Effects and Complications of Bevacizumab Use in Patients with Retinopathy of Prematurity: A Multicenter Study in Taiwan

Wei-Chi Wu, MD, PhD,[1] Po-Ting Yeh, MD,[2] San-Ni Chen, MD,[3] Chung-May Yang, MD,[2] Chi-Chun Lai, MD,[1] Hsi-Kung Kuo, MD[4]

Purpose: To investigate the effects and complications of the anti-vascular endothelial growth factor agent bevacizumab in the treatment of retinopathy of prematurity (ROP) in Taiwanese patients.

Design: A multicenter, retrospective case series study.

Participants: Twenty-seven patients (49 eyes) from 4 medical centers across Taiwan.

Methods: This study included patients receiving intravitreal injections of bevacizumab (IVB) (0.625 mg) for the treatment of ROP between 2007 and 2009 at 4 major medical centers in Taiwan. The effects and complications associated with this treatment were analyzed. Patients were followed for at least 6 months after bevacizumab injection.

Main Outcome Measures: Regression of ROP and the complications associated with the injection of bevacizumab.

Results: Forty-nine eyes of 27 patients (18 male and 9 female) were included in the study. Mean gestational age and birth weight were 26.0±2.4 weeks and 971.6±589.6 g, respectively. There were 41 eyes (23 patients) with stage 3 ROP, 6 eyes (3 patients) with stage 4A ROP, and 2 eyes (1 patient) with stage 5 ROP. All of the eyes received only a single injection of IVB. The mean injection time was 36.8±2.6 weeks postmenstrual age for eyes with stage 3 ROP. A total of 37 of 41 eyes (90%) with stage 3 ROP regressed after bevacizumab injection only. Four eyes (10%) required additional laser treatment to regress the ROP. Of 6 eyes (3 patients) with stage 4A ROP, 2 eyes (1 patient; 33%) regressed after bevacizumab injection and 4 eyes (67%) regressed after bevacizumab injection and subsequent vitrectomy. The 2 eyes with stage 5 ROP exhibited decreased vascular tortuosity after bevacizumab injection, but the retina failed to reattach after vitrectomy surgeries. Major complications included vitreous or pre-retinal hemorrhage in 4 eyes (8%) and transient vascular sheathing in 2 eyes (4%).

Conclusions: Bevacizumab injection seems effective and well tolerated in some cases of ROP, especially in stage 3 ROP. Ocular complications could result from the injection of bevacizumab in pediatric eyes.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2011;118:176–183*

Retinopathy of prematurity (ROP) is one of the leading causes of childhood blindness. In later stages of ROP, neovascularization arises because of retinal immaturity. Neovascularization leads to retinal traction, retinal detachment, hemorrhage, and a funnel configuration of the retina, eventually affecting vision. Neovascularization is mainly driven by vascular endothelial growth factor (VEGF).[1] The current recommended treatment for type 1 ROP is peripheral ablation. Although cryotherapy has been used in the past, laser therapy is now the preferred method of treatment. In addition, the timing of treatment has been moved to an earlier stage of the disease, as documented by the Early Treatment for Retinopathy of Prematurity study (ETROP).[2] Although laser or cryotherapy effectively halts the progression of stage 3 to 4 ROP in 90% of patients, these treatments actually destroy approximately two thirds of the retina. Some patients progress to retinal detachment despite laser or cryotherapy. The functional outcomes are still not satisfying in stage 4B or 5 ROP, even after vitrectomy or scleral buckling.[3–5] A new treatment that could decrease the need for laser treatment or vitreoretinal surgery or improve the success rate of vitreoretinal surgery would be worth pursuing.

Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA) is a humanized anti-VEGF monoclonal antibody.[6] It is the first antiangiogenic agent for the treatment of metastatic colorectal cancer. Bevacizumab has 2 binding sites and binds directly to VEGF. It has also been shown to inhibit more than 1 of the 9 VEGF isoforms. The drug has shown promising results in treating many retinopathies with VEGF up-regulation, including age-related macular degeneration,[7,8] diabetic retinopathy,[9–11] vitreous hemorrhage,[12,13] neovascular glaucoma,[14] and retinal vascular occlusion.[15–17] Vascular endothelial growth factor levels in vitreous fluid have been shown to be highly elevated in patients with ROP.[18,19] These results show the potential benefit of bevacizumab for the treatment of ROP.

So far, there have been only a few case reports or small case series of bevacizumab use in ROP.[20–29] The information about the effects and complications associated with this

ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2010.04.018

Table 1. Demographics of Patients Receiving Bevacizumab Treatment for Stage 3 Retinopathy of Prematurity

Eyes (patients)	41 (23)
Male/female	16/7
Mean gestational age (wks)	25.7±2.3
Mean birth weight (g)	845.0±221.4
Zone 1/zone 2	9/32
Mean injection time (postmenstrual age, wks)	36.8±2.6
No. of eyes with previous laser treatment	5
No. of eyes receiving laser treatment after bevacizumab injection	4
No. of eyes (%) with regression of ROP after bevacizumab treatment alone	37 (90)
Complications: pre-retinal and vitreous hemorrhage	4
Mean follow-up time (mos)	8.4±3.4

ROP = retinopathy of prematurity.

treatment remains scarce. We share our experience of using bevacizumab to treat ROP by collecting data from 4 major medical centers in Taiwan.

Patients and Methods

This is a multicenter, retrospective study of bevacizumab use in patients with ROP. The data were collected from medical centers in 4 cities across Taiwan. These centers included National Taiwan University Hospital in Taipei, Changhua Christian Hospital in Changhua, Chang Gung Memorial Hospital in Kaohsiung, and Chang Gung Memorial Hospital in Taoyuan. The study was approved by the institutional review board for each hospital. Each patient's parent or legal guardian signed a consent form before the administration of the intravitreal injection of bevacizumab (IVB). The data were collected from January 2006 to December 2008. Medical records for patients with ROP who were treated with IVB were collected from each center and pooled together for data analysis. For stage 3 ROP, the indications for treatment were patients whose retinopathy met the criteria of type 1 ROP used in the ETROP study.[2] For stage 4 or 5 ROP, the injection of bevacizumab was mainly used to reduce the chance of bleeding during the subsequent vitrectomy surgery. Patients were treated when a plus or pre-plus sign was present. Patients with a follow-up lasting less than 6 months were excluded.

The treatment technique is described as follows. The pupil was dilated with 1.25% phenylephrine (Phenylephrine, Wu Fu Laboratories Co Ltd., Yilan, Taiwan) and 1% tropicamide (Mydriacyl, sa Alcon-Couvreur nv, Puurs, Belgium) before intravitreal injection. The anesthesia involved the intravenous injection of midazolam (Dormicum, Cenexi SAS, Fontenay-sous-Bois, France) or fentanyl (Fentanyl-Fresenius, Bodene Limited, Port Elizabeth, South Africa) to sedate the infant before the intravitreal injection. Vital signs were monitored throughout the entire procedure. If the respiratory function of the infant was unstable, endotracheal intubation was performed to secure the airway. After the infant was sedated and the eyes were prepared in a standard fashion using 5% povidone/iodine and the topical antibiotic levofloxacin (Cravit, Santen Pharmaceutical Co., Osaka, Japan), 0.625 mg (0.025 ml) of bevacizumab was injected intravitreally via the pars plica. A nurse helped hold the infant during the injection. After the injection, intraocular pressure and retinal artery perfusion were checked, and patients received topical levofloxacin for 3 days. The patients were followed up after 1 day and 3 days, and then every week to document the progression of the disease.

