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Comparison of ranibizumab and conbercept treatment in type 1 prethreshold retinopathy of prematurity in zone II

Xiu-Mei Yang[1], Qiu-Ping Li[2], Zong-Hua Wang[1] and Mou-Nian Zhang[1*]

Abstract

Purpose The treatment with anti-VEGF for Retinopathy of prematurity (ROP) has already been widely applied in clinics even though there are still many concerns about this treatment. In this project we investigated the clinical outcomes of intra-vitreous conbercept (IVC) and ranibizumab (IVR) injection for treating type 1 prethreshold ROP in Zone II.

Methods The data of ROP infants receiving IVR or IVC from January 2017 to March 2020 who were followed up for at least 12 months in our hospital was studied in the present retrospective study. Regression, reactivation, complications, and ocular biological parameters were evaluated.

Results One hundred twenty-five eyes (64 infants) in IVC group and 229 eyes (117 infants) in IVR group were observed in the study. All infants showed good response to the two anti-VEGF agents. No eyes deteriorated during the observation. No significant difference was found between the two groups as to the regression within one week and one month, the reactivation rate, and the retreatment interval ($p > 0.05$) whereas retinal complete vascularization rate at 6 mons after the initial treatment and mean completion time of retinal vascularization after initial injection showed significant difference ($p < 0.05$). At 12 mons PMA the ocular parameters also presented no statistical difference between the two treated groups ($p > 0.05$). However, the ocular showed slight myopic tendency with the anti-VEGF treatment when compared to the control group ($p < 0.05$) whereas there was no statistical difference revealed between the two treated groups ($p > 0.05$).

Conclusions Both conbercept and ranibizumab for treating type 1 prethreshold ROP in Zone II are safe and effective. They had little effect on the development of ocular whereas there was a slight tendency of myopia after the treatment.

Keywords Retinopathy of prematurity, Conbercept, Ranibizumab, Treatment

Introduction

Retinopathy of prematurity (ROP) is one of the leading reasons for severe childhood vision loss in the world. ROP is a retinal vasoproliferative disorder which affects exclusively in preterm neonates. Especially in the developing countries, the survival rate of premature neonates has greatly increased, along with the improvement of neonatal care and respiratory support available today, thus leading to enlarged number of ROP patients [1, 2]. Numerous researches have proved that Vascular

*Correspondence:
Mou-Nian Zhang
zhangn301@163.com
[1] Department of Ophthalmology, Chinese People's Liberation Army General Hospital, Beijing 100039, China
[2] Department of Pediatrics, the Seventh Medical Center of Chinese People's Liberation Army General Hospital, Beijing 100700, China

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endothelial growth factor (VEGF) is a key regulator in ROP development [3, 4]. The peripheral avascular area induces an anoxic environment and hence elevates local VEGF level. Laser treatment is accepted to be the conventional standard treatment for type 1 and threshold ROP patients by ablating peripheral avascular retina for decades. It can decrease the elevated VEGF level and induce the recession of abnormal retinal neovascularization. However, this treatment also has several defects such as time-consuming, visual field loss and refractive error. Furthermore, laser therapy is limited to be undertaken for lens opacity or pupillary rigidity in severe ROP [5].

Several investigations have illustrated the effectiveness of intra-vitreous anti-VEGF injection on ROP, and so far several anti-VEGF drugs have demonstrated encouraging signs of biological activity in treating ROP including ranibizumab and conbercept [6–8]. Ranibizumab is known to be a recombinant humanized monoclonal antibody fragment derived from bevacizumab. Several studies including the RAINBOW study have estimated the effectiveness and safety of ranibizumab on ROP [9]. Except for the antibodies, soluble VEGF receptors also prove a very specific neutralization of VEGF thus leading to the anti-angiogenic activity [10]. Conbercept is a novel humanized VEGF decoy receptor. It is a recombinant humanized fusion protein which consists of partial VEGF receptor 1(domain 2) and partial VEGF receptor 2 (domain 3 and 4) fused to the constant region (Fc) of human IgG1 [11]. A series of recent published papers illustrated that conbercept was effective for treating aggressive ROP and type 1 ROP [7, 8, 12]. However, clinical comparison between the two anti-VEGF drugs (ranibizumab and conbercept) for treating type 1 prethreshold ROP in Zone II is still not adequate. Therefore, in the present research we planned to compare the safety and effectiveness of conbercept and ranibizumab treatment in type 1 prethreshold ROP in Zone II.

