Recurrence Risk Factors of Intravitreal Ranibizumab Monotherapy in Retinopathy of Prematurity: A Retrospective Study at One Center

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Research Article

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Abstract

Purpose: The risk factors for retinopathy of prematurity (ROP) recurrence in patients with intravitreal ranibizumab (IVR) treatments after long-term follow-up are unclear, so we aimed to identify risk factors of recurrence of this disorder after IVR monotherapy.

Methods: We retrospectively reviewed 33 eyes of 19 patients who underwent initial IVR treatments for type 1 ROP at our center between April 1, 2016 and December 31, 2017. Patient demographics, the side of ROP, multiple gestations, Apgar scores, zone, stage, plus disease, postmenstrual age at injection, surfactant therapy, blood transfusion therapy, hemorrhage before IVR, hemorrhage after IVR, gestational diabetes mellitus, pregnancy-induced hypertension, anemia, intraventricular hemorrhage, sepsis, respiratory distress syndrome, carbohemia, and congenital heart defects were recorded. Adjusted hazard ratios (HRs) and 95% confidence intervals were determined after adjusting for potential confounders using multivariate proportional Cox regression.

Results: Of the 33 eyes, 12 (36.4%) had ROP recurrences 45.3 (5.1, 50.9) months after initial IVR treatments. The independent risk factors for ROP recurrences were zone [vs. , hazard ratio (HR): 0.056, P = 0.003] and gestational diabetes mellitus (no vs. yes, HR: 0.095, P < 0.001). The mean uncorrected visual acuity for four recurrence eyes was 0.46 logMAR (0.13, 0.70) at 55.0 (51.0, 58.9) months after the initial IVR treatment. The mean uncorrected visual acuity for 10 eyes without recurrence was 0.46 logMAR (0.19, 0.63) at 48.0 (43.8, 58.4) months after the initial IVR treatment.

Conclusions: We identified two independent risk factors for type 1 ROP recurrence after IVR treatment involving zone and gestational diabetes mellitus, and the mean uncorrected visual acuity was 0.46 logMAR at 51.0 (44.0, 58.9) months. The findings of this study are important for follow-up management and for improving the visual function of ROP patients.

Introduction

Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retina, which is one of the leading causes of childhood blindness worldwide [1, 2]. Although the etiology of ROP is multifactorial and not fully understood, vascular endothelial growth factor (VEGF) is a key factor in the progression of ROP [3]. In phase 1, both relative hyperoxia and decreased levels of VEGF led to delayed physiological retinal vascular development, resulting in a peripheral avascular area of the retina. In phase 2, the relative hypoxia and increased levels of VEGF led to vasoproliferation in the form of intravitreal angiogenesis [4].

Conventional laser treatment aims to destroy avascular retina cells, which produce VEGF. However, it has several disadvantages, such as ametropia and loss of the peripheral visual field. Anti-VEGF agents reverse pathological angiogenic changes, and induce the progression of a physiological retinal vasculature. With increasing use of anti-VEGF agents to treat ROP, some studies have reported that there was a significantly decreased rate of myopia and very high myopia compared with laser treatment [5-7]. However, intravitreal anti-VEGF therapy increases the risk of intraocular infection, delayed or incomplete

vascularization, and potential local and systemic developmental effects; therefore, patients need a longer and more frequent follow-up.

The BEAT-ROP study, which was the first multicenter randomized prospective trial, showed a lower recurrence of ROP following intravitreal bevacizumab, when compared with laser therapy in Zone I stage 3+ ROP [8]. Bevacizumab is a full-size monoclonal anti-VEGF antibody, which contains an Fc fragment, while ranibizumab is a monoclonal antibody Fab fragment lacking the Fc region. The Fc fragment may facilitate large molecule transport across the blood-brain barrier [9]. A study in rabbits found that ranibizumab was cleared from the vitreous with a terminal half-life of approximately 2.88 days, which was shorter than the bevacizumab half-life of 4.32 days [10]. These results showed rapid clearing from the vitreous, theoretically making ranibizumab a better option because of its lower systemic side effects to premature infants during neurodevelopment [10, 11]. However, in the treatment of ROP, ranibizumab may be associated with a higher incidence of recurrence compared with other anti-VEGF agents [12-16]. To completely determine vascularization, a longer follow-up schedule is important for patients treated with ranibizumab. Limited studies have reported the associations between perinatal factors and the recurrence of ROP in patients using anti-VEGF agents [12, 17-19]. However, the risk factors for ROP recurrence in patients with intravitreal ranibizumab (IVR) after long-term follow-up have not been clearly identified. Furthermore, visual acuities of preschool patients and refractive errors of ROP patients treated with IVR have not been reported. In this study, we therefore identified risk factors for recurrence in ROP patients with IVR monotherapy after long-term follow-ups. We also reported visual outcomes of preschool age patients in a part of patients.

Methods

Patients

We retrospectively studied 25 patients who were referred to the neonatal intensive care units and underwent initial IVR monotherapy at our center between April 1, 2016 and December 31, 2017. Six patients were excluded from the study because of loss of follow-ups, missing data, or neurodevelopmental impairment. In total, 19 patients were included in the final analysis (Fig. 1). Ethical approval (Ethical Committee No. 2021PS657K) was provided by the Institutional Research and Ethics Committee of the Shengjing Hospital Affiliated China Medical Universtiy in Shenyang, China. Informed consent from all legal guardians of the patients was obtained. This study adhered to the contenets of the Declaration of Helsinki. This trial is registered with www.chictr.org.cn/index.aspx, ChiCTR2100051203.

