment was 26.9% (18/67 eyes), which was slightly higher than previously reported responses of 6.6% to 16.7%[12,14]. These differences may be related to the lesion zone and the degree of disease. The reactivation of ROP is related to zoning and the stage of the disease. The reactivation rate of Zone Ⅰ lesions is higher than that of Zone Ⅱ lesions, and the reactivation rate of A-ROP is higher than that of Type Ⅰ lesions. Feng *et al*[13] reported that the degree of eye lesions significantly impacts the primary success rate. In our study, A-ROP (lesions in area Ⅰ) accounted for 32.4%, which was higher than A-ROP reported by Li *et al* (10.5%)[14] and Huang *et al* (17.1%)[4]. Our study further confirmed that the single treatment efficiency of IVC was higher than intravitreal injection of Ranibizumab (IVR) (46.4%-61.0%)[4,12].

A total of 18 retreated eyes exhibited evident ridge proliferation, thickening, and distortion of the blood vessel diameters. The average recurrent GA was 5.6±0.5wk (5-7wk) after treatment, which was consistent with the reported similar half-life of Conbercept serum (20 days of serum)[15]. However, the recurrence time was shorter compared to previous reports with an average of 12.9wk after injection (corrected GA of 49.0wk)[14]. In our previous studies on the anti-VEGF treatment of ROP, we confirmed that GA is the main factor affecting the effect of ROP treatment[16]. Hittner *et al*[17] reported that the risk factors of recurrence after single intravitreal injection of Bevacizumab (IVB) treatment include A-ROP, long hospital stays, and low BW. Huang *et al*[4] found that relapse is more frequent after IVR treatment for gestational times ≤29.5wk. Hu *et al*[18] found that recurrence after IVR treatment of Stage 3 lesions in Zone Ⅱ was related to

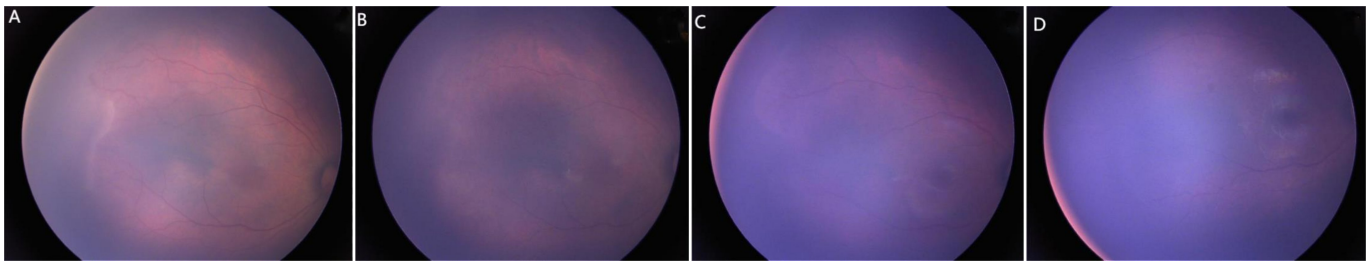

Figure 1 RetCam Ⅱ images of Type 1 patient (Case 13) treated with intravitreal Conbercept. A: Presence of vascularization and ridge before treatment; B: The ridge subsided 1wk after treatment; C: 1mo after the operation, an increased number of terminal vascular branches and crests were observed. D: 3mo after the operation, the ridge subsided, and the temporal peripheral retina was vascularized.

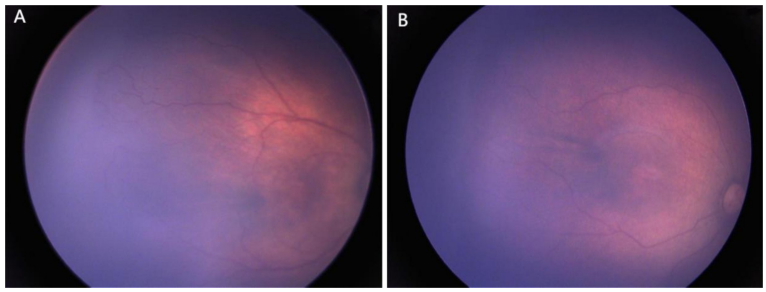

Figure 2 RetCam Ⅱ images of case 10 after IVC treatment. A: A partial arteriovenous short-circuit was observed in the temporal peripheral retina at 5mo after IVC treatment; B: 7mo after IVC treatment, the temporal peripheral retina was not vascularized.