Methods

This research was a single-center retrospective study comparing the difference of IVR and IVC treatment on type 1 prethreshold ROP in Zone II. The severity of ROP was diagnosed by the principles of the International Classification of Retinopathy of Prematurity [13]. One hundred eighty-one infants who were diagnosed as type 1 prethreshold ROP in Zone II with plus disease from February 2017 to March 2020 were enrolled in our research.

From 2013 to 2020 there are only two anti-VEGF drugs available in our hospital (ranibizumab and conbercept). An informed consent was signed by the guardian of each infant after informing and explaining the off-label use of the two agents for this disease and possible adverse effects of the treatment. It will be the parents to decide which one they will choose to be used for their children.

We performed the intravitreal injection following previous described procedure [14]. The treatment was carried out by topical anaesthesia with unpreserved oxybuprocaine eye drops or inhalation anaesthesia. 5% povidone iodine was used to sterilize eyelids and conjunctiva. After inserting a sterilized eyelid speculum 0.25 mg/0.025 mL ranibizumab (Lucentis, Novus, US) /conbercept (Chengdu Kanghong Biotechnologies Co. Ltd, Sichuan, China) was intra-vitreous injected through the pars plana 1.5 mm after the corneal limbus.

The inclusive criteria included (1) type 1 prethreshold ROP in Zone II receiving the initial anti-VEGF treatment and (2) the infants followed up at least for 12 months. While the exclusive criteria were (1) a history of ROP treatment, (2) combined with other ocular diseases which might interfere the development of ROP and (3) the infants were not recommended to receive anti-VEGF treatment for systemic defects.

Two experts confirmed the severity of the disease. Subsequent retinal changes of ROP during the follow-up were also observed by them. The pupil was dilated with 0.5% tropicamide and 0.5% phenylephrine and then the fundus was examined with indirect ophthalmoscopy routinely after topical anesthesia. The retinal findings before and after the treatment if needed were documented with RetCam II (Natus Medical, Inc., Pleasanton, CA, USA). The infants were followed up at day 1 and day 7 after surgery and then the frequency was either decreased or increased according to the severity of the disease. Normally we examined the infants every 2–3 weeks.

Patients were examined following the principles of Chinese expert consensus for ROP. At 12 mons postmenstrual age (PMA) retinoscopy, A and B ultrasonic were performed to compare the refractive status and ocular biological parameters between the two groups by general anaesthesia.

The reactivation was defined as the return of retinal ridge or plus signs after the initial recession. Additional treatment should follow the rules of Retinopathy of Prematurity (ETROP) protocol if reactivation needed [15].

The quantitative data were compared with the Mann–Whitney U-test and Student's t-test while qualitative data were analysed with the chi-square test or Fisher's exact test. Statistical software SPSS (StatLab, SPSS for Windows, version 19.0; SPSS Inc., Chicago, Illinois, USA) was taken for statistical analysis in this study. $P < 0.05$ was considered statistically significant.

Results

One hundred eighty-one infants (354 eyes) diagnosed as type 1 prethreshold ROP in Zone II in our hospital from January 2017 to March 2020 were included in this study in total. Among them 229 eyes of 117 premature infants (60 M/57F) enrolled in the IVR group while 125 eyes of 64 premature infants (27 M/37F) in the IVC group. The demographics of the enrolled patients were illustrated in Table 1.

No systemic or severe local adverse effects were observed during the follow-up time. The main complications for anti-VEGF injection were preretinal hemorrhage and subconjunctival hemorrhage. No significant difference was observed between these two groups and the hemorrhage could be absorbed spontaneously.

After the initial intravitreal injections, all eyes showed good response to the two drugs including regression of plus disease and at least partial regression of the ridge of ROP. One week after the injection the complete regression rate for the disease for ranibizumab group and the conbercept group was 90/163 eyes (55.21%) and 61/103 eyes (59.22%), respectively. And the complete regression rate increased to 107/168 eyes (63.69%) and 67/84 eyes (79.76%) at one month after the treatment. The two groups showed no statistical significance concerning the initial treatment effectiveness, and regression of the disease ($P > 0.05$).

