Short Communication

Intravitreal Ranibizumab for Aggressive Posterior Retinopathy of Prematurity

Xiu-Juan Li1, Xiao-Peng Yang2, Shuang Sun3, Xiao-Bei Lyu1, Heng Jia1

1Department of Ophthalmology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China
2Department of Medical Equipment, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China
3Department of Ophthalmology, Children’s Hospital of Zhengzhou, Zhengzhou, Henan 450052, China

Key words: Aggressive Posterior Retinopathy of Prematurity; Intravitreai Injection; Ranibizumab

Introduction

Retinopathy of prematurity (ROP) is a proliferative disease that affects infants of young gestational age (GA) and low birth weight (BW). Aggressive posterior ROP (AP-ROP) is a rapidly progressing and severe presentation of ROP. It is characterized as posterior location (zone I or posterior zone II), Stage 3, and with plus disease (arterial tortuosity and venous dilation). It can quickly lead to retinal detachment and blindness if not treated in time.

Recently, vascular endothelial growth factor (VEGF) has been believed to play an important role in the pathogenesis of ROP.[1] The aim of our study was to determine the effectiveness and safety of intravitreal ranibizumab (IVR) for the treatment of AP-ROP.

Methods

Subjects

This study was a retrospective analysis of 32 eyes (16 patients) with AP-ROP (according to the International Classification of ROP revised in 2005) that were treated with IVR at our hospital between January 2014 and January 2015. The study was approved by Zhengzhou University and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the parents.

Inclusion criteria included patients diagnosed definitely with AP-ROP, transparent, or mildly opaque refractive media that did not affect clear visualization of the fundus, and follow-up period for at least 6 months. Patients were excluded from the study if they had life-threatening systemic disease or severe opaque refractive media.

Surgical procedures

The injections were performed in the surgical room. Ranibizumab (10 mg/ml; Novartis, Basel, Switzerland) was simultaneously injected in both eyes within 24 h after definite diagnosis. Preoperatively, tropicamide drops (0.25%) were used to dilate the pupil for every 10 min for 4 times. Povidone-iodine was applied for disinfection. The injections of 0.3 mg (0.03 ml) of ranibizumab were injected at 1.5 mm posterior to the corneal limbus using a 30-G needle under topical anesthesia with oxybuprocaine eye drop. After that, the intraocular pressure (IOP) was evaluated by bulbus palpation. If necessary, anterior chamber paracentesis was performed.

In cases of relapse, laser photocoagulation was performed under general anesthesia. Laser photocoagulation (0.3 s and 100–200 mW power) was applied from the avascular retina to the ora serrata in all quadrants (360°) with near-confluent impacts. Eye drops of antibiotic and steroids were used for every 6 h for 5 days after IVR or laser photocoagulation.

Outcome analyses

The follow-ups were performed at 24 h, 48 h, 72 h, 1 week, 2 weeks, 3 weeks, and 4 weeks after the treatment, and then depending on the regression of ROP and the status of the injection.

Address for correspondence: Dr. Xiao-Peng Yang, Department of Medical Equipment, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China
E-Mail: zdxyyx@sina.com

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Received: 18-07-2016 Edited by: Yi Cui
How to cite this article: Li XJ, Yang XP, Sun S, Lyu XB, Jia H. Intravitreal Ranibizumab for Aggressive Posterior Retinopathy of Prematurity. Chin Med J 2016;129:2879-81.
of vascularization of peripheral retina. All patients were followed up for at least 6 months. All patients were assessed by binocular indirect ophthalmoscopy and the RetCam Imaging System (Clarity Medical Systems, Pleasanton, CA, USA) preoperatively and at every follow-up visit. Systemic conditions were continuously monitored in the neonatal intensive care unit during peri- and post-operative periods.

Primary success was defined as regression of retinal neovascularization and plus disease, continued vascularization of the avascular retina, and without relapse during the whole follow-up visits. Relapse was defined as increased plus disease and progression of retinal neovascularization or membrane formation extending into the vitreous from the retina.

**RESULTS**

**Patients**

Thirty-two eyes (16 patients) were included in the study. Six patients were female. Mean GA at birth was 29.1 ± 2.2 weeks (range: 26–33 weeks), BW was 1336 ± 391 g (range: 900–2100 g), and postconceptional age (PCA) at treatment was 35.7 ± 1.3 weeks (range: 32–39 weeks). AP-ROP in zone I was diagnosed in 22 eyes (68.75%) and posterior zone II was diagnosed in 10 eyes (31.25%). Iris neovascularization occurred in 4 eyes (12.50%).

