Treatment for non-type 1 retinopathy of prematurity by intravitreal injection of anti-vascular endothelial growth factor drugs

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Article

Keywords: Retinopathy of prematurity, Non-type 1, Anti-vascular endothelial growth factor, Intravitreal injection, treatment

Posted Date: April 27th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1560023/v1

Abstract

To explore clinical characteristics and treatment reasons for intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs in the treatment of non-type 1 retinopathy of prematurity (ROP). A retrospective study was conducted to screen the non-type 1 ROP from the collected ROP patients who received intravitreal injection of anti-VEGF drugs in Henan Eye Hospital from September 2018 to June 2021. A total of 138 ROP cases (262 eyes) were included in this study, including 39 cases (28.3%) 65 eyes (24.8%) were the non-type 1 ROP. Compared with the type 1 ROP group, the non-type 1 ROP group had slightly later treatment time (41.1±8.9 weeks vs 38.6±5.5 weeks, P<0.05) and a higher proportion of fusion protein drugs(87.2% vs 54.5%, P<0.05). After intravitreal injection of anti-VEGF drugs, 27 eyes (41.5%) were cured and 38 eyes (58.5%) were improved in the non-type 1 ROP group, without recurrence and aggravation cases. There were more lesions in zone II (63 eyes, 96.9%), stage 2 (41 eyes, 63.1%) and stage 3 (22 eyes, 33.8%), and 58 eyes (89.2%) showed pre-plus in the non-type 1 ROP group. Treatment reasons included pre-plus in 58 eyes (89.2%), ridge changes in 22 eyes (33.8%), simultaneous treatment of the contralateral eye in 9 eyes (13.8%), no regression of lesions in persistent stage 2 or 3 over 44 weeks of follow-up in 8 eyes (12.3%), and logistical considerations in 4 eyes (6.2%). Considering some peculiar clinical characteristic, personalized treatment by intravitreal injection of anti-VEGF drugs may be necessary for some non-type 1 ROP in critical conditions.

Introduction

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disease that occurs in premature and low-weight infants, and it most afflicts both eyes and may cause retinal detachment and blindness. Current treatment methods of ROP include laser coagulation and intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs. The Early Treatment for Retinopathy of Prematurity (ETROP) and the latest expert consensus or guidelines recommend treatment for type 1 ROP cases and close follow-up for Type 2 ROP cases [1,2]. However, some ROP eyes have special manifestations in clinical practices, although they have not reached the level of type 1 ROP, manifested as gradually thickened or widened ridges without typical manifestation of plus disease, or no regression of the retinal lesions for a long time of follow-up. This kind of ROP is more serious than type 2 ROP, and it is difficult to decide whether to continue follow-up or give treatment. These non-type 1 ROP eyes may be recommended for treatment to avoid unnecessary medical disputes or irreversible vision damage caused by the aggravation of the disease.

Previous studies have reported that 9–27% affected eyes of patients with non-Type 1 ROP receive treatment in different countries [3–6]. In recent years, intravitreal injection of anti-VEGF agent for the treatment of ROP, with advantages of simple operation, minimal invasion and continuous growing of retinal vessels to the periphery after injection, has gradually become an important treatment method[7–9]. There is a lack of relevant research on the treatment of intravitreal injection of anti-VEGF drugs for non-type 1 ROP patients in critical conditions. In this study, non-type 1 ROP cases who had received intravitreal injection of anti-VEGF drugs in our hospital were enrolled to analyze the treatment effect, clinical characteristics, and treatment reasons and to explore the personalized diagnosis and treatment for ROP cases with special clinical characteristics.

Methods

Subjects and data

This was a retrospective study. ROP infants who had received intravitreal injection of anti-VEGF drugs were collected in the Department of Ophthalmology of Henan People's Hospital (Henan Eye Hospital) from September 2018 to June 2021, of whom, type 1 and non-type 1 ROP cases were subgrouped. This study was conducted with the approval of the Medical Ethics Committee of Henan Eye Hospital (Approval Number HNEECKY-2021 (49)) and performed in accordance with the Declaration of Helsinki. All methods were confirmed to be performed with relevant regulations. All infant's parents or legal guardians signed the written informed consent prior to treatment.

Inclusion And Exclusion Criteria

Diagnostic criteria for type 1 ROP were as follows [1]: (1) ROP at stages 1–3 with plus in zone I; and ROP at stage 3 without plus in zone I (2) stage 2 or 3 ROP with plus in zone II; (3) aggressive ROP (A-ROP). Those who did not meet any above conditions and received intravitreal injection of anti-VEGF drugs were defined as non-type 1 ROP. Infants with unstable vital signs caused by systemic diseases in the heart, brain, and lung or accompanied by other fundus lesions were excluded.