The prevalence of reactivation was 36 eyes (19 infants, 15.72%) in IVR group and 18 eyes (10 infants, 14.4%) in IVC group and it made no statistical significance between these two groups ($P > 0.05$). For the IVR group, 193 eyes accepted only one intravitreal injection, and 36 eyes accepted a second treatment. Among the recurrent eyes 18 eyes received a second single injection while 14 eyes received laser treatment only and 4 eyes received a combination treatment of a second injection and laser ablation. At the meantime for the IVC group, 107 eyes accepted only one injection, while 16 eyes received a second injection and 2 eyes received a second anti-VEGF injection combined with laser photocoagulation. The interval between the treatment and retreatment was 7.87 ± 3.81 wks (range: 2.86 to 15.29 wks) in the ranibizumab group and 9.63 ± 3.90 wks (range: 3 to 14.43 wks) in the conbercept group which made no statistical significance ($P > 0.05$). Retinal vascular reached at least zone III in all eyes at the final exam. Complete retinal vascularization was seen in 170/205 eyes (82.93%) and 49/71 eyes (69.01%) in both the IVR group and the IVC group at 6 mons after the initial treatment, respectively ($P < 0.05$). Mean completion time of retinal vascularization after initial treatment was 6.43 ± 3.73 mons and 7.97 ± 3.71 mons, respectively, which made a statistic significance ($P < 0.05$). The comparison of treating effects of the two treated groups is stated in Table 2.

Table 1 The demographics of patients with ROP treated with intravitreal injection of two anti-VEGF drugs

	IVR	IVC	*P* Value
Number of infants	117	64	
Number of eyes	229	125	> 0.05
M/F	60/57	27/37	> 0.05
BW, mean ± SD (range)	1057.91 ± 337.37 g (range: 480.0 to 3300.0 g)	1078.33 ± 243.99 g (range: 600.0 to 1780.0 g)	> 0.05
GA, mean ± SD (range)	27.76 ± 1.80 weeks (range: 24.57 to 34.00 weeks)	28.26 ± 1.89 weeks (range: 24.29 to 32.57 weeks)	> 0.05
PMA at treatment, mean ± SD (range)	37.99 ± 2.94 weeks (range: 32.29 to 50.0 weeks)	38.67 ± 2.56 weeks (range: 33.14 to 47.57weeks)	> 0.05
follow-up time, mean ± SD (range)	16.32 ± 3.39 mons (range: 12.00 to 23.00 mons)	18.30 ± 7.44 mons (range: 6.00 to 39.4.00 mons)	> 0.05

Abbreviations: *M/F* Male/Female *BW*, Birth weight, *GA* Gestational age, *PMA* post menstrual age, *Mon* Month

Table 2 Comparison of two anti-VEGF drugs on treating ROP

	IVR	IVC	*P* Value
Initial treatment effective	229 eyes (100%)	125 eyes (100%)	> 0.05
Complete regression of the disease within 1 week	90/163 eyes (55.21%)	61/103 eyes (59.22%)	> 0.05
Complete regression of the disease within 1 mon	107/168 eyes (63.69%)	67/84 eyes (79.76%)	> 0.05
Completion of retinal vascularization after 6 mon	170/205 eyes (82.93%)	49/71 eyes (69.01%)	< 0.05
Mean completion time of retinal vascularization after initial treatment	6.43 ± 3.73 mons	7.97 ± 3.71 mons	< 0.05
Reactivation	36 eyes (19 infants, 15.72%)	18 eyes (10 infants, 14.4%)	> 0.05
Mean interval between the treatment and retreatment	9.99 ± 3.24 wks (range: 4 to 15.29 wks)	10.57 ± 3.06 wks (range:7.29 to 14.43 wks)	> 0.05

At 12 months PMA the ocular biological parameters of the two treated groups were also measured and compared with ROP infants who received no treatment and the ROP disease recessed naturally: the mean anterior chamber depth for ranibizumab group was 3.21 ± 0.24 mm, while that was 3.09 ± 0.17 mm for conbercept group. Mean lens thickness was 3.85 ± 0.15 mm and 3.82 ± 0.10 mm for ranibizumab group and conbercept group respectively. The mean axial length for the former group was 20.52 ± 0.77 mm and 20.75 ± 1.01 mm for the latter. All these parameters made no statistical significance compared to the control group ($P > 0.05$). As to the refractive status the results showed that both IVR group and IVC group presented a significant difference compared to control group when comparing the mean spherical equivalence and mean spherical power ($P < 0.05$). The astigmatism rate also increased after the treatment ($P < 0.05$). As to the mean cylinder power the two treated groups made no statistical difference compared to the control group ($P > 0.05$). The data of comparing the ocular biological parameters and the refractive status after the treatment was listed in Table 3.