Table 4 Completion of vascularization after treatment with reactivation and no retreatment

Group (lesion area)	No. of eyes	Incomplete vascularization rate in Zone Ⅲ (%)	χ^2	P
Zone Ⅰ	30	26.7 (8/30)	3.419a	0.064[a]
Zone Ⅱ and posterior Zone Ⅱ	26	7.7 (2/26)		

6 cases (11 eyes) were excluded. [a]P<0.10.

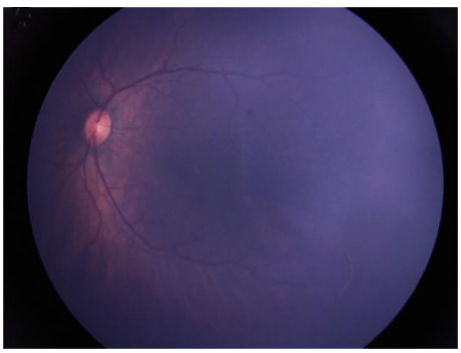

Figure 3 Retcam image of case 15. White lesions are observed in the temporal peripheral retina 6mo after IVC treatment.

preretinal hemorrhage. These data indicate that the stability of the disease may be related to the severity of ROP after anti-VEGF treatment. Reactivation is likely to be more severe in Zone Ⅰ compared to Zone Ⅱ. Gestational times of ≤29.5wk and preretinal hemorrhage are also associated with recurrence. In this study, the cases of retreatment were all A-ROP children with severe conditions. Premature children with lower BW and lower GA had a higher frequency of re-treatment, which is in agreement with previous studies[16].

In the recurrent cases, 8 eyes received a repeated injection of Conbercept to control the condition. The other 10 eyes received laser photocoagulation that eventually resulted in scaring of the surrounding retina. During the follow-up, ROP was controlled in 49 eyes following one treatment with IVC. Vascularization was completed in Zones Ⅱ and Ⅲ. These included 10 eyes (20.4%) without vascularization, 29 eyes (59.2%) with vascularization, and 10 eyes (20.4%) with white lesions around the temporal retina. A comparison of the disease zones showed that the rate of Type 1 vascularization in Zone Ⅱ was significantly shorter than in A-ROP. Further, the completion rate of vascularization in the Zone Ⅰ group was lower than that in Zone Ⅱ and the posterior Zone Ⅱ groups. A previous study showed that the non-vascularization rate (non vascularization of the peripheral retina) in the peripheral retina varied from 3% - 80% after anti-VEGF treatment in children with ROP[19]. Our results show that the rate of vascularization after IVR treatment was higher than that reported by Huang *et al*[4]. We hypothesize that this may be related to the effect of multi-targeting and high-affinity of Conbercept to the anti-VEGF receptor. The regression characteristics of ROP lesions include whitening of the neovascular tissue. The vascular abnormalities after anti-VEGF drug treatment include capillary loss and arteriovenous short circuits in the completed vascularization area[8]. During follow-up, the white lesions around the retina appear similar to areas of vascular reconstruction in the surrounding avascular retina. The residual vascular fibrosis at the original ridge did not resemble recurrence. Previously, we reported that vascularization after anti-VEGF treatment is not related to the drug dose. A comparison of anti VEGF drugs (Bevacizumab, Ranibizumab, and Conbercept) in the treatment of

retinopathy of preterm infants has shown that lower doses exhibit better retinal vascularization with no significant differences in the curative effects[19-23].

Complete retinal vascularization after anti-VEGF treatment can maximize retinal visual function without the reactivation of ROP caused by the overexpression of VEGF. The time of anti-VEGF treatment significantly affects the natural course of the disease. The role of anti-VEGF drugs in the inhibition of angiogenesis remains to be fully understood. Prolonging the observation period and increasing the frequency of follow-ups will contribute toward a better understanding of the impact of anti-VEGF treatments on the visual function development in children.

