Research Article

Treatment for Nontype 1 Retinopathy of Prematurity by Intravitreal Injection of Antivascular Endothelial Growth Factor Drugs

Haitao Zhang,1 Xin Yang,1 Fangfang Zheng,2 Xiangke Yin,1 and Suhua Wan1

1Henan Provincial People’s Hospital, Henan Eye Hospital, Henan Eye Institute, People’s Hospital of Zhengzhou University, Zhengzhou 450003, China
2Neonatal Intensive Care Unit of Henan Provincial People’s Hospital, People’s Hospital of Zhengzhou University, Zhengzhou 450003, China

Correspondence should be addressed to Haitao Zhang; zhanghaitaobiology@163.com

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Background. To explore clinical characteristics and treatment reasons for intravitreal injection of antivascular endothelial growth factor (anti-VEGF) drugs in the treatment of nontype 1 retinopathy of prematurity (ROP).

Methods. A retrospective study was conducted to screen the nontype 1 ROP from the collected ROP patients who received intravitreal injections of anti-VEGF drugs in Henan Eye Hospital from September 2018 to June 2021.

Results. A total of 138 ROP cases (262 eyes) were included in this study, including 39 cases (28.3%), 65 eyes (24.8%) that were the nontype 1 ROP. Compared with the type 1 ROP group, the nontype 1 ROP group had slightly later treatment time (39.8 ± 2.7 weeks vs 38.1 ± 2.6 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%) improved in the nontype 1 ROP group, without recurrence and aggravation cases. There were more lesions in zone II (63 eyes, 96.9%), with stage 2 (40 eyes, 61.5%) and stage 3 (23 eyes, 35.4%), and 58 eyes (89.2%) showed preplus in the nontype 1 ROP group. Treatment reasons included preplus in 58 eyes (89.2%), ridge aggravation in 22 eyes (33.8%), simultaneous treatment of the contralateral eye in 9 eyes (13.8%), no regression of lesions in the persistent stage 2 or 3 over PMA 44 weeks of follow-up in 8 eyes (12.3%), and logistical considerations in 4 eyes (6.2%).

Conclusions. Considering some peculiar clinical characteristics, treatment by intravitreal injection of anti-VEGF drugs may be considered carefully for some nontype 1 ROP in critical conditions.

1. Introduction

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disease that occurs in premature and low-weight infants, and it mostly affects both eyes and may cause retinal detachment and blindness. Current treatments of ROP include laser photocoagulation and intravitreal injection of antivascular endothelial growth factor (anti-VEGF) drugs. The Early Treatment for Retinopathy of Prematurity (ETROP) and the latest expert consensus or guidelines recommend treatment for type 1 ROP and close follow-up for type 2 ROP [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 nontype 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 nontype 1 ROP receive treatment in different countries [3–6]. In recent years, intravitreal injection of anti-VEGF drugs 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 nontype 1 ROP in critical conditions. In this study, the nontype 1 ROP cases who had received intravitreal injection of anti-VEGF drugs were enrolled in our hospital were categorized to analyze the treatment effect, clinical characteristics, and treatment reasons and to explore the personalized diagnosis and treatment for ROP with special clinical characteristics.

2. Methods

2.1. 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 nontype 1 ROP cases were subgrouped. This study was conducted with the approval of the Medical Ethics Committee of Henan Eye Hospital (Approval Number HNNECKY-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.

2.2. 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 nontype 1 ROP. Infants with unstable vital signs caused by systemic diseases in the heart, brain, lung, or accompanied by other fundus lesions were excluded.

2.3. 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 professor (Haitao Zhang, associated professor), and then, diagnosis and treatment suggestions were made. Information of name, gender, gestational age (GA), birth weight (BW), and the time of examination and injection were 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 (0.25 mg/0.025 ml), conbercept (0.25 mg/0.025 ml), and aflibercept (1 mg/0.025 ml). 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 ocular infection, and the first eye review was conducted within 7 days. The interval of the next review (1–3 weeks) should be determined according to the retinal manifestations, and patients should 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 the 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 nontype 1 ROP group. The curative effect, retinal pathological characteristics, and causes for the treatment of nontype 1 ROP were analyzed according to the number of eyes. The characteristics of included subjects were analyzed according to the number of cases.