Discussion

In recent research, VEGF has been believed to be the main mediator for ROP development illustrated in both animal models and in humans [16–18]. Several anti-VEGF drugs so far are available including bevacizumab, ranibizumab, aflibercept and conbercept in treating ROP [6–8, 12]. Ranibizumab is the most widely used in treating ocular neovascularization related diseases. As a humanized monoclonal antibody it shows high binding affinity to VEGF-A thus renders it inactive. Whereas conbercept is a novel agent. As a soluble receptor decoy it can target to VEGF-A, VEGF-B and placental growth factor[12].

In this study, we found both conbercept and ranibizumab had a strong initial effect on type 1 prethreshold ROP in Zone II. Plus disease recessed in all infants soon after the treatment. 1 week after injection retinal ridge completely diminished in 90/163 eyes 55.21% and 61/103 eyes (59.22%) while the rate increased to 107/168 eyes (63.69%) and 67/84 eyes (79.76%) in one month in both the IVR and IVC groups, respectively. The initial injection periods found in previous studies vary between 32 to 36 weeks PMA while in our cases the timepoint for treatment is 37.99 ± 2.94 weeks (range: 32.29 to 50.0 weeks) and 38.67 ± 2.56 weeks (range: 33.14 to 47.57 weeks) for IVR and IVC groups respectively [19, 20]. The prolonged treating time may be because in the previous studies the stages of ROP were mainly zone I and posterior zone II patients which were more severe than ours. Another reason could be racial difference, screening criterion difference. In Fig. 1 we showed two cases who accepted either IVC or IVR treatment illustrated both the complete regression and partial regression of the disease.

In this study the reactivation occurred in 36 eyes (19 infants, 15.72%) for IVR group and 18 eyes (10 infants, 14.4%) for IVC group which was lower compared with the previous studies. [1, 6–8] The recurrent rate variation may be because of the small size of the study and the severity difference also could be a possible reason. For IVR treatment in China, in the previous studies, the mean reactivation interval was 8.57 ± 3.73 weeks in Feng et al.'s study, 8.3 ± 2.7 weeks in Huang et al.'s study and 8.40 ± 0.88 (6–10.5) weeks in Zone II ROP in Cheng et al.'s study [6, 12, 21]. Our results showed that the mean reactivation interval for IVR was 9.99 ± 3.24 weeks (range: 4 to 15.29 weeks) which was consistent with previous studies. Moreover, in our study we found that the interval for IVC group is slightly longer than the IVR group even though it made no statistical significance. This may be associated with the different structure and the prolonged half-time of conbercept compared with ranibizumab. Even though the exact underlying pathogenesis remains to be further explored and verified.

The previous studies estimated that even though intravitreal anti-VEGF injection could dramatically

Table 3 Comparison of the ocular biological parameters and the refractive status after the treatment

	IVR	IVC	Ctrl	*P* Value
Anterior chamber depth (mm)	3.21 ± 0.24	3.09 ± 0.17	3.17 ± 0.25	> 0.05
Lens thickness (mm)	3.85 ± 0.15	3.82 ± 0.10	3.87 ± 0.22	> 0.05
Axial length (mm)	20.52 ± 0.77	20.75 ± 1.01	20.46 ± 0.62	> 0.05
Mean spherical equivalence	-0.97 ± -2.01*	-1.19 ± -3.22*	0.78 ± 1.02	< 0.05
Mean spherical power	-0.64 ± -1.87*	-0.76 ± -3.23*	1.03 ± 0.89	< 0.05
Mean cylinder power	-0.40 ± 1.56	-0.52 ± 2.28	-0.58 ± 1.79	> 0.05
Astigmatism rate	8/20 (40.00%)*	9/24 (37.50%)*	1/22 (4.55%)	< 0.05