Study Selection

The retinal examination of ROP infants was performed in the neonatal intensive care unit (NICU) and ophthalmic clinic by two experienced doctors under topical anesthesia after mydriasis with RetCam 3. All abnormal retinal images were judged by a senior pediatric retinal professional (Haitao Zhang, associated professor), then diagnosis and treatment suggestions were made. Information of name, gender, gestational age, birth weight, and the time of examination and injection was recorded after the retinal examination. The zone, stage, range, and plus disease of binocular retinal lesions were recorded according to ICROP3 [10].

Anti-VEGF drugs used in the study were ranibizumab (0.25mg/0.025ml), conbercept (0.25mg/0.025ml), and aflibercept (1mg/0.025ml). The latter two drugs were fusion proteins. Intravitreal injection for ROP was performed under topical anesthesia. After local disinfection, a 29G needle-equipped syringe was used to penetrate the eyeball wall at 1.0-1.5 mm posterior of the limbus to the vitreous cavity parallel to the optical axis. Antibiotic eye drops were used for 3–5 days to prevent eye infection and the first eye review was conducted within 7 days The interval of the next review (1–3 weeks) shall be determined according to the retinal manifestations, and patients shall be followed up until complete retinal vascularization or for at least 24 weeks.

The characteristics of included subjects were analyzed according to the number of cases. The grouping criteria were as follows: ROP cases were included in the type 1 ROP group if both eyes met the above criteria and received intravitreal injection of anti-VEGF drugs, or one eye met the criteria and received intravitreal injection while the contralateral eye with mild lesions did not receive treatment. ROP infants whose one eye or both eyes did not meet the criteria of type 1 ROP and received intravitreal injection were included in the non-type 1 ROP group. The curative effect, retinal pathological characteristics, and causes for the treatment of non-type 1 ROP

were analyzed according to the number of eyes. The characteristics of included subjects were analyzed according to the number of cases.

Quality Assessment

The treatment effect was evaluated as follows: (1) Cured, complete retinal vascularization. Retinal vessels gradually grew to the ora serrata or less than 1 PD (Papillary Diameter) away from the ora serrata around zone III; (2) Improved, the retina was not completely vascularized. The retinal vessels had reached zone III, and there were still non-vascular areas, but without obvious active lesions at the last follow-up. (3) Recurrence. The tortuous dilation of retinal vessels was relived and the ridge became flattened in the early stage after the operation, but then the tortuous dilation of vessels, ridge aggravation, and neovascularization occurred again in the retina. (4) Aggravation. The tortuous dilation of retinal vessels was not significantly reduced, and the proliferation and traction were aggravated, even leading to retinal detachment. The improved cases still required regular examination. The recurrent cases were treated with intravitreal injection of anti-VEGF drugs again or retinal laser photocoagulation. The aggravating cases were treated with laser photocoagulation according to the retinal manifestations or surgery in case of retinal detachment.

The reasons for the treatment of non-Type 1 ROP were as follows: (1) pre-plus diseases in the retina, (2) ridge changes, shown as more obvious ridges or ridge extension, or locally thickened and widened ridges, with a risk of increased proliferation. (3) simultaneous treatment of the contralateral eye; (4) no regression of lesions in persistent stage 2 or 3 for over 44 weeks of follow-up; (5) logistical considerations: follow-up might not be timely due to various reasons (such as living far away, parents' poor understanding, and epidemic control policy, etc.).

Data Analyses

Data analyses were performed using the SPSS19.0 statistical software. The differences in birth gestational age (GA), birth weight (BW), hospitalization in NICU, first injection time, and follow-up time were compared by *t*-test, and the differences in gender and drug types were compared by χ^2 test. The treatment effect was analyzed according to the number of afflicted eyes and compared by χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Subject characteristics

A total of 138 cases (262 eyes) of ROP, including 124 cases (89.9%) with both eyes and 14 cases (10.1%) with unilateral eyes, were included in the study. There were 99 cases (71.1%) in the type 1 ROP group and 39 cases (28.3%) in the non-type 1 ROP group, including 26 bilateral cases (18.8%) (52 eyes, 19.8%) and 13 unilateral cases (9.4%) (13 eyes, 5.0%). Of unilateral cases, 6 cases (4.3%) had type 1 ROP in one eye and non-type 1 ROP in the contralateral eye.