**Surgical outcomes**

Iris neovascularization regressed significantly at 72 h follow-up visit and disappeared at 1-week follow-up visit in the 4 eyes and it was not noted in any eye during the subsequent follow-up visits. The regression of retinal neovascularization and plus disease was observed in all patients at 1-week follow-up visit. Among them, a total of 25 eyes (78.13%) achieved primary success after the use of IVR injection only once in each eye [Figure 1]. Relapse occurred in 7 eyes (21.88%) at 2–8 week follow-up visits [Table 1]. Compared with the averages, recurrent cases showed smaller GA, lower BW, and smaller PCA at treatment. The location of recurrent cases was all in zone I. Among them, four cases had iris neovascularization with poorly dilating pupils. Near-confluent laser photoocoagulation in the avascular area was performed in patients with relapse. Two weeks later, regression of retinal neovascularization and plus disease and gradual vascularization of the avascular retina were observed in these patients [Figure 2]. No other relapse occurred during the subsequent follow-up visits. No eyes developed retinal detachment during the follow-up period.

The potential ocular complications secondary to injection such as endophthalmitis, cataract formation, retinal hemorrhage, and tear or elevated IOP were not observed in any patient. No systemic side effects occurred during the follow-up period.

**DISCUSSION**

The role of VEGF in the pathogenesis of ROP has been well defined. The avascular area of the retina induces VEGF production and the accumulated VEGF leads to neovascularization and may eventually lead to retinal detachment if not treated promptly. Laser photoocoagulation has been used for the treatment of avascular retina to destroy the cells that produce VEGF, but the structural and functional outcomes in patients with severe ROP affecting zone I or posterior zone II were usually unsatisfactory.

Recently, anti-VEGF agents were the most studied drugs for ROP treatment with effective results. Sato et al [2] showed that bevacizumab can escape from the vitreous into the systemic circulation and reduce systemic VEGF concentrations for weeks to months in ROP infants whereas Carneiro et al [3] reported that ranibizumab did not alter systemic VEGF concentrations in adults. This was a very important point for the use of ranibizumab in premature infants under organogenesis period. Hence, we chose ranibizumab for the treatment of AP-ROP in our study.

In our study, 32 eyes with AP-ROP were treated with IVB (0.3 mg, 0.03 ml). Our results showed that the primary success rate was 78.13%. Menke et al [4] performed IVB monotherapy to treat ROP zone II, Stage 3 with plus disease, and without prior laser or other intravitreal therapy. All the eyes in their study showed complete retinal vascularization with no recurrence after 6 months. Our results differed from theirs. The reason may be that the conditions of our patients were more serious, for the fundus diseases in our study were located in the more posterior area (zone I or posterior zone II). In our study, we also found that relapse following the regression of neovascularization and plus disease occurred in 7 eyes (21.88%). The relapse may be associated with the

![Figure 1: Fundus images of aggressive posterior retinopathy of prematurity before and after intravitreal ranibizumab. (a) Before intravitreal ranibizumab, fundus images showed neovascularization and plus disease in zone I. (b) One week after intravitreal ranibizumab, neovascularization and plus disease has regression significantly. (c) Six months after intravitreal ranibizumab, retinal vascularization was complete.](image-url)
smaller GA, the lower BW, the smaller PCA at treatment, the more posterior location (zone I), and iris neovascularization with poorly dilating pupils. The similar recurrence was reported by Wong et al. and it was considered to be related to the shortened half-life of ranibizumab. However, the initial IVR was very important for the next treatment of AP-ROP. It may contribute to the forward growth of retinal vessels from the vascular area, which may provide a chance for laser therapy and effectively reduce the range of laser and the damage to the vision field. Hence, we used near-confluent laser photocoagulation in patients with relapse, and our results were positive. Regression of ROP and gradual vascularization of the peripheral retina were observed in these patients. No serious ocular and systemic adverse effects occurred during the follow-up period.

In summary, the present study showed that IVR was effective in treating AP-ROP without serious ocular or systemic complications. A further study with a larger sample size and longer follow-up period or a prospective study should be performed to evaluate the long-term safety and effectiveness of IVR for the treatment of AP-ROP.

**Financial support and sponsorship**

This study was supported by grants from the Projects of Henan Health and Family Planning Commission (No. 20140005), Henan Health Department (No. 201304007), and Henan Science and Technology Department (No. 142102310110).

**Conflicts of interest**

There are no conflicts of interest.

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**Table 1: Data of recurrent cases after the initial IVR**

| Recurrent cases | GA (weeks) | BW (g) | PCA at treatment (weeks) | Zone | Iris neovascularization |
|-----------------|------------|--------|-------------------------|------|-------------------------|
| 1               | 26         | 900    | 32                      | I    | Yes                     |
| 2               | 26         | 900    | 32                      | I    | Yes                     |
| 3               | 26         | 930    | 34                      | I    | Yes                     |
| 4               | 26         | 930    | 34                      | I    | Yes                     |
| 5               | 27         | 950    | 35                      | I    | No                      |
| 6               | 27         | 950    | 35                      | I    | No                      |
| 7               | 27         | 940    | 35                      | I    | No                      |

GA: Gestational age; BW: Birth weight; PCA: Postconceptional age; IVR: Intravitreal ranibizumab.