2.4. 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 nonvascular areas, but without obvious active lesions at the last follow-up. (3) Recurrence. The tortuous dilation of retinal vessels was relieved 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 nontype 1 ROP were as follows: (1) preplus diseases in the retina; (2) ridge aggravation, 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 the persistent stage 2 or 3 over PMA (postmenstrual age) 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).

2.5. Data Analyses. Data analyses were performed using the SPSS 19.0 statistical software. The differences in birth gestational age (GA), birth weight (BW), hospitalization days in NICU, first injection time, and follow-up time were compared by the t-test, and the differences in gender and drug types were compared by the $\chi^2$ test. The treatment effect was analyzed according to the number of afflicted eyes and compared by the $\chi^2$ test. $P < 0.05$ was considered statistically significant.
3. Results

3.1. 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 nontype 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 nontype 1 ROP in the contralateral eye.

The characteristics of subjects with the nontype 1 ROP and type 1 ROP are shown in Table 1. There was no significant difference in GA, BW, 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 nontype 1 ROP group was slightly later than that of the type 1 ROP group ($39.8 \pm 2.7$ weeks vs $38.1 \pm 2.6$ weeks, $P < 0.01$). The difference in the types of anti-VEGF drugs was significant ($P < 0.05$), with a higher proportion of fusion protein drugs in the nontype 1 ROP group (87.2%) than that in the type 1 ROP group (54.5%).

3.2. Effect Assessment. According to the number of eyes ($n = 262$), 65 eyes (24.8%) were nontype 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 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 retinal conditions improved.

3.3. Reasons for the Treatment. Of all treated eyes with nontype 1 ROP ($n = 65$) (Table 3), 63 eyes (96.9%) had ROP lesions in zone II, of which there were 5 eyes (3.1%) in posterior zone II and 2 eyes (3.1%) with ROP in zone I. In terms of stage, there were more lesions in stages 2 and 3, with 40 eyes (61.5%) and 23 eyes (35.4%), respectively. In terms of plus diseases, 58 eyes (89.2%) showed preplus. As for treatment reasons, the main reason was preplus in 58 eyes (89.2%), followed by ridge aggravation 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 PMA 44 weeks of follow-up in 8 eyes (12.3%), and logistical considerations in 4 eyes (6.2%). The above reasons could exist simultaneously (Figure 1). The preoperative features and specific reasons for treated nontype 1 ROP cases are shown in Table 4.

4. Discussion

Some previous studies analyzed the treatment reasons of nonype 1 ROP (Table 5) [3, 5, 11, 12], but the main treatment method in these studies was laser photocoagulation. No literature had been retrieved to explore the effect of intravitreal injection of anti-VEGF drugs on the treatment of nontype 1 ROP currently. Laser photocoagulation and anti-VEGF therapy are the main options for ROP currently. Laser therapy led to permanent destruction of the peripheral retina, and peripheral retinal vessels continued to develop after anti-VEGF agents’ treatment [13]. As to efficacy compared to laser therapy, anti-VEGF agents as primary treatments had potential advantages for the eyes with posterior ROP (zone I type 1 ROP and A-ROP), and for the eyes with zone II type 1 ROP, anti-VEGF agents therapy showed similar efficacy; however, there was a significantly higher rate of reactivation [14]. Laser-treated eyes had a greater trend to myopia and astigmatism than anti-VEGF therapy [14, 15]. For the above reasons, anti-VEGF therapy performed under topical anesthesia was preferred for treatment with ROP during our clinical practice, and laser therapy was the used option for ROP with the risk of obvious fibrosis or the recurrent eyes. In addition, laser coagulation for ROP needed to be operated under general anesthesia which most parents of neonates were reluctant to choose in China.

Of the 263 eyes treated in this study, 65 eyes (24.8%) were nontype 1 ROP, showing a higher proportion than that in previous studies (9.5–13.7%) [3, 5, 11]. Because of that, the treatment for ROP cases in this study was an intravitreal injection of anti-VEGF drugs, which are simpler operated and more minimally invasive than laser therapy [13]. In this study, lesions in all eyes with nontype 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 the nontype 1 ROP eyes was better than that of type 1 ROP eyes, which may mainly be related to the milder condition. In this study, the proportion of fusion protein drugs used was higher in the nontype 1 ROP group (87.2%) than that in the type 1 ROP group (54.5%). This might be another potential reason for the difference in treatment effects between the two groups. Some retrospective studies found that the recurrence rate of the ROP eyes treated with fusion protein drugs (conbercept or aflibercept) was lower than that of the ROP eyes treated with ranibizumab [16, 17]. But a multicentric prospective trial comparing clinical outcomes of conbercept vs ranibizumab treatment for ROP found there was no significant statistical difference in the recurrence rate between the two anti-VEGF agents [18]. It is still controversial whether there is a difference between the efficacy of ranibizumab and fusion protein drugs in the treatment of ROP. The different proportion of drug selection in our study was associated with the time to market in China.