Inclusion and exclusion criteria

ROP screening was according to the Chinese screening criteria [20]. Infants were screened if they were born at gestational age of less than 32 weeks, or their birth weight was less than 2,000 g, or if they had an unstable clinical course as determined by the infant's neonatologist. The diagnosis and treatment standards were in accordance with the ETROP trial [21], and the international classification of ROP revisited [22]. Treatment was performed in all cases of type 1 ROP. Patients who were treated with laser

therapy and those who had a follow-up lasting less than 4 weeks after the initial IVR treatment were excluded.

Intervention

Treatment was performed within 72 hours, once type 1 ROP was diagnosed. Intravitreal injection of ranibizumab (Lucentis; Novartis, Basel, Switzerland) was performed using topical anesthesia in a standard ophthalmic operating room. Mydriasis before the injection was achieved by using eye drops containing 0.5% tropicamide and 0.5% phenylephrine, with one drop to the eyes, three times at 10 minute intervals. Topical anesthesia was administered using oxybuprocaine hydrochloride eye drops (Benoxil; 80 mg oxybuprocaine hydrochloride/20 mL; Santen, Osaka, Japan). Disinfection of the injection side was conducted using 5% betadine. The eye was stabilized using toothed forceps while a dose of 0.25 mg/0.025 mL ranibizumab was injected into the vitreous cavity using a 30 gauge needle, aiming the needle directly toward the direction of the optic nerve, through the conjunctiva, approximately 1.5 mm behind the corneoscleral junction. Ophthalmic antibiotic eye drops (Tobrex; 15 mg tobramycin/5 mL; Novartis Pharma, Vilvoorde, Belgium) were administered four times per day for 7 days after treatment. Mydriasis before the fundus examination and cycloplegic refraction was conducted by administering eye drops containing 0.5% tropicamide and 0.5% phenylephrine, with one drop to the eyes, for three times at 10 minute intervals.

Outcomes

Type 1 ROP was defined as any stage of ROP with plus disease or stage 3 ROP in zone I, or stage 2 or 3 ROP with plus disease in zone II, based on the ETROP Trial study [21]. ROP recurrences were defined as the reappearance of ridge and/or plus disease in eyes after an initial resolution of ROP. Any recurrence in one or both eyes was defined as a ROP recurrence.

Potential risk factors obtained from clinical characteristics were the patient gestational age (GA), gender, birth weight (BW), side, multiple gestations, Apgar score, postmenstrual age (PMA) of IVR treatment, factors during pregnancy including gestational diabetes mellitus [23] and pregnancy-induced hypertension, patient comorbidities including surfactant (pulmonary surfactant was used at least once after birth), blood transfusion (red blood cell transfusion), anemia (hemoglobin < 110 g/L), sepsis (positive blood cultures), intraventricular hemorrhage [24], respiratory distress syndrome [25], carbohemia ($PaCO_2$ > 50 mmHg), and congenital heart defect. The diagnosis of intraventricular hemorrhage was according to clear and accepted disease definitions using magnetic resonance imaging [24]. Hemorrhage before or after treatments involved preretinal or vitreous hemorrhage, and none of the eyes involved the visual axis or required vitrectomy. Pregnancy-induced hypertension was defined as diastolic blood pressure of 90 mmHg or higher and/or systolic blood pressure of 140 mmHg or higher, when measured during the gestation period [26]. The refractive error data involved spherical power, cylindrical power, and spherical equivalent. Cycloplegic refraction was performed using an automatic computer optometer (AR-

1; Nidek, Tokyo, Japan). Snellen uncorrected visual acuity was measured and converted to the logarithm of the maximum angle of resolution (logMAR).

Follow-up

Photographic documentation was conducted using Retcam3 (Clarity Medical Systems, Pleasanton, CA, USA) or Optos ultrawide-field retinal imaging (Optos PLC, Dunfermline, UK). Binocular indirect ophthalmoscopy with scleral indentation was performed as needed. Each infant was independently examined by two experienced retina specialists, and eligibility was confirmed by both specialists. All patients were re-examined the following day, the third day after treatment, 1 week after treatment, the second week after treatment, 1 month after treatment, and then depending on regression of ROP and the status of vascularization of the avascular retina.

Statistical analysis

Data were analyzed using SPSS statistical software for Windows, version 25.0 (SPSS., Chicago, IL, USA). Continuous variables with non-normal distributions were expressed as the median (interquartile range), and; categorical variables were reported as numbers (percentages). Univariate analysis to determine the association between risk factors and the recurrence was conducted using univariate proportional Cox regression. Baseline variables with a value of $P < 0.15$ or clinically relevant in the univariate analysis were included in a multivariate proportional Cox regression model. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were also determined after adjusting for potential confounders using multivariate proportional Cox regression. A value of $P < 0.05$ was considered statistically significant.

Results

A total of 33 eyes of 19 infants were treated with IVR. Patient demographics and characteristics are listed in Table 1. Recurrences occurred in 12 eyes at a mean of 8.6 ± 2.0 weeks (4.9–11.3 weeks) after initial IVR treatment (between 37.0 weeks and 50.1 weeks at the PMA). Ten out of 12 eyes required a second intravitreal injection (83.3%). Two eyes of one patient (16.7%) progressed to retinal detachment and were treated with vitrectomies 5 weeks after the initial IVR treatment (43.4 weeks at the PMA), which resolved the retinal detachment.