The characteristics of subjects with non-type 1 ROP and type 1 ROP were shown in Table 1. There was no significant difference in gestational age, birth weight, gender proportion, hospitalization days in NICU, and follow-up time between the two groups ($P > 0.05$). While the time of the first treatment of the non-type 1 ROP group was slightly later than that of the type 1 ROP group (41.1 ± 8.9 weeks vs 38.6 ± 5.5 weeks) ($P < 0.05$). The difference in the types of anti-VEGF drugs was statistically significant ($P < 0.05$), with a higher proportion of fusion protein drugs in the non-type 1 ROP group (87.2%) than that in the type 1 ROP group (54.5%).

Table 1
Characteristics of subjects with type 1 and non-type 1 ROP (N = 138)

Parameters [α]	Non-type Type I ROP group (N = 39)	Type 1 ROP group (N = 99)	Statistic[β]	P[β]
GA (w)	28.5 ± 1.9	28.9 ± 2.2	1.033	0.303
BW (kg)	1.16 ± 0.35	1.19 ± 0.37	0.504	0.615
Gender (male, N (%))	21(53.8)	65(65.7)	1.662	0.197
length of stay in NICU (d)	56.3 ± 23.2	53.6 ± 28.8	0.521	0.603
Time of the first treatment (week)	41.1 ± 8.9	38.6 ± 5.5	2.021	0.045
Follow-up time (week)	29.5 ± 10.1	33.6 ± 15.4	1.537	0.127
Anti-VEGF drug (N (%))	5(12.8)	45(45.5)	12.896	0.000
Ranibizumab	34(87.2)	54(54.5)		
Fusion proteins (conbercept and aflibercept)				

[α] GA gestational age; BW birth weight.

[β] Difference of gender was analyzed by χ^2 test and the remaining parameters were tested using t-test

Effect Assessment

According to the number of eyes (n = 262), 65 eyes (24.8%) were non-type 1 ROP. After treatment,27 eyes (41.5%) were cured and 38 eyes (58.5%) were improved. There was no recurrence and aggravation. There were 197 eyes of type 1 ROP. After treatment, 79 eyes were cured (40.1%),100 eyes were improved (50.8%), and 18 eyes recurred (9.1%), without aggravation cases. The difference in treatment effects between the two groups was statistically significant ($P < 0.05$, Table 2). All 18 recurrent eyes in the type 1 ROP group received intravitreal injection of the same anti-VEGF drugs and then the condition improved.

Table 2
Comparison of effects for eyes with type 1 and non-type 1 ROP after intravitreal injection of anti-VEGF drugs (N = 262)

	Non-type 1 ROP eyes	Type 1 ROP eyes	statistic[α]	P[α]
cured	27(41.5)	79(40.1)	6.514	0.02
Improved	38(58.5)	100(50.8)		
Recurrence	0(0.0)	18(9.1)		
Total	65(100)	197(100)		
[α] χ^2 test was used.				

Reasons For The Treatment

Of all treated eyes with non-type 1 ROP (n = 65) (Table 3), 63 eyes (96.9%) had more lesions in zone II. In terms of stage, there were more lesions in stages 2 and 3, with 41 eyes (63.1%) and 22 eyes (33.8%), respectively. In terms of plus diseases, 58 eyes (89.2%) showed pre-plus. As for treatment reasons, the chief reasons were pre-plus in 58 eyes (89.2%), followed by ridge changes in 22 eyes (33.8%), simultaneous treatment in 9 eyes (13.8%) due to contralateral eye treatment, no regression of lesions in stage 2 or 3 for over 44 weeks of follow-up in 8 eyes (12.3%), and logistical considerations in 4 eyes (6.2%). The above reasons can exist simultaneously (Fig. 1). The preoperative features and specific reasons for treated non-type 1 ROP cases are shown in Table 4.

Table 3
Characteristics of pathological manifestation of non-Type 1 ROP receiving treatment.

Characteristics		Non-Type 1 treated eyes (N = 65)	
		N	%
Zone	□	2	3.1
	□	63	96.9
	posterior □	5	7.7
	Non-posterior □	58	89.2
Stage	1	2	3.1
	2	41	63.1
	3	22	33.8
Plus disease[α]	-	7	10.8
	±	58	89.2
Reasons	pre-plus	58	89.2
	ridge changes	22	33.8
	contralateral eye	9	13.8
	follow-up time ≥ 44w	8	12.3
	logistical considerations	4	6.2

[α]± representation pre-plus diseases.