IVR or IVC versus ctrl

* $P < 0.05$

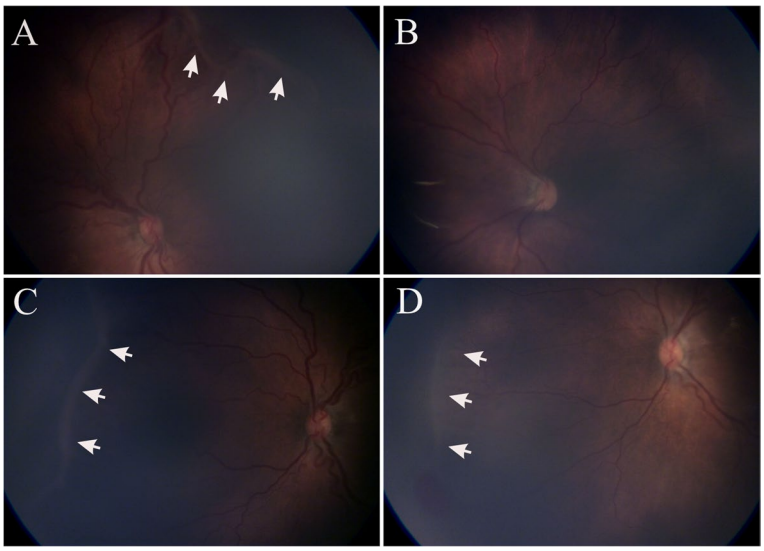

Fig. 1 Zone 2 stage 3^{+} ROP before treatement (white arrow, **A**) and 1 week after intravitreal conbercept injection with complete regression (**B**). Patient1 information: male, GA:29^{+1}w, BW 1050 g, PMA 38^{+5}w; Zone 2 stage 3^{+} ROP before treatment (white arrow, **C**) and partial regression after intravitreal ranibizumab injection (white arrow, **D**). Patient2 information: female, GA: 27w, BW 1100 g, PMA 38w

decrease the systemic VEGF level however the inhibition effect was temporary (one week for ranibizumab and two weeks for conbercept) and hence may not cause severe system side effects [10, 22]. Nevertheless, as VEGF is a pleiotropic protein and the ROP patients are undergoing organogenesis we still cannot exclude long-term systemic advert events of the drugs. Therefore, a much longer follow-up time and an enlarged population for study are strongly recommended.

VEGF is essential for retinal vascular growth. A preliminary research estimated that anti-VEGF treatment might be able to postpone retinal vascularization in ROP [23]. This phenomenon could because of the loss of microglia due to hypoxia during the development of ROP since some researchers believed that microglial cells are essential for proper retinal vascular formation [24, 25]. Previous results showed that the rate of complete retinal vascularization was 71.41% with ranibizumab and 76.21% with conbercept and 72% with bevacizumab in ROP [12, 23]. While the rate was even more lower in Tahija's study nearly 45% [26]. Complete retinal vascularization at 6 months after the initial treatment in our study is 170/205 eyes (82.93%) in IVR group and 49/71 eyes (69.01%) in IVC group. There is a statistic difference between the two groups concerning the rate of retinal vascularization. We still do not know the exam reason for the difference. One possible reason might be the different structure and the prolonged halftime of conbercept compared with ranibizumab. More researches are needed to explore this phenomenon.

As to the ocular biological parameters which include the anterior chamber depth, lens thickness and axial length they showed no difference comparing to the control group. For the refractive status the two treated groups showed mild myopic tendency comparing with the control group. These findings were consistent with other previous researches [27].

Conclusions

Hence in the current research, we disclosed that anti-VEGF treatment with either ranibizumab or conbercept was effective and safe as monotherapy for type 1 prethreshold ROP in Zone II infants and did not show any serious systemic or local side effects. However, the increased risk of reactivation compared with laser treatment and the prolonged retinal complete vascularizaiton alerts the ophthalmologists a demand for a longer follow-up.

Authors' contributions

Dr. xiu-mei Yang; Dr zong-hua wang and Dr qiu-ping Li performed the clinical work for the paper. Dr. xiu-mei Yang; Dr zong-hua wang together collected the data and following statistical analysing. Dr. xiu-mei Yang wrote the paper while Dr qiu-ping Li and Prof. mou-nian zhang revised the paper before submitting. All authors reviewed the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All experimental protocols were approved by the Ethics Committee of Seventh Medical Center of Chinese PLA General Hospital. And informed consent was obtained from their legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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