Eyes with recurrences had a lower GA (26.4 vs. 28.0 weeks, $P = 0.049$), when compared with eyes without recurrences. A higher percentage of females (66.7% vs. 19.0%, $P = 0.021$), single gestation (47.6% vs. 30.7%, $P = 0.014$), zone □ disease (16.7% vs. 0.0%, $P = 0.024$), and mothers with gestational diabetes mellitus (50.0% vs. 0.0%, $P = 0.001$) were noted in eyes of patients with ROP recurrences, when compared with those without recurrences. All of these variables were significant, based on univariate analysis and were then included in the multivariate analysis (Table 2). There were two independent risk factors for recurrence, based on multivariate proportional Cox regression: Zone □ [□ vs. □, odds ratio (OR): 0.056, $P = 0.003$] and gestational diabetes mellitus (no vs. yes, OR: 0.095, $P < 0.001$) (Table 2).

We observed that retinal blood vessels continued to develop, but not all blood vessels from infants reached zone III. Two eyes of one female patient received third intravitreal injections because of the second recurrences at 54.1 weeks at PMA (11.6 weeks after recurrence). Her post-treatment photographs even showed terminated vascularization of the peripheral retina for up to 4 years (Fig. 2). At the last follow-up, no infant developed endophthalmitis, vitreous hemorrhage, or cataract, and none of these eyes developed a recurrence. At the most recent follow-up (43–58.9 months after the initial IVR treatment), uncorrected visual acuity could be measured in 14 of 33 eyes (eight infants), showing a mean 0.46 logMAR (0.19, 0.70) (range: 0.1–1.0 logMAR). There was no significant difference in visual outcomes (spherical power, cylindrical power, spherical equivalent, uncorrected visual acuity, and strabismus) between the recurrence eyes and those without recurrences. No abnormality using slit-lamp microscope was seen in these 14 eyes.

Discussion

Compared with other anti-VEGF agents, ranibizumab is a monoclonal antibody Fab fragment lacking the Fc region. A short half-life and rapid clearing from the vitreous and the absence of a Fc region theoretically makes it a better option for ROP treatment, because of its lower systemic side effects to premature infants during neurodevelopment [10-11]. However, IVR treatment for ROP may be associated with a higher incidence of recurrence, when compared with other anti-VEGF agents [12-16]. Recurrence rates after IVR monotherapy varied greatly in previous retrospective studies, which ranged from 0%–83% with different recurrence definitions, inclusion criteria, IVR dosages, and follow-up schedules [14, 15, 18, 27, 28]. Moreover, the risk factors for ROP recurrence in patients with IVR after long-term follow-up are scarce.

In the present study, zone disease and gestational diabetes mellitus were found to be independent risk factors for recurrence after IVR monotherapy. In our experience, IVR was effective in curing type 1 ROP for extended periods of time; however, successful treatment could not be achieved in all eyes with a single injection. The overall recurrence after IVR monotherapy was 36.4%, and recurrences occurred before 50.1 weeks at PMA (11.3 weeks following the initial IVR treatment). Two eyes of one patient had a second recurrence 54.1 weeks at PMA (11.6 weeks after recurrence). A previous study also reported that follow-up in the first 12 weeks after IVR treatment was important for timely identification of ROP recurrences [18]. Several late recurrence cases (even 2.5 years later) have shown the need for long-term examinations after anti-VEGF agent monotherpy for ROP [29-31]. Thus, after the initial IVR treatment, it is important to conduct follow-ups in the first 12 weeks for timely identification of ROP recurrences.

Zone I consists of a circle, the radius of which extends from the center of the optic disc to twice the distance from the center of the optic disc to the center of the macula [22]. It has been an important predictor for prognosis of ROP, and is associated with a high risk of adverse anatomic outcomes [32-34]. Aggressive posterior ROP has been most commonly observed in zone I [22], and has been identified as a risk factor for recurrence after IVB treatment [12], which is consistent with our results. Lyu et al. [18]

reported that zone I did not correlate with ROP recurrence. One of the reasons for the discrepancy may be that they enrolled only patients with severe forms of type 1 ROP and poor systemic conditions.

Another independent factor for ROP recurrence in our study was gestational diabetes mellitus. Based on the pathogenesis, ROP and diabetic retinopathy are both retinal vascular diseases, in which there is leakage and/or neovascularization from damaged retinal vessels, based on retinal ischemia. Moreover, Opara et al. [35] have suggested that maternal diabetes is associated with ROP, with the strength of association increasing with increasing severity of ROP. Ling et al. [15], however, reported that gestational diabetes did not correlate with ROP recurrences after IVR treatments. The mean GA (26.2 ± 1.6 weeks) and mean BW (827.9 ± 187.3 g) in their study were lower, whereas our study patients had an older GA of 28.0 (26.1, 28.1) weeks and higher BW 993.0 (926.0, 1,114.0) g. These infants with lower GA and BW may have been more ill and with more advanced ROP.

Most retinal vessels of patients progressed anteriorly within the retina after IVR treatments. As an additional word of caution, two eyes of one patient had second recurrences 54.1 weeks at PMA, leaving the partially stopped vascularization retina. We recommend that follow-up examinations need to continue for several months after each injection, because of the lack of standard follow-up recommendations, especially for those patients with initial zone disease and/or mothers with gestational diabetes mellitus.

After the anti-VEGF agent treatment for ROP, persistent avascular areas in the peripheral retina were common. How to deal with the avascular area is still debatable. Although it was associated with shallower anterior chamber depths and more refractive errors [6], some studies have used laser ablation, to inhibit late recurrence [18, 36, 37]. However, we did not find recurrence after 54.1 weeks at PMA for even 5 years when only using anti-VEGF therapy.

Our study reported visual outcomes of a subgroup of eight patients, which made statistical comparisons difficult. Visual rehabilitation is the final objective of ROP treatment. Although depth increases with age, amblyopia remains treatable until 60 months, with a decline in treatment effectiveness after an age of 5 years [38]. Eyewear corrections are often needed for associated refractive errors and strabismus or amblyopia. During this study, amblyopia trainings was already conducted by a local ophthalmologist for one child. At the end of the study, one child was ready for strabismus surgery.