REFERENCES

1 Fierson WM; American academy of pediatrics section on ophthalmology; American academy of ophthalmology; American association for pediatric ophthalmology and strabismus; American association of certified orthoptists. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2013; 131(1): 189-195

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

3 Gunay M, Alyamac Sukgen E, Celik G, *et al*. Comparison of bevacizumab, ranibizumab, and laser photocoagulation in the treatment of retinopathy of prematurity in Turkey. *Curr Eye Res* 2017;42(3):462-469

4 Huang QJ, Zhang Q, Fei P, *et al*. Ranibizumab injection as primary treatment in patients with retinopathy of prematurity: anatomic outcomes and influencing factors. *Ophthalmology* 2017;124(8):1156-1164

5 Cheng Y, Liang JH, Li XX. Intravitreal injection of conbercept for aggressive posterior retinopathy of prematurity. *Chin. J. Ocul. Fund. Dis.* 2017;33(2):144-147

6 Wu WC, Shih CP, Lien RY, *et al*. Serum vascular endothelial growth factor after bevacizumab or ranibizumab treatment for retinopathy of prematurity. *Retina* 2017;37(4):694-701

7 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

8 Chiang MF, Quinn GE, Fielder AR, *et al*. International classification of retinopathy of prematurity, third edition. *Ophthalmology* 2021; 128(10):e51-e68

9 Pediatric Retinology Group of Ophthalmology Professional Committee of Cross-Strait Medical and Health Exchange Association, Fundus Disease Group of Chinese Medical Association Ophthalmology Branch. Expert consensus on intravitreal injection of anti-vascular endothelial growth factor drugs for retinopathy of prematurity. *Chin. J. Ocul. Fundus. Dis.* 2021;37(11): 836-840

10 VanderVeen DK, Melia M, Yang MB, *et al*. Anti-vascular endothelial growth factor therapy for primary treatment of type 1 retinopathy of prematurity: a report by the American academy of ophthalmology. *Ophthalmology* 2017;124(5):619-633

11 Li XX, Xu GZ, Wang YS, *et al*. Safety and efficacy of conbercept in neovascular age-related macular degeneration: results from a 12-month randomized phase 2 study: aurora study. *Ophthalmology* 2014;121(9): 1740-1747

12 Wu ZQ, Zhao JF, Lam W, *et al*. Comparison of clinical outcomes of conbercept versus ranibizumab treatment for retinopathy of prematurity: a multicentral prospective randomised controlled trial. *Br J Ophthalmol* 2022;106(7):975-979

13 Feng J, Qian J, Jiang YR, *et al*. Efficacy of primary intravitreal ranibizumab for retinopathy of prematurity in China. *Ophthalmology* 2017;124(3):408-409

14 Li MH, Wang L, Zhang ZF, *et al*. Comparison of the effectiveness of Conbercept versus Ranibizumab in the treatment of type 1 retinopathy of prematurity. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2021;21(5):866-871

15 Jin EZ, Bai YJ, Luo L, *et al*. Serum levels of vascular endothelial growth factor before and after intravitreal injection of ranibizumab or conbercept for neovascular age-related macular degeneration. *Retina* 2017;37(5):971-977

16 Yin X, Yang H, Fu Z, *et al*. Risk factors for recrudescence of ROP after anti-VEGF treatment. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2020;20(6):1105-1108

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

18 Hu QR, Bai YJ, Chen XL, *et al*. Recurrence of retinopathy of prematurity in zone II stage 3+ after ranibizumab treatment: a retrospective study. *J Ophthalmol* 2017;2017:5078565

19 Cheng Y, Meng QY, Linghu DD, *et al*. A lower dose of intravitreal conbercept effectively treats retinopathy of prematurity. *Sci Rep* 2018;8(1):10732

20 Wallace DK, Kraker RT, Freedman SF, *et al*. Assessment of lower doses of intravitreous bevacizumab for retinopathy of prematurity: a phase 1 dosing study. *JAMA Ophthalmol* 2017;135(6):654-656

21 Stahl A, Lepore D, Fielder A, *et al*. 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

22 Zhang HT, Yang X, Wang SH, *et al*. Comparison of therapeutic effects of different doses of conbercept intravitreal injection in the treatment of retinopathy of prematurity. *Chin. J. Fund. Dis*. 2020, 36(8):595-599

23 Bai YC, Nie HJ, Wei SY, *et al*. Efficacy of intravitreal conbercept injection in the treatment of retinopathy of prematurity. *Br J Ophthalmol* 2019;103(4):494-498