Table 4
List of non-type 1 ROP cases received intravitreal injection of anti-VEGF drugs (N = 39)

ID.	Gender	BMA (w)	BW (kg)	Eye	Zone	Stage	Plus[a]	Range (hr)	Medicine[β]	Reasons for treatment [γ]
1	male	26.6	0.95	OD		2	±	7	C	pre-plus
				OS		2	±	7	C	pre-plus
2	male	27.6	1.00	OD		2	±	6	C	follow-up time ≥ 44w, ridge changes, pre-plus
				OS		2	±	6	C	follow-up time ≥ 44w, pre-plus
3	male	30.0	1.30	OD		3	±	6	C	ridge changes, pre-plus
				OS		2	-	6	C	ridge changes, contralateral eye
4	female	29.0	0.90	OD		2	-	5	C	follow-up time ≥ 44w, logistical considerations
				OS		2	-	5	C	follow-up time ≥ 44w, logistical considerations
5	male	28.7	1.30	OD		1	±	12	C	pre-plus, logistical considerations
				OS		1	±	12	C	pre-plus, logistical considerations
6	female	30.0	1.66	OD		2	±	5	R	pre-plus
				OS		3	±	5	R	pre-plus

[α] GA gestational age.

[β] BW birth weight.

[γ] ± representation pre-plus.

[δ] R ranibizumab, C conbercept, A aflibercept, NA untreated.

[γ] One eye of type 1 ROP and the contralateral eye of non-type 1 ROP in 6 cases (ID. 10,12,15,34,38,39). One eye of non-type 1 ROP and contralateral eye untreated in 7cases (ID.13,16,19,20,27,30,35).

ID.	Gender	BMA (w)	BW (kg)	Eye	Zone	Stage	Plus[a]	Range (hr)	Medicine[β]	Reasons for treatment [γ]
7	female	27.6	1.10	OD		3	±	12	R	ridge changes, pre-plus
				OS		3	±	12	R	ridge changes, pre-plus
8	female	27.0	0.98	OD		2	±	5	C	pre-plus
				OS		2	±	5	C	pre-plus
9	male	29.4	1.10	OD		2	±	6	R	pre-plus
				OS		2	±	6	R	pre-plus
10	male	32.0	1.50	OD		3		6	R	type 1
				OS		3	±	6	R	ridge changes, pre-plus, contralateral eye
11	male	30.7	1.66	OD		2	±	5	C	pre-plus
				OS		2	±	7	C	pre-plus
12	male	30.0	1.63	OD		3		5	A	type 1
				OS		3	±	5	A	ridge changes, pre-plus, contralateral eye
13	male	26.9	0.72	OD		3	±	12	C	pre-plus
				OS		2	-	12	NA	untreated
14	female	28.4	1.05	OD		3	-	5	C	follow-up time ≥ 44w, ridge changes
				OS		3	-	5	C	follow-up time ≥ 44w, ridge changes

[α] GA gestational age.

[β] BW birth weight.

[γ] ± representation pre-plus.

[δ] R ranibizumab, C conbercept, A aflibercept, NA untreated.

[γ] One eye of type 1 ROP and the contralateral eye of non-type 1 ROP in 6 cases (ID. 10,12,15,34,38,39). One eye of non-type 1 ROP and contralateral eye untreated in 7cases (ID.13,16,19,20,27,30,35).

ID.	Gender	BMA (w)	BW (kg)	Eye	Zone	Stage	Plus[a]	Range (hr)	Medicine[β]	Reasons for treatment [γ]
15	female	28.9	1.13	OD	posterior II	2	-	12	C	contralateral eye
				OS	posterior II	2	□	12	C	type 1
16	female	27.0	0.73	OD	□	2	-	3	NA	untreated
				OS	□	3	±	4	C	ridge changes, pre-plus
17	female	26.7	0.71	OD	□	2	±	6	C	pre-plus
				OS	□	2	±	6	C	pre-plus
18	male	27.3	1.10	OD	□	2	±	10	C	pre-plus
				OS	□	2	±	10	C	pre-plus
19	female	25.6	0.90	OD	□	2	-	3	NA	untreated
				OS	□	3	±	3	C	ridge changes, pre-plus
20	male	26.7	0.85	OD	□	3	±	7	C	ridge changes, pre-plus
				OS	□	2	-	6	NA	untreated
21	female	25.9	0.86	OD	posterior II	2	±	10	C	pre-plus
				OS	posterior II	2	±	10	C	pre-plus
22	male	26.9	0.68	OD	□	2	±	12	A	pre-plus
				OS	□	2	±	12	A	pre-plus
23	male	27.6	1.10	OD	posterior II	3	±	12	A	pre-plus
				OS	posterior II	2	±	12	A	pre-plus

[α] GA gestational age.