Hu et al. [17] reported that preretinal hemorrhage before treatment was an important risk factor that was associated with the recurrence of ROP, but hemorrhages before treatment were not associated with the recurrence of ROP in our study. The study by Hu et al. [17] excluded Zone I disease. Other possible reasons for the discrepancy may be that ROP specialists defined plus disease differently, but they tended to be internally consistent [39], thus resulting in different treatment criteria for ROP and clinical diagnoses of ROP recurrence.

There were several limitations to this study. First, it was a retrospective study with a small sample size. Second, some variables that may be related to ROP recurrence were not included, such as oxygen requirement, necrotizing enterocolitis, and hospital duration. Fluorescein angiography was not performed

for all patients. Additionally, the possibility that screening and treatment of our population consisted of Chinese patients with older GAs and higher BWs than most other clinical trials may have influenced the clinical findings.

Declarations

Ethical statement

The institutional research and ethics committee of Shengjing Hospital Affiliated to China Medical University provided ethical approval on August 23, 2021 (Ethical Committee No. 2021PS657K). All centers meet this ethical standard. All eligible subjects obtained informed consent. The clinical study registration number is ChiCTR2100051203. The research program is in line with the ethical guidelines of the 1975 Declaration of Helsinki.

Conflict of interest

There is no conflict of interest.

Funding

No

Data Availability

Data are available on reasonable request. Fengyue Wu had full access to all the data in the study and takes responsibility for the integrity of the data and the the accuracy of the data analysis. Data are available to reasonable request (23840212@163.com)

Consent for publication

Informed consent from all eligible patients was obtained.

Availability of data and materials

Not applicable

Competing interests

Fengyue Wu, Wenting Yu, Daixin Zhao, Wei Pu, Xue Zhang and Chunliu Gai declare that they have no competing interests.

Author's contributions:

Chunliu Gai had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.Chunliu Gai: Protocol/project development

Fengyue Wu, Wenting Yu, Xue Zhang and Chunliu Gai: Data collection or management

Fengyue Wu, Daixin Zhao, Wei Pu and Chunliu Gai: Data analysis

Fengyue Wu and Chunliu Gai: Manuscript writing/editing

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References

1. W. Tasman, “Retinopathy of prematurity: do we still have a problem? The Charles L. Schepens lecture,” JAMA Ophthalmology, vol. 129, no 8, pp. 1083–1086, 2011.
2. H. A. Mintz-Hittner, “Treatment of retinopathy of prematurity with vascular endothelial growth factor inhibitors,” Early Human Development, vol. 88, no. 12, pp. 937–941, 2012.
3. L. E. H. Smith,“Through the eyes of a child: understanding retinopathy through ROP: the Friedenwald lecture”Investigative Ophthalmology & Visual Science, vol. 49, no. 12, pp. 5177–5182, 2008.
4. M. E. Hartnett, J. S. Penn, “Mechanisms and management of retinopathy of prematurity,” The New England Journal of Medicine, vol. 367, no. 26, pp. 2515–2526, 2012.
5. M. M. Geloneck, A. Z. Chuang, W. L. Clark et al., “Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial,” JAMA Ophthalmology, vol. 132, no. 11, pp. 1327–1333, 2014.
6. Y. S.Lee, L. C. See, S. H. Chang et al., “Macular Structures, Optical Components, and Visual Acuity in Preschool Children after Intravitreal Bevacizumab or Laser Treatment,” American Journal of Ophthalmology, vol. 192, pp. 192:20–30, 2018.
7. B. Mueller, D.J. Salchow, E. Waffenschmidt et al., “Treatment of type I ROP with intravitreal bevacizumab or laser photocoagulation according to retinal zone,” British Journal of Ophthalmology, vol. 101, no. 3, pp. 365–370, 2017.
8. H. A. Mintz-Hittner, K.A. Kennedy, and A.Z. Chuang, “Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity,”The New England Journal of Medicine, vol. 364, no. 7, pp.603–315, 2011.
9. M. S.Kariolis, R. C. Wells, J. A. Getz et al., “Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys,” Science Translational Medicine, vol. 12, no. 545, pp.eaay1359, 2020.
10. S. J. Bakri, M. R. Snyder, J.M. Reid, et al., “Pharmacokinetics of intravitreal ranibizumab (Lucentis),” Ophthalmology, vol. 114, no. 12, pp. 2179–2182, 2007.