Of the eyes with nontype 1 ROP treated in this study, 63 cases (96.9%) had more lesions in zone II, and 40 eyes (61.5%) and 23 eyes (35.4%) had more lesions in stages 2 and 3, respectively. The characteristics of pathological manifestation were similar to those of the finding of Gupta 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 preplus 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 the nontype 1 ROP eyes in this study was the preplus disease (89.2%), which was different from the previous studies [3, 5, 11]. In the study of Gupta et al. and Rajan 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]. Preplus disease (33.3%) was the second reason in the study of Rajan 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 preplus (30%) [5]. As for preplus and plus disease, ICROP3 defined it as a continuous spectrum of retinal vascular changes from normal to preplus and finally to plus disease. Consistent judgments of different scholars are only in the normal and last plus stages [10]. This suggests a high possibility of clinical disagreement over preplus lesions, resulting in no typical plus lesions in some ROP eyes and a 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 preplus in the ROP examination.

The second cause of treatment in this study was ridge aggravation (33.8%), shown as more obvious or/and more extension, or thickened and widened locally. Actually, the ridge aggravation was often accompanied by preplus (Figure 1). Koucheki et al. confirmed that preplus was significantly correlated with increased ridges (≥2 continuous clock hours of the persistent stage 3 crossing the temporal horizontal midline) in the eyes with stage 3 ROP persisting ≥40 weeks of PMA [12]. The ridge aggravation in this study was slightly milder than the structural changes such as macular traction, retinal traction, or folds produced due to

| Parameters | Nontype type I ROP group (N = 65) | Type 1 ROP group (N = 197) | Statistic value | P |
|------------|---------------------------------|---------------------------|----------------|----|
| GA (week)  | 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 |
| Hospitalization days in NICU (day) | 56.3 ± 23.2              | 53.6 ± 28.8               | 0.521          | 0.603 |
| Time of the first treatment (week) | 39.8 ± 2.7               | 38.1 ± 2.6                | 3.461          | 0.001 |
| Follow-up time (week) | 29.5 ± 10.1                | 33.6 ± 15.4               | 1.537          | 0.127 |
| Anti-VEGF drugs (N (%)) | Ranibizumab 5 (12.8) | 45 (45.5)                 | 12.896         | 0.000 |
| Fusion proteins (conbercept and aflibercept) | 34 (87.2)                   | 54 (54.5)                 |                |     |

**Table 1: Characteristics of subjects with type 1 and nontype 1 ROP (N = 138).**

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

| Parameters | Nontype type I ROP eyes | Type 1 ROP eyes | χ² value | P |
|------------|-------------------------|----------------|----------|----|
| 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)      |          |     |

**Table 3: Characteristics of pathological manifestation of nontype 1 ROP receiving treatment.**

| Characteristics | Nontype 1 treated eyes (N = 65) |
|-----------------|----------------------------------|
| Zone            |                                  |
| I               | 2                                |
| II              | 63                               |
| Posterior II    | 5                                |
| Periphery II    | 58                               |
| Stage           |                                  |
| 1               | 2                                |
| 2               | 40                               |
| 3               | 23                               |
| Plus disease    |                                  |
| –               | 7                                |
| ±               | 58                               |
| Reasons         |                                  |
| Preplus         | 58                               |
| Ridge aggravation | 22                             | 33.8 |
| Contralateral eye | 9                              | 13.8 |
| Follow-up time ≥ PMA44w | 8                        | 12.3 |
| Logistical considerations | 4                             | 6.2  |

α, referred to preplus diseases.
Table 4: List of nontype 1 ROP cases that received intravitreal injection of anti-VEGF drugs (N = 39).

