Review Article

Fibrovascular proliferation of retinopathy of prematurity in zone II after initial ranibizumab treatment

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Abstract: This study was designed to explore the prevalence of fibrovascular proliferation not regressed in zone II stage 3 retinopathy of prematurity (ROP) after initial intravitreal ranibizumab (IVR) injections and to explore the possible influence factors. Fifty-seven patients (108 eyes) with ROP who underwent intravitreal injection of ranibizumab between January 2013 and July 2014 participated in the retrospective study. Based on regress of fibrovascular tissue or not after initial injections of ranibizumab, eligible eyes were divided into two groups. Data was collected and analyzed with SPSS 16.0. In the study, 108 eyes of 57 patients (18 females, 39 males) underwent initial intravitreal injection. The mean birth weight was 1,440.0±357.7 g and the mean gestational age was 30.5±2.0 weeks. Eight of 57 (14.0%) patients showed unfavorable fibrovascular proliferation after initial ranibizumab treatment within 2 weeks. Among them, 11 eyes were controlled by further laser treatment and 3 eyes underwent vitrectomy. The difference of occurrence rate in hemorrhage between the two groups was significant (P<0.030), and the unfavorable group required more laser treatment (P<0.001). The incidence of unfavorable fibrovascular proliferation was relatively high, and intraocular hemorrhage was possibly associated with the progress in zone II stage 3 ROP after initial IVR injection.

Keywords: Retinopathy of prematurity (ROP); ranibizumab; treatment; fibrovascular proliferation; risk factor

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Introduction

Retinopathy of prematurity (ROP) remains an important cause of preventable blindness in children (1,2). Abnormal growth of retinal blood vessels is the mainly pathogenic pathway of ROP which is mainly modulated by vascular growth factors (3,4). Therefore, blocking the action of vascular endothelial growth factor (VEGF) might be expected to reduce the vascular activity. Recently, sufficient publications have described anti-VEGF drugs' application in premature for their efficiency in reducing pathologic angiogenesis (5). It is not surprised that anti-VEGF drugs have experienced a promise application prospect (6,7).

However, it is not uncommon to see the diseases developed against the expectation in some cases, which are witnessed by vitreoretinal traction, retinal detachment in ROP after IV treatment (8-10). Still there are patients who showed no regress of fibrovascular proliferation and even fibrosis aggravating ultimately. The potential influence factors why those patients did not respond to the drugs and fibrosis proliferation progress are worth to explore.

Our study concerned about the progress fibrovascular proliferation after initial intravitreal injections of

bevacizumab and the susceptible risk factor in zone II ROP.

Methods

The medical records of infants who met criteria for ROP screening and developed zone II stage 3 were reviewed retrospectively at our department from January 2013 to July 2014, including all preterm infants who accepted intravitreal injection of ranibizumab as an initial treatment after informed consent were obtained. Eyes with zone II stage 3 ROP and plus disease were included; those who accepted laser treatment, cryotherapy, anti-vascular endothelial growth factor (anti-VEGF) drugs before and did not accomplish the follow-up were excluded. The details of retinal changes for ROP in all examinations were performed by senior ophthalmologists. A weekly or biweekly basis examination was performed initially, depending on the retinal findings and continued until vascularization had reached zone III. If the fibrovascular proliferation do not regressed or even progressed, further treatment will be required. Data collected from the infants' record: gender, gestational age, birth weight and oxygen exposure. ROP findings included the preoperative ROP zone and intraocular hemorrhage, iris neovascularization. ROP findings were recorded by detailed retinal drawings and RetCam.

Statistical analysis

The eyes were divided into two groups based on regress of fibrovascular tissue or not after initial ranibizumab treatments within 2 weeks. Statistical analyses were performed to compare the two groups using statistical software (StatLab, SPSS for Windows, version 16.0; SPSS, Inc., Chicago, Illinois, USA). Univariate analyses to determine the association risk factors were performed using the Mann-Whitney U test, the *t* test, and the Fisher exact test.

Results

A total of 108 eyes of 57 patients (18 females, 39 males) underwent initial intravitreal injection of ranibizumab. The mean birth weight was 1,440.0±357.7 g with a mean gestational age of 30.5±2.0 weeks and a mean follow-up of 7.0±3.8 months. Eight of 57 (14.0%) patients' diseases did not regress after initial intravitreal injection within 2 weeks observation period. Eleven of the 14 eyes (78.6%) underwent laser treatment, mean at 2.3±2.3 weeks after initial ranibizumab treatment. Three eyes (21.4%) progressed to surgery.