11. A. G. Salman, and A. M. Said, “Structural, visual and refractive outcomes of intravitreal aflibercept injection in high-risk prethreshold type 1 retinopathy of prematurity,” Ophthalmic Research, vol. 53, no. 1, pp.15–20, 2015.
12. H. A. Mintz-Hittner, M. M. Geloneck, and A. Z. Chuang, “Clinical Management of Recurrent Retinopathy of Prematurity after Intravitreal Bevacizumab Monotherapy,” Ophthalmology, vol. 123, no. 9, pp.1845–1855, 2016.
13. E. A. Sukgen, and Y. Koçluk, “Comparison of clinical outcomes of intravitreal ranibizumab and aflibercept treatment for retinopathy of prematurity,” Graefe’s Archieve for Clinical Experimental Ophthalmology, vol. 257, no. 1, pp. 49–55, 2019.
14. R. K. Wong, S. Hubschman, and I. Tsui, “Reactivation of retinopathy of prematurity after ranibizumab treatment,” Retina, vol. 35, no. 4, pp. 675–680, 2015.
15. K. P. Ling, P. J. Liao, N. K. Wang et al., “Rates and risk factors for recurrence of retinopathy of prematurity after laser or intravitreal anti-vascular endothelial growth factor montherapy,” Retina, vol. 40, no. 9, pp. 1793–1803, 2020.
16. G. Zhang, M. Yang, J. Zeng et al., “Comparison of intravitreal injection of ranibizumab verse laser therapy for zone II treatment-requiring retinopathy of prematurity,” Retina, vol. 37, no. 4, pp. 710–717, 2017.
17. Q. R.Hu, Y. J. Bai, X. L. Chen et al., “Recurrence of Retinopathy of Prematurity in Zone II Stage 3+ after Ranibizumab Treatment: A Retrospective Study,” Journal of Ophthalmology, Article ID 5078565,2017.
18. J. Lyu, Q, Zhang, C. L. Chen, Y.Xu et al., “Recurrence of Retinopathy of Prematurity After Intravitreal Ranibizumab Monotherapy: Timing and Risk Factors,”Investigative Ophthalmology & Visual Science, vol. 58, no. 3, pp.1719–1725, 2017.
19. E. S. Draper, J. Zeitlin, B. N. Manktelow et al., “EPICE cohort: two-year neurodevelopmental outcomes after very preterm birth,”*Archives of Disease in Childhood: Fetal & Neonatal*Eidition, vol. 105, no. 4, pp. 350–356, 2020.
20. Ocular Fundus Disease Group of Chinese Ophthalmology, “The Chinese screening guide of retinopathy of prematurity (2014),” Chinese Journal of Ophthalmology, vol. 50, no. 12, pp. 933– 935, 2014.
21. Early Treatment for Retinopathy of Prematurity Cooperative Group, “Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial,” JAMA Ophthalmology, vol. 121, no. 12, pp.1684–1694, 2003.
22. International Committee for the Classification of Retinopathy of Prematurity, “The international classification of retinopathy of prematurity revisited,” JAMA Ophthalmology, vol. 123, no. 7, pp.123:991–999, 2005.
23. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, “International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy,” Diabetes Care, vol. 33, no. 3, pp. 676–682, 2010.

24. L. A. Papile, J. Burstein, R. Bursteinet al., “Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm,” The Journal of Pediatrics, vol. 92, no. 4, pp. 529–534, 1978.
25. J. J. Downes, D. Vidyasagar, T. R. Boggs et al., “Respiratory distress syndrome of newborn infants. I. New clinical scoring system (RDS score) with acid–base and blood-gas correlations,” Clinical Pediatrics, vol. 9, no. 6, pp. 325– 331, 1970.
26. M. A.Brown, M. D. Lindheimer, M. de. Swiet et al., “The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP),” Hypertens Pregnancy, vol. 20, no. 1, pp.IX–XIV, 2001.
27. M. N. Menke, C. Framme, M. Nelle et al., “Intravitreal ranibizumab monotherapy to treat retinopathy of prematurity zone II, stage 3 with plus disease,” BMC Ophthalmology, vol. 15, pp.20, 2015.
28. J. Feng, J. Qian, Y. R. Jiang et al., “Efficacy of Primary Intravitreal Ranibizumab for Retinopathy of Prematurity in China,” Ophthalmology, vol. 124, no. 3, pp. 408–409,2017.
29. S. Ittiara, M. P. Blair, M. J. Shapiro et al., “Exudative retinopathy and detachment: a late reactivation of retinopathy of prematurity after intravitreal bevacizumab,”**Journal of the American Association for Pediatric Ophthalmology and Strabismus,** vol. 17, no. 3, pp.323-325, 2013.
30. L. L. Snyder, J. M. Garcia-Gonzalez, M. J. Shapiro et al., “Very Late Reactivation of Retinopathy of Prematurity After Monotherapy With Intravitreal Bevacizumab,” Ophthalmic Surgery Lasers Imaging Retina,vol. 47, no. 3, pp. 280-283, 2016.
31. A. Stahl, M. C. Bründer, W. A. Lagrèzeet al., “Ranibizumab in retinopathy of prematurity - one-year follow-up of ophthalmic outcomes and two-year follow-up of neurodevelopmental outcomes from the CARE-ROP study,” Acta Ophthalmologica,vol. 100, no. 1, pp. e91-e99, 2022.
32. C. K. Hwang, G. B. Hubbard, A. K. Hutchinson et al.,“Outcomes after Intravitreal Bevacizumab versus Laser Photocoagulation for Retinopathy of Prematurity: A 5-Year Retrospective Analysis,” Ophthalmology,vol. 122, no. 5, pp.1008-1015, 2015.
33. A.Stahl, D. Lepore, A. Fielderet al.,“Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial,” The Lancet,vol. 394, no. 10208, pp.1551-1559, 2019.
34. Y. Cheng, X. M. Zhu, D. Linghuet al.,“Comparison of the effectiveness of conbercept and ranibizumab treatment for retinopathy of prematurity,” Acta Ophthalmologica,vol. 98, no. 8, pp. e1004-e1008, 2020.
35. C. N. Opara, M. Akintorin, A. Byrdet al.,“Maternal diabetes mellitus as an independent risk factor for clinically significant retinopathy of prematurity severity in neonates less than 1500g,” PLOS ONE,vol. 15, no. 8, pp.e0236639, 2020.
36. J.Lyu, Q. Zhang, C. L. Chenet al.,“Ranibizumabinjection and laser photocoagulationto treat type 1 retinopathyof prematurity after 40 weeks post menstrual age: a retrospective case series study,” BMC Ophthalmology,vol. 19, no. 1, pp.60, 2019.