[β] BW birth weight.

[γ]± representation pre-plus.

[δ] R ranibizumab, C conbercept, A aflibercept, NA untreated.

[γ] One eye of type 1 ROP and the contralateral eye of non-type 1 ROP in 6 cases (ID. 10,12,15,34,38,39). One eye of non-type 1 ROP and contralateral eye untreated in 7cases (ID.13,16,19,20,27,30,35).

ID.	Gender	BMA (w)	BW (kg)	Eye	Zone	Stage	Plus[a]	Range (hr)	Medicine[β]	Reasons for treatment [γ]
24	male	28.0	1.17	OD		2	±	10	C	pre-plus
				OS		2	±	10	C	pre-plus
25	male	31.0	1.75	OD		3	±	5	A	ridge changes, pre-plus
				OS		2	-	5	A	contralateral eye
26	female	27.9	1.13	OD		2	±	5	C	pre-plus
				OS		2	±	5	C	pre-plus
27	female	29.4	1.00	OD		2	±	6	C	pre-plus
				OS		2	-	5	NA	untreated
28	female	27.0	1.10	OD		3	±	5	C	ridge changes, pre-plus
				OS		3	±	5	C	ridge changes, pre-plus
29	female	27.3	1.08	OD		2	±	5	C	pre-plus
				OS		2	±	5	C	pre-plus
30	male	28.4	1.19	OD		2	-	4	NA	untreated
				OS		3	±	4	C	pre-plus
31	male	26.7	0.75	OD		2	±	10	C	pre-plus
				OS		2	±	10	C	pre-plus
32	female	29.7	1.25	OD		3	±	6	C	ridge changes, pre-plus
				OS		3	±	6	C	ridge changes, pre-plus

[α] GA gestational age.

[β] BW birth weight.

[γ] ± representation pre-plus.

[δ] R ranibizumab, C conbercept, A aflibercept, NA untreated.

[γ] One eye of type 1 ROP and the contralateral eye of non-type 1 ROP in 6 cases (ID. 10,12,15,34,38,39). One eye of non-type 1 ROP and contralateral eye untreated in 7cases (ID.13,16,19,20,27,30,35).

ID.	Gender	BMA (w)	BW (kg)	Eye	Zone	Stage	Plus[a]	Range (hr)	Medicine[β]	Reasons for treatment [γ]
33	female	33.1	1.80	OD		2	±	5	C	ridge changes, pre-plus, follow-up time ≥ 44w
				OS		3	±	6	C	ridge changes, pre-plus, follow-up time ≥ 44w
34	male	27.9	0.97	OD		2		12	R	type 1
				OS		2	±	12	R	pre-plus, contralateral eye
35	female	27.9	1.18	OD		2	-	3	N A	untreated
				OS		3	±	3	C	ridge changes, pre-plus
36	male	31.9	2.28	OD		2	±	6	A	contralateral eye, pre-plus
				OS		3	±	6	A	ridge changes, pre-plus
37	male	25.6	0.74	OD		2	±	12	C	pre-plus
				OS		2	±	12	C	pre-plus
38	male	30.6	1.50	OD		2	±	6	A	pre-plus, contralateral eye
				OS		2		6	A	type 1
39	female	29.0	1.26	OD		3		5	C	type 1
				OS		2	±	6	C	ridge changes, pre-plus, contralateral eye

[α] GA gestational age.

[β] BW birth weight.

[γ]± representation pre-plus.

[δ] R ranibizumab, C conbercept, A aflibercept, NA untreated.

[γ] One eye of type 1 ROP and the contralateral eye of non-type 1 ROP in 6 cases (ID. 10,12,15,34,38,39). One eye of non-type 1 ROP and contralateral eye untreated in 7cases (ID.13,16,19,20,27,30,35).

Discussion

Some previous studies analyzed the treatment reasons of non-Type 1 ROP (seen in Table 5)[3,5,11,16], but the main treatment method in these studies was laser coagulation. No literature had been studied the effect of intravitreal injection of anti-VEGF drugs on the treatment of non-type 1 ROP currently.