| ID. | Gender | GA (w) | BW (kg) | Eyes | Zonea | Stage | Plusb | Range (hr) | Time of the first treatment (week) | Medicinec | Reasons for treatmentd |
|-----|--------|--------|---------|------|--------|-------|-------|------------|----------------------------------|------------|----------------------------|
| 1   | Male   | 26.6   | 0.95    | OD   | II     | 2     | ±     | 7          | 42.2                              | C          | Preplus                    |
| 2   | Male   | 27.6   | 1.00    | OD   | II     | 2     | ±     | 6          | 43.6                              | C          | Follow-up time ≥44 w, ridge aggravation, preplus |
| 3   | Male   | 30.0   | 1.30    | OD   | II     | 2     | ±     | 6          | 41.3                              | C          | Ridge aggravation, preplus |
| 4   | Female | 29.0   | 0.90    | OD   | II     | 2     | -     | 5          | 42.3                              | C          | Ridge aggravation, contralateral eye |
| 5   | Male   | 28.7   | 1.30    | OD   | I      | 1     | ±     | 12         | 34.0                              | C          | Preplus, logistical considerations |
| 6   | Female | 30.0   | 1.66    | OD   | II     | 2     | ±     | 5          | 38.0                              | R          | Preplus                    |
| 7   | Female | 27.6   | 1.10    | OD   | II     | 2     | ±     | 6          | 38.6                              | R          | Ridge aggravation, preplus |
| 8   | Female | 27.0   | 0.98    | OD   | II     | 2     | ±     | 5          | 36.3                              | C          | Preplus                    |
| 9   | Male   | 29.4   | 1.10    | OD   | II     | 2     | ±     | 6          | 40.7                              | R          | Preplus                    |
| 10  | Male   | 32.0   | 1.50    | OD   | II     | 3     | ±     | 6          | 40.9                              | R          | Type 1                     |
| 11  | Male   | 30.7   | 1.66    | OD   | II     | 2     | ±     | 5          | 35.6                              | C          | Preplus                    |
| 12  | Male   | 30.0   | 1.63    | OD   | II     | 3     | ±     | 5          | 38.4                              | A          | Ridge aggravation, preplus, contralateral eye |
| 13  | Male   | 26.9   | 0.72    | OD   | II     | 3     | ±     | 12         | 37.6                              | C          | Preplus                    |
| 14  | Female | 28.4   | 1.05    | OD   | II     | 3     | -     | 5          | 44.7                              | C          | Follow-up time ≥44 w, ridge aggravation |
| 15  | Female | 28.9   | 1.13    | OD   | Posterior II | 2   | +    | 12         | 39.8                              | C          | Contralateral eye           |
| 16  | Female | 27.0   | 0.73    | OD   | III    | 2     | -     | 4          | 39.7                              | C          | Ridge aggravation, preplus |
| 17  | Female | 26.7   | 0.71    | OD   | II     | 2     | ±     | 6          | 39.8                              | C          | Preplus                    |
| 18  | Male   | 27.3   | 1.10    | OD   | II     | 2     | ±     | 10         | 37.7                              | C          | Preplus                    |
| 19  | Female | 25.6   | 0.90    | OD   | II     | 2     | -     | 3          | 39.6                              | C          | Ridge aggravation, preplus |
| 20  | Male   | 26.7   | 0.85    | OD   | II     | 2     | ±     | 7          | 43.3                              | C          | Ridge aggravation, preplus |