37. B. C.Toy, I. H. Schachar, G. S. Tanet al.,“Chronic vascular arrest as a predictor of bevacizumab treatment failure in retinopathy of prematurity,”Ophthalmology,vol. 123, no. 10, pp.2166-2175, 2016.
38. S. P. Donahue, B. Arthur, D. E. Neelyet al.,“Guidelines for automated preschool vision screening: A 10-year, evidence-based update,”**Journal of the American Association for Pediatric Ophthalmology and Strabismus,** vol. 17, no. 1, pp.4-8, 2013.
39. J. P. Campbell, E. Ataer-Cansizoglu, V. Bolon-Canedo et al.,“Expert diagnosis of plus disease in retinopathy of prematurity from computer-based image analysis,” JAMA Ophthalmology,vol. 134, no. 6, pp. 651–657, 2016.

Tables

Table 1. Demographics and characteristics of patients in this cohort

Variables	All patients (%)	Patients with recurrence (%)	Patients without recurrence (%)	P
Number of patients (%)	19 (100%)	6.0 (31.6)	13.0 (68.4)	
Number of eyes (%)	33 (100%)	12.0 (36.4)	21.0 (63.6)	
Follow-up (months)	45.3 (5.1, 50.9)	48.6 (10.3, 51.2)	44.2 (3.7, 50.6)	
Demographic data				
GA (weeks)	28.0 (26.1, 28.1)	26.4 (26.0, 28.0)	28.0 (27.7, 28.6)	0.049
Gender (male/female)	21.0 (63.6)/12 (36.4)	4.0 (33.3)/8.0 (66.7)	17.0 (81.0)/4.0 (19.0)	0.021
BW (g)	993.0 (926.0, 1114.0)	958.5 (852.0, 1015.0)	1025.0 (930.0, 1189.0)	0.108
Baseline characteristics for infants				
Side (bilateral vs. unilateral)	28 (84.8)/5 (15.2)	12.0 (100.0)/0 (0.0)	16.0 (76.2)/5.0 (23.8)	0.346
Multiple gestations (yes vs. no)	14.0 (42.4)/19.0 (57.6)	2.0 (16.7)/10.0 (83.3)	12.0 (57.1)/9.0 (42.9)	0.049
Apgar score at 1 min	7.0 (6.0, 7.5)	7.0 (6.0, 7.0)	7.0 (6.0, 8.0)	0.602
Apgar score at 5 min	9.0 (8.0, 9.0)	9.0 (8.0, 9.0)	9.0 (8.0, 9.0)	0.343
Zone (vs.)	2.0 (6.1)/31.0 (93.9)	2.0 (16.7)/10.0 (83.3)	0.0 (0.0)/21.0 (100.0)	0.024
Stage (2 vs. 3)	2.0 (6.1)/31.0 (93.9)	0.0 (0.0)/12.0 (100.0)	2.0 (9.5)/19.0 (90.5)	0.519
Plus (yes vs. no)	33.0 (100.0)/0.0 (0.0)	12.0 (100.0)/0.0 (0.0)	21.0 (100.0)/0.0 (0.0)	1.000
PMA at injection (weeks)	37.3 (35.9, 39.7)	37.4 (36.1, 37.9)	37.3 (35.7, 40.7)	0.263
Surfactant (yes vs. no)	31.0 (93.9)/2.0 (6.1)	12.0 (100.0)/0.0 (0.0)	19.0 (90.5)/2.0 (9.5)	0.629
Blood transfusion (yes vs. no)	33.0 (100.0)/0.0 (0.0)	12.0 (100.0)/0.0 (0.0)	21.0 (100.0)/0.0 (0.0)	1.000
Hemorrhage before treatment (yes vs. no)	8.0 (24.2)/25.0	4.0 (33.3)/8.0 (66.7)	4.0 (19.0)/17.0 (81.0)	0.405

	(75.8)			
Hemorrhage after treatment (yes vs. no)	10.0 (30.3)/23.0 (69.7)	6.0 (50)/6 (50)	4.0 (19.0)/17.0 (81.0)	0.086
Factors during pregnancy				
Gestational diabetes mellitus (yes vs. no)	6.0 (18.2)/27.0 (81.8)	6.0 (50.0)/6.0 (50.0)	0.0 (0.0)/21.0 (100.0)	0.001
Pregnancy-induced hypertension (yes vs. no)	5.0 (15.2)/28.0 (84.8)	0.0 (0.0)/12.0 (100.0)	5.0 (23.8)/16.0 (76.2)	0.297
Neonatal Comorbidities				
Anemia (yes vs. no)	33.0 (100.0)/0.0 (0.0)	12.0 (100.0)/0.0 (0.0)	21.0 (100.0)/0.0 (0.0)	1.000
Intraventricular hemorrhage (yes vs. no)	9.0 (27.3)/24.0 (72.7)	2.0 (16.7)/10.0 (83.3)	7.0 (33.3)/14.0 (66.7)	0.357
Sepsis (yes vs. no)	25 (75.8)/8.0 (23.2)	8.0 (66.7)/4.0 (33.3)	17.0 (81.0)/4.0 (19.0)	0.193
RDS (yes vs. no)	30 (90.9)/3 (9.1)	12.0 (100.0)/0.0 (0.0)	18.0 (85.7)/3.0 (14.3)	0.426
Carbohemia (yes vs. no)	33.0 (100.0)/0.0 (0.0)	12.0 (100.0)/0.0 (0.0)	21.0 (100.0)/0.0 (0.0)	1.000
Congenital heart defect (yes vs. no)	13.0 (39.4)/20.0 (60.6)	6.0 (50.0)/6.0 (50.0)	7.0 (33.3)/14.0 (66.7)	0.503

Continuous variables with non-normal distribution were expressed as median (interquartile range); categorical variables were reported as number (percentage).