Of the 263 eyes treated in this study, 65 eyes (24.8%) were non-type 1 ROP, showing a higher proportion than that in previous studies (9.5–13.7%)[3,5,11]. Because that the treatment for ROP cases in this study was intravitreal injection of anti-VEGF drugs, which are simpler and more minimally invasive than laser coagulation[14]. Some lesions in critical conditions at risk of aggravation were suggested to be treated. In this study, lesions in all eyes with non-type 1 ROP were relieved after treatment, which was similar to the results of previous studies [11]. It was also found that the treatment effect of non-type 1 ROP eyes was better than that of type 1 ROP eyes, which may be related to the mild condition and the use of different types of anti-VEGF drugs. In this study, the proportion of fusion protein drugs used was higher in the non-type 1 ROP group (87.2%) than that in the type 1 ROP group (54.5%). This might be other potential reason for statistically significant difference in treatment effects between the two groups. Some studies found that the recurrence rate of ROP eyes treated with fusion protein drugs (conbercept or aflibercept) was lower than that of ROP eyes treated with ranibizumab [12,13]. The drug selection in our study was associated with the time to market in China.

Table 5
Studies of non-type 1 ROP treatment.

Investigator	Time published	Country	Method	Case	Treatment	Reasons of treatment[β]
Gupta MP et al[3]	2016	USA	multicenter retrospective study	A total of 137 eyes treated,13 eyes with non-Type 1 ROP	laser	concerning structural changes; persistent ROP at an advanced PMA (41w); vitreous hemorrhage; active ROP with the fellow eye being treated for type 1 ROP
LiuT et al [5]	2019	USA	multicenter retrospective study	A total of 1004 eyes,126 eyes with non-Type 1 ROP	Laser in 122 eyes and IVR[α] in 4 eyes	fellow eye with type 1 ROP;stage 3 ROP with pre-plus;others: concerning structural changes in the retina; persistent stage 3 for ≥ 6 weeks without regression; stage 3 with no plus; stage 3, zone III with plus; logistical considerations; stage 2 disease.
Rajan RP et al[11]	2020	India	retrospective study	A total of 241eyes treated,33eyes with non-Type 1 ROP	Laser in 32 eyes, IVR[α]in 1 eye	structural changes; pre-plus disease;persistent stage 3 ROP that did not show any sign of regression for 6 weeks; active ROP with fellow eye being treated.
Koucheki R et al[16]	2020	Canada	retrospective study	2,356 Cases, and 115 cases (172 eyes) with stage-3 ROP persisting ≥ PMA 40w	Of 21 cases (33 eyes) treated by laser, 17 eyes with non-type 1 ROP	≥ 2 continuous clock hours of persistent stage 3 crossing the temporal horizontal midline and pre-plus

[α]IVR: intravitreal injection of bevacizumab.

[β]Reasons of treatment were arranged in descending order of proportion.

Of eyes with non-type 1 ROP treated in this study, 63 cases (96.9%) had more lesions in zone II, and 41 eyes (63.1%) and 22 eyes (33.8%) had more lesions in stages 2 and 3, respectively. The characteristics of pathological manifestation were similar to those of the finding of Gupta MP et al [3], in which, 11 eyes (84.6%)

had lesions in zone II, and 12 eyes (92.3%) had lesions in stages 2 and 3. While in the study of Liu T et al[5], most eyes (66%) had pre-plus lesions in zone II stage 3. The above evidence suggests that ROP should be checked carefully about the changes of lesions at stage 2 or 3 in zone II.

The main treatment reason for non-type 1 ROP eyes in this study was the pre-plus disease (89.2%), which was different from previous studies. In the study of Gupta MP et al and Rajan RP et al., the most important treatment reason was structural changes in the fundus caused by the traction of the ridge (69.2% and 72.7%, respectively) [3,11]. Pre-plus disease (33.3%) was the second reason in the study of Rajan RP et al[11]. The major reason in Liu et al's study was the contralateral eye with type 1 ROP (43%), followed by stage 3 ROP with pre-plus (30%)[5]. As for pre-plus and plus disease, ICROP3 defined it as a continuous spectrum of retinal vascular changes from normal, to pre-plus, and finally to plus disease. Consistent judgments of different scholars only in the normal and last plus stages[10]. This suggests a high possibility of clinical disagreement over pre-plus lesions, resulting in no typical plus lesions in some ROP eyes and further risk of retinal traction with progressive worsening of the ridge. Due to the use of anti-VEGF drugs, we paid more attention to the judgment of pre-plus in the ROP examination.