The number of patients with intraocular hemorrhage in the unfavorable group was more than the other group, and the difference was significant (P<0.030). The hemorrhage mainly occurred around the rages within one quadrant avoiding macular zone (*Figure 1*). The macular zone was covered by hemorrhage in four eyes.

For the diseases mainly by fibrovascular membranes proliferation or aggravated after intravitreal ranibizumab (IVR), photocoagulation was the priority recommendation. The number of patients applied photocoagulation in the unfavorable group was more than the no regress group (P<0.001). There were no differences between the two groups in the other baseline characteristics. The data and statistics are summarized in *Table 1*.

Discussion

In our study, 14 out of 108 eyes (13.0%) treated with ranibizumab had unfavorable fibrovascular proliferation after response to the initial treatment within 2 weeks. The rages of those cases presented a remarkable fibrovascular proliferation or even aggravate fibrosis proliferation with pale membrane appearance at the posterior pole. For the unfavorable eye mainly by fibrovascular membranes proliferation, photocoagulation was the priority recommendation. Three infants progressing rapidly turned to vitrectomy.

Anti-VEGF drug is a good way to treat ROP which is characterized by abnormal retinal vascular (11). However, in some cases, as a response to the decreased levels of VEGF by the drugs, the rapid neovascular involution causes the progression of accelerated fibrosis and posterior hyaloid (12,13). The contraction of the fibrovascular membrane in the course of ROP treatments phenomenon is frequently observed clinically. This kind of performance often indicates a poor prognosis. One previous study reported a case of advanced ROP which showed an acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab (14). The vascular component of the fibrovascular membrane regressed, and the appearance became fibrotic, which caused a deterioration of tractional retinal detachment. Previous study had showed differential role of VEGF isoforms in retinal physiological angiogenesis in a rabbit model. Ranibizumab is an aptamer which specifically blocks VEGF [165], affecting the blood vessel