Univariate proportional cox regression was used to determine P value of variables.

Abbreviations: GA, gestational age; BW, birth weight; PMA, postmenstrual age; RDS, respiratory distress syndrome.

Table 2. Multivariate proportional cox regression of recurrence

Variable	HR	95% CI	P
GA (weeks)	0.756	0.344-1.659	0.422
Gender (female vs.male)	1.791	0.267-11.989	0.542
BW (g)	1.001	0.994-1.009	0.686
Multiple gestations (no vs. yes)	0.389	0.034-4.382	0.771
Zone (vs.)	0.056	0.008-0.375	0.003
Hemorrage after treatment (no vs. yes)	0.635	0.15-2.684	0.413
Gestational diabetes mellitus (no vs. yes)	0.095	0.026-0.344	< 0.001

The hazard ratio and 95% confidence interval were measured through multivariate proportional cox regression.

HR, hazard ratio; CI, confidence interval; GA, gestational age; BW, birth weight.

Table 3. Refractive errors and visual acuity of patients in this cohort

Variables	All patients (%)	Patients with recurrence (%)	Patients without recurrence (%)
Number of patients (%)	8 (100%)	2.0 (25.0)	6.0 (75.0)
Number of eyes (%)	14 (100%)	4.0 (28.6)	10.0 (71.4)
Follow-up (months)	51.0 (44.0, 58.9)	55.0 (51.0, 58.9)	48.0 (43.8, 58.4)
Spherical power (D)	1.13 (0.69, 2.00)	1.38 (1.06, 1.88)	0.88 (0.44, 2.00)
Cylindrical power (D)	0.25 (-0.38, 0.56)	-0.38 (-2.06, 0.94)	0.25 (0.13, 0.50)
Spherical equivalent (D)	1.19 (0.34, 2.13)	1.19 (0.03, 2.34)	1.19 (0.63, 2.13)
Uncorrected VA (logMAR)	0.46 (0.19, 0.70)	0.46 (0.13, 0.70)	0.46 (0.19, 0.63)
Strabismus (yes vs. no)	3.0 (37.5)/5.0 (62.5)	1.0 (50.0)/1.0 (50.0)	2.0 (33.3)/4.0 (66.7)

Continuous variables with non-normal distribution were expressed as median (interquartile range); categorical variables were reported as number (percentage).

Abbreviations: D, diopters; VA, visual acuity; logMAR, logarithm of the minimum angle of resolution.