The second cause of treatment in this study was ridge changes (33.8%), shown as more obvious or/and more extent, or thickened and widened locally. Actually, the ridge changes were often accompanied by pre-plus (Fig. 1). Koucheki R et al confirmed that pre-plus was significantly correlated with increased ridges (≥2 continuous clock hours of persistent stage 3 crossing the temporal horizontal midline) in the eyes with stage-3 ROP persisting ≥40 weeks of PMA[16]. The ridge changes in this study were slightly lighter than the structural fundus changes mentioned in previous studies[3,5,11], and no macular traction, retinal traction, or folds were produced due to the tangential traction caused by the straightening of the temporal vessels in the fundus. Under these proliferation conditions, intravitreal injection of anti-VEGF drugs may not be recommended because of the risk of aggravated proliferation[17,18].

In this study, the simultaneous treatment of contralateral eyes accounted for 13.8%. Most previous studies considered that acute ROP commonly occurs in both eyes. For example, 79.1% of ROP infants have high-risk pre-threshold disease in both eyes at the time of enrollment in an ETROP study[1]. A study on Telemedicine Approaches to Evaluating of Acute-Phase Retinopathy of Prematurity (e-ROP) found that 72.7% of infants had the same severity of ROP in both eyes among ROP image sessions[15].

However, our study does not recommend arbitrary early treatment for non-type 1 ROP. Previous studies suggested that ROP with stage 3 can be treated when no regression is found after 41 weeks of PMA[3] or continuous 6 weeks of follow-up[5,11]. In this study, the average time of the first treatment for eyes with type 1 ROP was 38.6 weeks, while the follow-up of another 6 weeks was 44 weeks for non-type I ROP eyes with some of the above particular retinal features. Meanwhile, due to the use of anti-VEGF drugs, in order to avoid obvious fibrosis, we paid attention to the progression of lesions at stage 2 and stage 3. Therefore, our study considered a treatment for ROP infants with lesions at persistent stages 2 and 3 without regression at the corrected gestational age of 44 weeks or more, and whether there were other retinal manifestations was also taken into consideration. In this study, 4 cases (8 eyes) (12.3%) were followed up for ≥ 44 weeks and then received drug treatment, but the fundus was accompanied by pre-plus lesions or ridge aggravation or logistical considerations before treatment.

In this study, 4 eyes (6.2%) were treated for the logistical considerations that result in not timely follow-up. The logistical considerations of Liu T et al 's study were the difficulty in follow-up or general anesthesia for non-ROP surgery (3%)[5]. The intravitreal injection for ROP infants in this study was performed under topical anesthesia and there was no treatment under general anesthesia due to other diseases. For some ROP cases with difficulty in follow-up, detailed communication with the family before treatment is recommended to emphasize the importance of follow-up, especially after anti-VEGF drug treatment that requires longer follow-up.

This study still had some limitations. To avoid medical disputes caused by delayed treatment during clinical practice, no control group was set. So, it was unable to accurately judge the progression of non-type 1 ROP that did not receive treatment. The sample in the study group shall gradually be increased to collect untreated cases with non-type 1 ROP so as to investigate reasonable treatment methods in the future.

To summarize, non-type 1 ROP with some characteristics, such as pre-plus, ridge changes, treatment with contralateral eyes, no regression in persistent stage 2 or 3 for follow-up time ≥ 44 weeks, and logistical considerations, were cured or improved after intravitreal injection of anti-VEGF drugs. It is suggested that in clinical practice, personalized treatment can be carefully considered for some ROP in critical conditions based on expert consensus or guidelines.

Declarations

Acknowledgements

Funded by Project of Henan Science and Technology Development Plan (182102311209).

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Competing interests

The author(s) declare no competing interests.

Privacy Statements

This study was conducted with the approval of the Medical Ethics Committee of Henan Eye Hospital (Approval Number HNEECKY-2021 (49)). All infants' legal guardian(s) signed written informed consent including research purpose, process, benefits and risks, privacy protection, etc. In the privacy protection part of each informed consent, it was written informed that all research members and research related parties must keep the identities of infants and their guardians confidential. All data files would be kept in a locked filing cabinet for researchers' reference only. When necessary, members of the government administration or Medical Ethics Committee could access your personal data in the research unit according to regulations. If some information or images may be involved in an online open-access publication, patient names must be removed to protect children's privacy.