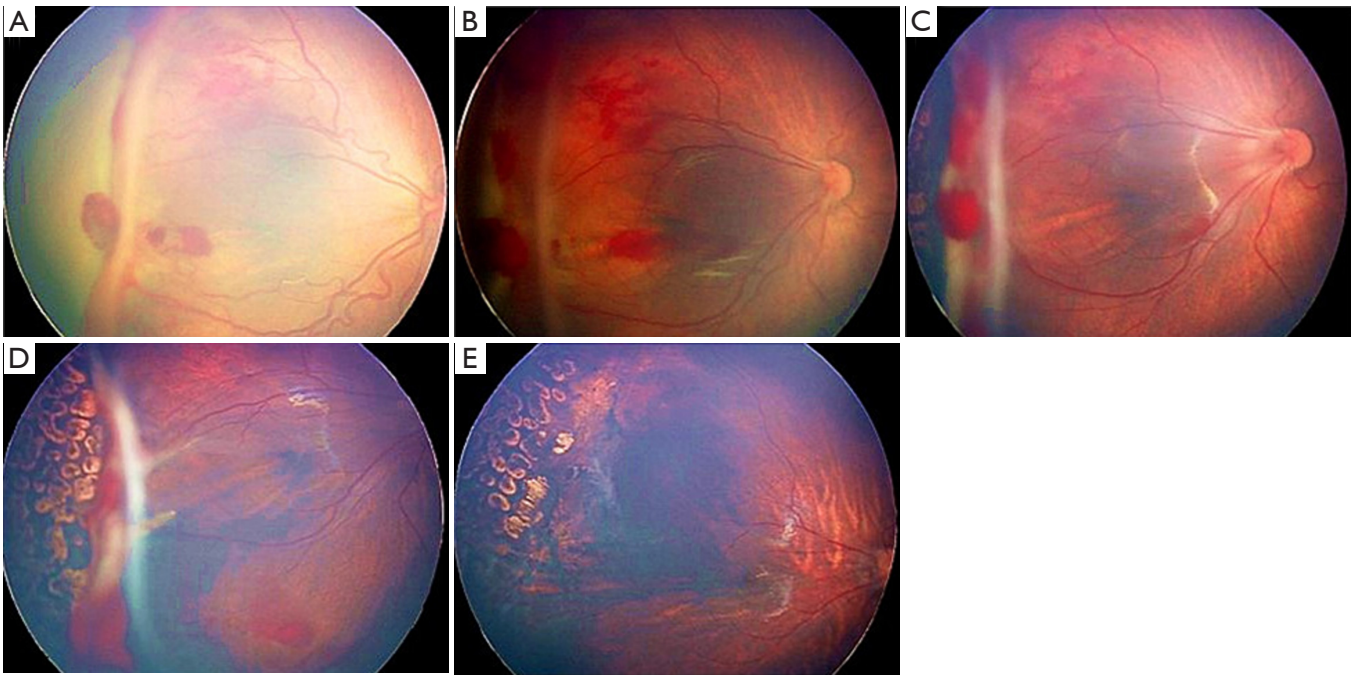

Figure 1 Fundus photographs of one 7 weeks male infant (weight 1,500 g and gestational age 31 weeks). (A) View of zone II stage 3+ retinopathy of prematurity (ROP) with hemorrhage around the rage; (B) view of fundus photograph 1 week later after ranibizumab treatment. Substantial amounts of fibrosis proliferation were seen infiltrating into the vitreous posterior; (C) view of fundus photograph by laser treatment 2 weeks later after ranibizumab treatment. Retinal traction was obvious; (D) view of fundus photograph by laser treatment 6 weeks later after ranibizumab treatment. The proliferation was progress; (E) view of fundus by vitrectomy 8 weeks later after ranibizumab treatment.

Table 1 Univariate analysis of baseline demographics in the eyes with ROP in zone II stage 3 after ranibizumab treatment

Clinical data	Unfavorable group	Regress group	P value
No. eyes/patients	14/8	94/49	–
Birth weight (g)	1,293.8±209.5	1,469.3±372.5	0.065[#]
Gestation age (weeks)	34.5±2.0	30.3±1.39	0.155[#]
Oxygen administration	4	22	0.542[†]
Preretinal hemorrhage	9	32	0.030*
Iris neovascularization	0	5	1.000[†]
Laser treatment	11	30	0.001*

*, Mann-Whitney U test; [#], independent samples *t* test; [†], Fisher exact test; ROP, retinopathy of prematurity.

growth, but VEGF [189] is rather involved in fibrosis (15). This explained why ranibizumab treatment may result in the progression of fibrosis in ROP.

There are statistical differences between the two groups in hemorrhage in our study. Significant preretinal hemorrhages are likely to contribute to abnormal vitreous organization, resulting in an unfavorable outcome (6). In Nazari *et al.* series, vitreous hemorrhages often lead to irreparable retinal detachment despite surgical intervention (16). A prospective interventional clinical case series by Krishna A. Rao suggested that vitreous hemorrhage was the only independent risk factor for severe ROP (17). Ehrenberg *et al.* found that

after the injection of blood into the vitreous, almost all eyes developed glial membranes on the peripheral retina and fibrous membranes caused local retinal contraction. Untreated premacular hemorrhages usually cause surface wrinkling or traction macular detachment due to the progressive fibrovascular proliferation and contraction along the posterior surface of the vitreous (18). It is reasonable to consider that hemorrhages, a severe destruction of vessels form, may cause a high recurrence of ROP and detachment by proliferation and contraction.

Oxygen is considered a critical factor in the pathogenesis of ROP (19,20). Inadequate oxygen expose resulted in the extent of ROP (21). But in our study there was no evidence that the factors had impact on the abnormal response of ROP. Another possible cause is that regular doses of bevacizumab which has a short terminal half-life may not be effective in inducing regression of sever ROP, so the fibrovascular organization continued to aggravate (8,22). Further studies are required to verify it.

Although the initial responses to part of the patients were poor, the patients' overall prognoses are favorable after laser treatment in our study, but the structural damage by laser may require long-term extended observation. In conclusion, the incidence of fibrovascular proliferation not regressed was not high, and the presence of hemorrhages was a possible influence factor of progression to the unfavorable ROP after ranibizumab treatment. A close screening examination and follow-up and timely intervention are needed for the management of ROP.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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