Figures

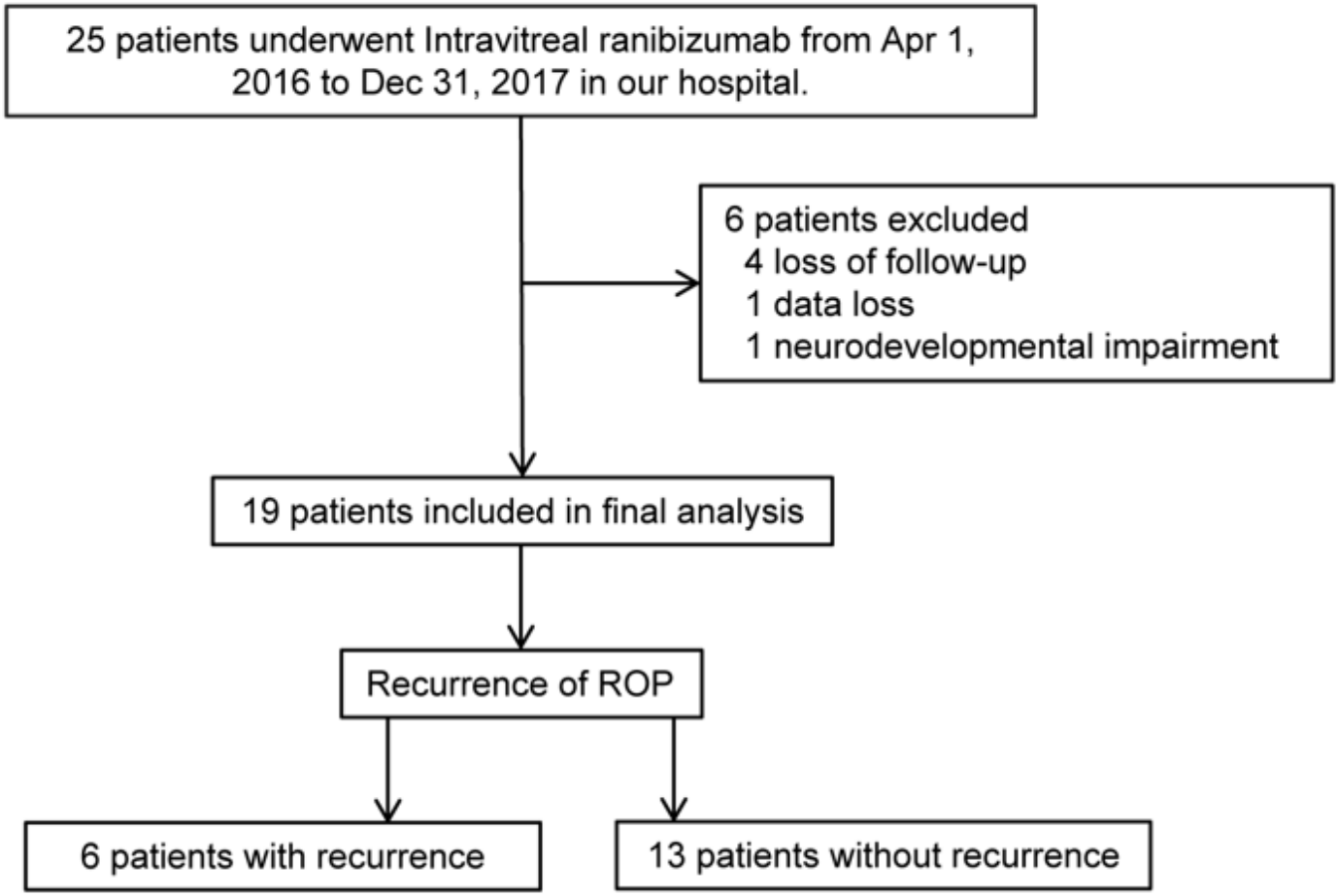

Figure 1

Flow diagram of the study.

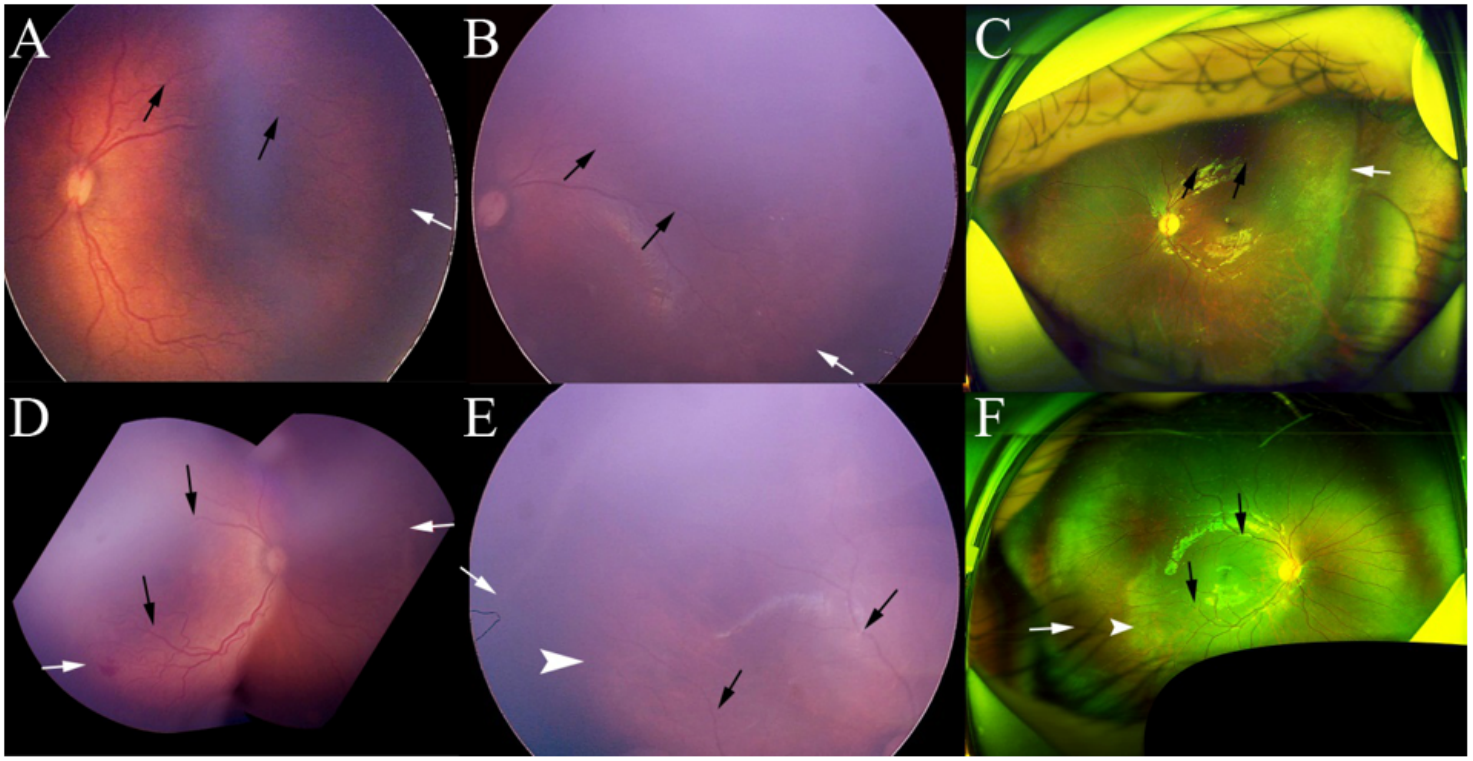

Figure 2

Fundus photographs taken from one patient and her twin brother in the study.

The female's post-treatment photographs show stopped vascularization of the peripheral retina.

The male's post-treatment photographs show continued vascularization of the peripheral retina.

A: Left retina of one female patient before initial intravitreal ranibizumab (IVR) [32.9 weeks at postmenstrual age (PMA)].

B: Left retina of the female patient after a second intravitreal injection because of recurrence (44.7 weeks at PMA).

C: Four years after primary IVR treatment, the fundus photograph of the left retina of the female patient after three intravitreal injections because of another recurrence.

D: Right retina of the male patient before initial IVR (32.9 weeks at PMA).

E: Right retina of the male patient after initial IVR (45.7 weeks at PMA).

F: Four years after primary IVR, the fundus photograph of the right retina of the male patient after one IVR without recurrence.

Arrowheads indicate the extent of vascularization at the time of primary IVR.

Black arrows indicate identical retinal points for comparison before and after treatment, and white arrows indicate the extent of vascularization at each time point.