a: Zone
b: Stage
c: Medicine
d: Reasons

Note: NA: Not applicable
| ID. | Gender | GA (w) | BW (kg) | Eyes | Zone<sup>a</sup> | Stage | Plus<sup>b</sup> | Range (hr) | Time of the first treatment (week) | Medicine<sup>c</sup> | Reasons for treatment<sup>d</sup> |
|-----|--------|--------|---------|------|-----------------|-------|-------------|-----------|-----------------------------------|----------------|----------------------------------|
| 21  | Female | 25.9   | 0.86    | OD   | Posterior II    | 2     | ± 10        | 38.0      | C                                 | Preplus         |                                  |
| 22  | Male   | 26.9   | 0.68    | OD   | Posterior II    | 2     | ± 12        | 37.2      | A                                 | Preplus         |                                  |
| 23  | Male   | 27.6   | 1.10    | OD   | Posterior II    | 3     | ± 12        | 36.6      | A                                 | Preplus         |                                  |
| 24  | Male   | 28.0   | 1.17    | OD   | Posterior II    | 2     | ± 10        | 37.1      | C                                 | Preplus         |                                  |
| 25  | Male   | 31.0   | 1.75    | OD   | II              | 3     | ± 5         | 38.9      | A                                 | Ridge aggravation, preplus |                      |
| 26  | Female | 27.9   | 1.13    | OD   | II              | 2     | ± 5         | 40.5      | C                                 | Preplus         |                                  |
| 27  | Female | 29.4   | 1.00    | OD   | II              | 2     | ± 6         | 43.4      | C                                 | Preplus         |                                  |
| 28  | Female | 27.0   | 1.10    | OD   | II              | 3     | ± 5         | 42.6      | C                                 | Ridge aggravation, preplus |                      |
| 29  | Female | 27.3   | 1.08    | OD   | II              | 2     | ± 5         | 37.7      | C                                 | Preplus         |                                  |
| 30  | Male   | 28.4   | 1.19    | OD   | II              | 2     | ± 4         | 43.8      | C                                 | Preplus         |                                  |
| 31  | Male   | 26.7   | 0.75    | OD   | II              | 2     | ± 10        | 40.8      | C                                 | Preplus         |                                  |
| 32  | Female | 29.7   | 1.25    | OD   | II              | 3     | ± 6         | 40.0      | C                                 | Ridge aggravation, preplus |                      |
| 33  | Female | 33.1   | 1.80    | OD   | II              | 3     | ± 6         | 44.8      | C                                 | Ridge aggravation, preplus, follow-up time ≥44 w |                      |
| 34  | Male   | 27.9   | 0.97    | OD   | II              | 2     | ± 12        | 36.9      | R                                 | Type 1          |                                  |
| 35  | Female | 27.9   | 1.18    | OD   | II              | 2     | ± 3         | 39.8      | C                                 | Ridge aggravation, preplus |                      |
| 36  | Male   | 31.9   | 2.28    | OD   | II              | 2     | ± 6         | 39.0      | A                                 | Contralateral eye, preplus |                      |
| 37  | Male   | 25.6   | 0.74    | OD   | II              | 2     | ± 12        | 39.0      | C                                 | Preplus         |                                  |
| 38  | Male   | 30.6   | 1.50    | OD   | II              | 2     | ± 6         | 37.7      | A                                 | Preplus, contralateral eye |                      |
| 39  | Female | 29.0   | 1.26    | OD   | II              | 3     | ± 6         | 40.9      | C                                 | Ridge aggravation, preplus, contralateral eye |                      |

<sup>a</sup>II referred to periphery zone II. <sup>b</sup>± referred to preplus. <sup>c</sup>R, C, and A represent ranibizumab, conbercept, and aflibercept. NA refers untreated. <sup>d</sup>One eye of type 1 ROP and the contralateral eye of nontype 1 ROP in 6 cases (ID. 10, 12, 15, 34, 38, 39). One eye of nontype 1 ROP and contralateral eye untreated in 7 cases (ID. 13, 16, 19, 20, 27, 30, 35).
the tangential traction caused by the straightening of the temporal vessels in the fundus mentioned in previous studies [3, 5, 11]. Under these fibrosis conditions, intravitreal injection of anti-VEGF drugs may not be recommended because of the risk of aggravated traction [19, 20].

In this study, the simultaneous treatment of the contralateral eyes accounted for 13.8%. Most previous studies considered that acute ROP commonly occurs in both the eyes. For example, 79.1% of ROP infants have high-risk prethreshold disease in both the 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 the eyes among ROP image sessions [21].

However, our study does not recommend arbitrary early treatment for nontype 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 the eyes with type 1 ROP was 38.1 weeks, while the follow-up of another 6 weeks was 44 weeks for the nontype I ROP eyes with some of the above particular retinal features. Meanwhile, due to the use of anti-VEGF drugs, in