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Figures

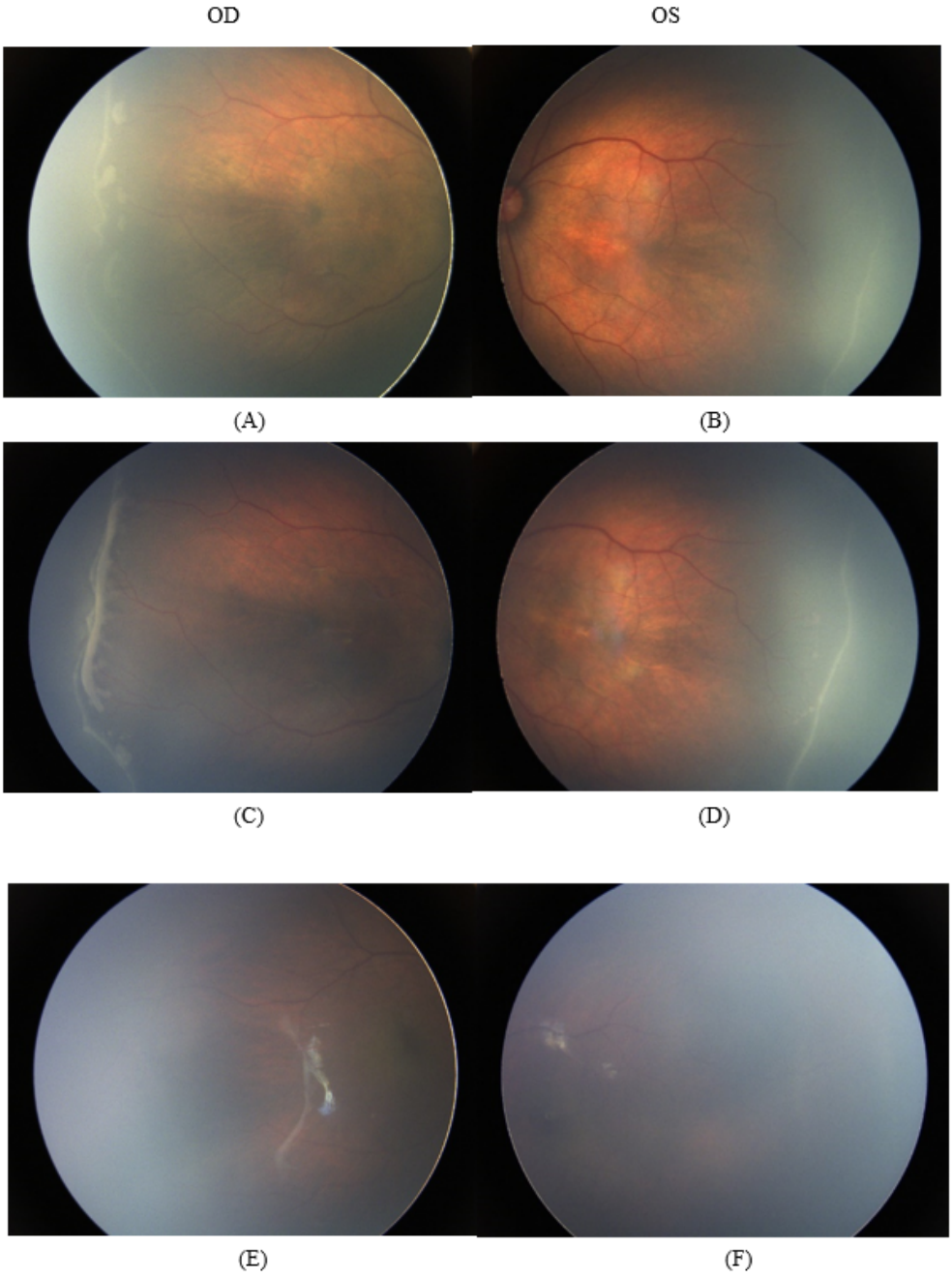

Figure 1

Retinal manifestation of non-Type 1 ROP. Case # 3, male, GA 30w, BW 1.3kg. the infants with zone II, stage 2 with plus (-) in both eyes was transferred to the first examination in PMA 39.1w (A, B). After 2 weeks (PMA 41.1w), the temporal ridge was thickened and widened with pre-plus in right eye, which was zone II, stage 3 with pre-plus (C). As the contralateral eye, the ridge was more obvious and extended, which was still zone II,stage 2 with plus (-) (D). The bilateral retinal vessels grew to the periphery of zone IIIat 27.9 weeks(PMA 69.0w) after intravitreal injection of conbercept (E, F).