**Figure 1:** Nontype 1 ROP eyes considered to be treated due to multiple reasons. Case no. 3, male, GA 30 w, BW 1.3 kg. ROP in zone II, stage 2 with plus (−) in both the eyes was transferred to examination in PMA 39.1w (a, b). After 2 weeks (PMA 41.1w), the temporal ridge was thickened and widened with preplus in the right eye, which was ROP in zone II, stage 3 with preplus (c). As the contralateral eye, the ridge was more obvious and extended, which was still ROP in zone II, stage 2 with plus (−) (d). The bilateral retinal vessels grew to the periphery of zone III at 27.9 weeks (PMA 69.0w) after intravitreal injection of conbercept (e, f).
| Investigator         | Time published | Country | Method                        | Cases                                                                 | Treatment | Reasons of treatment<sup>a</sup>                                                                 |
|----------------------|----------------|---------|-------------------------------|----------------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------|
| Gupta et al. [3]     | 2016           | USA     | Multicenter retrospective study | A total of 137 eyes treated, 13 eyes with nontype 1 ROP              | Laser     | Concerning structural changes, persistent ROP at an advanced PMA (41 w), vitreous hemorrhage, and active ROP with the fellow eye being treated for type 1 ROP Fellow eye with type 1 ROP, stage 3 ROP with preplus, and 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. |
| Liu et al. [5]       | 2019           | USA     | Multicenter retrospective study | A total of 1004 eyes, 126 eyes with nontype 1 ROP                    | Laser in 122 eyes and IVR<sup>b</sup> in 4 eyes | Structural changes, preplus disease, persistent stage 3 ROP that did not show any sign of regression for 6 weeks, and active ROP with the fellow eye being treated. |
| Rajan et al. [11]    | 2020           | India   | Retrospective study           | A total of 241 eyes treated, 33 eyes with nontype 1 ROP              | Laser in 32 eyes, IVR<sup>b</sup> in 1 eye | Stage 3 crossing the temporal horizontal midline and preplus                                       |
| Koucheki et al. [12] | 2020           | Canada  | Retrospective study           | 2,356 cases and 115 cases (172 eyes) with stage 3 ROP persisting ≥PMA 40 w | Of 21 cases (33 eyes) treated by laser, 17 eyes with nontype 1 ROP | ≥2 continuous clock hours of persistent stage 3 crossing the temporal horizontal midline and preplus |

<sup>a</sup>IVR, intravitreal injection of bevacizumab. <sup>b</sup>Reasons of treatment were arranged in the descending order of proportion.
order to avoid obvious fibrosis, we paid more 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 PMA 44 weeks or more and whether there were other retinal manifestations were also taken into consideration. In this study, 4 cases (8 eyes) (12.3%) were followed up for ≥ PMA 44 weeks and then received anti-VEGF treatment, and the fundus was simultaneous with preplus lesions or ridge aggravation or logistical considerations before treatment. During the struggling follow-up period, more attention should be paid to the changes of extraretinal neovascular proliferation, and the anti-VEGF therapy should be performed in time before the fibrosis is obvious. Once obvious fibrosis has formed, laser coagulation will be recommended because retinal traction may be aggravated after anti-VEGF treatment [19, 20]. Unlike other ocular neovascular conditions (e.g., wetAMD), in which VEGF is continually released, there is a single burst of VEGF that promotes neovascularization in ROP [22]. The delayed anti-VEGF therapy given at a period when VEGF levels are decreasing may promote fibrosis driven by transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF) [23–25]. Traction from fibrosis may cause retinal detachments.

In this study, 4 eyes (6.2%), 2 cases (Nos. 4 and 5, Table 4) were treated for the logistical considerations, that is, follow-up might not be timely due to various reasons. Their parents lived far away or affected by epidemic control reasons (all eyes accompanied by other reasons, such as preplus or follow-up time ≥ PMA44w) and might not be followed up in time, and treatment was chosen considering that the retinal lesions tended to aggravate at the same time. The logistical considerations of Liu et al.’s study were the difficulty in follow-up or general anesthesia for non-ROP surgery (3%) [5]. The intravitreal injections for ROP infants in our study were 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 parents before treatment was recommended to emphasize the importance of follow-up, especially after anti-VEGF drug treatment that requires longer follow-up. In fact, the 2 cases were followed up in our hospital within 4 weeks after treatment. Then, the following examinations from the 6th week were started in the local hospital and the regular examination results including some retinal images would be transmitted to our research group through WeChat or the network of telemedicine.

Our study had some limitations. First, to avoid medical disputes caused by delayed treatment during clinical practice, there was no control group set. So, it was unable to accurately judge the progression of nontype 1 ROP with aggravating tendency if not treated. The sample in the study was performed under topical anesthesia, and in our study were performed under topical anesthesia, and in our study were performed under topical anesthesia, and no regression in the persistent stage 2 or 3 for follow-up ≥ PMA 44 weeks, and logistical considerations, can be considered carefully to receive intravitreal injection of anti-VEGF drugs based on current expert consensus or guidelines.

5. Conclusions

Nontype 1 ROP with some characteristics, such as preplus, ridge aggravation, treatment with contralateral eyes, no regression in the persistent stage 2 or 3 for follow-up ≥ PMA 44 weeks, and logistical considerations, can be considered carefully to receive intravitreal injection of anti-VEGF drugs.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

A preprint has previously been published [31].

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] W. V. Good, “Early Treatment for Retinopathy of Prematurity Cooperative Group Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial,” *Transactions of the American Ophthalmological Society*, vol. 102, pp. 233–248, 2004.

[2] W. M. Fierson, W. Good, D. Phelps et al., “Screening examination of premature infants for retinopathy of prematurity,” *Pediatrics*, vol. 142, no. 6, Article ID e20183061, 2018.

[3] M. P. Gupta, R. P. Chan, R. Anzures, S. Ostmo, K. Jonas, and M. F. Chiang, “Practice patterns in retinopathy of prematurity treatment for disease milder than recommended by guidelines,” *American Journal of Ophthalmology*, vol. 163, pp. 1–10, 2016.

[4] B. A. Darlow, K. Lui, S. Kusuda et al., “International variations and trends in the treatment for retinopathy of prematurity,” *British Journal of Ophthalmology*, vol. 101, no. 10, pp. 1399–1404, 2017.

[5] T. Liu, L. A. Tomlinson, G. S. Ying, M. B. Yang, and G. Binenbaum, “Treatment of non-type 1 retinopathy of prematurity in the postnatal growth and retinopathy of prematurity (G-ROP) study,” *Journal of American Association for Pediatric Ophthalmology and Strabismus*, vol. 23, no. 6, 2019.

[6] M. A. Sekeroglu, E. Hekimoglu, H. T. Sekeroglu, and U. Arslan, “Retinopathy of prematurity: a nationwide survey to evaluate current practices and preferences of ophthalmologists,” *European Journal of Ophthalmology*, vol. 23, no. 4, pp. 546–552, 2013.

[7] Q. Huang, Q. Zhang, P. Fei et al., “Ranibizumab injection as primary treatment in patients with retinopathy of prematurity: anatomic outcomes and influencing factors,” *Ophthalmology*, vol. 124, no. 8, pp. 1156–1164, 2017.

[8] N. Marlow, A. Stahl, D. Lepore et al., “2-year outcomes of ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (rainbow extension study): prospective follow-up of an open label, randomised controlled trial,” *The Lancet Child & Adolescent Health*, vol. 5, no. 10, pp. 698–707, 2021.

[9] M. J. Sankar, J. Sankar, and P. Chandra, “Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity,” *Cochrane Database of Systematic Reviews*, vol. 1, Article ID CD009734, 2018.

[10] M. F. Chiang, G. E. Quinn, A. R. Fielder et al., “International classification of retinopathy of prematurity, third edition,” *Ophthalmology*, vol. 128, no. 10, pp. e51–e68, 2021.

[11] R. P. Rajan, P. Kohli, N. Babu, C. Dakshayini, M. Tandon, and K. Ramasamy, “Treatment of retinopathy of prematurity (ROP) outside international classification of ROP (ICROP) guidelines,” *Graefes Archive for Clinical and Experimental Ophthalmology*, vol. 258, no. 6, pp. 1205–1210, 2020.

[12] R. Koucheki, M. Isaac, N. N Tehrani, and K. Mireskandari, “Natural history and outcomes of stage 3 retinopathy of prematurity persisting beyond 40 weeks of post-menstrual age: dilemma for treatment and follow up,” *Clinical and Experimental Ophthalmology*, vol. 48, no. 7, pp. 956–963, 2020.

[13] H. A. Mintz-Hittner, K. A. Kennedy, and A. Z. Chuang, “Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity,” *New England Journal of Medicine*, vol. 364, no. 7, pp. 603–615, 2011.

[14] D. Linghu, Y. Cheng, X. Zhu et al., “Comparison of intravitreal anti-VEGF agents with laser photoagulation for retinopathy of prematurity of 1, 627 eyes in China,” *Frontiers of Medicine*, vol. 9, Article ID 911095, 2022.

[15] Q. Q. Tan, S. P. Christiansen, and J. Wang, “Development of refractive error in children treated for retinopathy of prematurity with anti-vascular endothelial growth factor (anti-VEGF) agents: a meta-analysis and systematic review,” *PLoS One*, vol. 14, no. 12, Article ID e0225643, 2019.

[16] Y. Cheng, X. Zhu, D. Linghu, and J. Liang, “Comparison of the effectiveness of conbercept and ranibizumab treatment for retinopathy of prematurity,” *Acta Ophthalmologica*, vol. 98, no. 8, pp. e1004–e1008, 2020.

[17] E. A. Sukgen and Y. Koçluk, “Comparison of clinical outcomes of intravitreal ranibizumab and aflibercept treatment for retinopathy of prematurity,” *Graefes Archive for Clinical and Experimental Ophthalmology*, vol. 257, no. 1, pp. 49–55, 2019.

[18] Z. Wu, J. Zhao, W. Lam et al., “Comparison of clinical outcomes of conbercept versus ranibizumab treatment for retinopathy of prematurity: a multicentric prospective randomised controlled trial,” *British Journal of Ophthalmology*, vol. 106, no. 7, pp. 975–979, 2022.

[19] S. Honda, H. Hirabayashi, Y. Tsukahara, and A. Negi, “Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity,” *Graefes Archive for Clinical and Experimental Ophthalmology*, vol. 246, no. 7, pp. 1061–1063, 2008.

[20] E. H. Wood, P. Rao, S. N. Moyoisi et al., “Fellow eye anti-VEGF ‘crunch’ effect in retinopathy of prematurity,” *Ophthalmic Surg Lasers Imaging Retina*, vol. 49, no. 9, pp. e102–e104, 2018.

[21] G. S. Ying, W. Pan, G. E. Quinn, E. Daniel, M. X. Repka, and A. Baumritter, “Intereye agreement of retinopathy of prematurity from image evaluation in the telemedicine Approaches to evaluating of acute-phaseROP (e-ROP) study,” *Ophthalmology Retina*, vol. 1, no. 4, pp. 347–354, 2017.

[22] J. A. Micieli, M. Sorkont, and A. F. Smith, “A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity,” *American Journal of Ophthalmology*, vol. 148, no. 4, 2009.

[23] K. A. Drnser, “Anti-angiogenic therapy in the management of retinopathy of prematurity,” *Developments in Ophthalmology*, vol. 44, pp. 89–97, 2009.

[24] I. Klaassen, R. J. van Geest, E. J. Kuiper, C. J. van Noorden, and R. O. Schlingemann, “The role of CTGF in diabetic retinopathy,” *Experimental Eye Research*, vol. 133, pp. 37–48, 2015.

[25] M. E. Hartnett, “Vascular endothelial growth factor antagonist therapy for retinopathy of prematurity,” *Clinics in Perinatology*, vol. 41, no. 4, pp. 925–943, 2014.

[26] W. C. Wu, C. P. Shih, R. Lien et al., “Serum vascular endothelial growth factor After bevacizumab or ranibizumab treatment for retinopathy of prematurity,” *Retina*, vol. 37, no. 4, pp. 694–701, 2017.

[27] X. Chen, L. Zhou, Q. Zhang, Y. Xu, P. Zhao, and H. Xia, “Serum vascular endothelial growth factor levels before and after intravitreal ranibizumab injection for retinopathy of prematurity,” *Journal of Ophthalmology*, vol. 2019, Article ID 2985161, 6 pages, 2019.

[28] Y. Cheng, S. Sun, X. Deng et al., “Systemic conbercept pharmacokinetics and VEGF pharmacodynamics following intravitreal injections of conbercept in patients with
retinopathy of prematurity,” *British Journal of Ophthalmology*, vol. 106, no. 9, pp. 1295–1300, 2021.

[29] C. Y. Huang, R. Lien, N. K. Wang et al., “Changes in systemic vascular endothelial growth factor levels after intravitreal injection of aflibercept in infants with retinopathy of prematurity,” *Graefes Archive for Clinical and Experimental Ophthalmology*, vol. 256, no. 3, pp. 479–487, 2018.

[30] M. Fidler, B. W. Fleck, A. Stahl et al., “Ranibizumab population pharmacokinetics and free VEGF pharmacodynamics in preterm infants with retinopathy of prematurity in the RAINBOW trial,” *Translational Vision Science & Technology*, vol. 9, no. 8, p. 43, 2020.

[31] H. Zhang, X. Yang, and F. Zheng, “Treatment for non-type 1 retinopathy of prematurity by intravitreal injection of anti-vascular endothelial growth factor drugs,” *Research Square*, 2022.