If the patients did not respond positively to this treatment in 2 to 3 weeks, conventional laser treatment of ROP was performed. No second injection of bevacizumab was given to patients. Positive responses included the disappearance of tunica vasculosa lentis, dilation of the pupils, disappearance or decrease in retinal vessel tortuosity and neovascularization, and vascularization toward the peripheral retina. After treatment, patients were followed every 1 to 2 weeks until full vascularization of the retina was observed. Examinations were performed under anesthesia if needed. Some cases were photographed by the RetCam Imaging System (Clarity Medical System, Pleasanton, CA) before and after the injection of bevacizumab.

Results

During the study period, 40 patients received a single bevacizumab injection. Thirteen patients were excluded from the study because of a follow-up time of less than 6 months. In the end, 49 eyes of 27 patients (18 male and 9 female) were included in the study. Six patients were from National Taiwan University Hospital in Taipei, 5 patients were from Changhua Christian Hospital in Changhua, 10 patients were from Chang Gung Memorial Hospital in Kaohsiung, and 6 patients were from Chang Gung Memorial Hospital in Taoyuan. Mean gestational age and birth weight were 26.0±2.4 weeks and 971.6±589.6 g, respectively. In total, there were 41 eyes (23

Table 2. Patients with Stage 4 or 5 Retinopathy of Prematurity Treated with Bevacizumab

Cases/Eyes/ Gender/Eye	GA (wks)	BW (g)	Zone	Stage	Laser	Age at Injection (wks)	Age at Vitrectomy (wks)	Final Retinal Reattachment	Complications	FU (mos)
1/1/F/OD	29	1435	1	4A	y	39	—	y	—	6
1/2/F/OS	29	1435	1	4A	y	39	—	y	—	6
2/3/M/OD	29	3880	2	4A	y	40	41, 45	y	Transient vessel sheathing	9
2/4/M/OS	29	3880	2	4A	y	40	41	y	Transient vessel sheathing	9
3/5/M/OD	24	690	2	4A	y	33	34	y		6
3/6/M/OS	24	690	2	4A	y	33	34	y		6
4/7/F/OD	28	1148	1	5	y	35	36	n		12
4/8/F/OS	28	1148	1	5	y	35	36, 39	n		12

BW = birth weight; F = female; FU = follow-up; GA = gestational age; M = male; OD = right eye; OS = left eye.

patients) with stage 3 ROP (Table 1), 6 eyes (3 patients) with stage 4A ROP, and 2 eyes (1 patient) with stage 5 ROP (Table 2).

Of the 41 eyes with stage 3 ROP, 9 eyes (22%) were zone 1 ROP, and 32 eyes (78%) were zone 2 ROP. All of the eyes with stage 3 ROP received treatment when they met the criteria of type 1 ROP as defined by the ETROP study.[2] In eyes with stage 3 ROP, 36 eyes (88%) received bevacizumab as the primary treatment for ROP, and 5 eyes (12%) received bevacizumab as the salvage treatment after no response from previous laser treatment. The mean injection time was 36.8±2.6 weeks postmenstrual age for eyes with stage 3 ROP. Five eyes from 3 patients had tunica vasculosa lentis with poor pupil dilation. One to three days after injection, tunica vasculosa lentis diminished and pupil dilation was noted in all of the eyes (Fig 1A, B). All of the eyes had decreased vessel tortuosity after bevacizumab injection. In 36 eyes that received bevacizumab as the primary treatment for ROP, 32 (89%) showed ROP regression. Four eyes (11%) required additional laser treatment to regress the ROP because of the lack of a positive response 2 to 3 weeks after bevacizumab treatment. In 5 eyes (3 patients) that received bevacizumab as the salvage treatment after laser treatment, all 5 (100%) later displayed ROP regression. After a mean follow-up of 8.4±3.4 months, 37 eyes (90%) with stage 3 ROP had regressed with full vascularization after bevacizumab injection alone and 4 eyes (10%) had regressed after bevacizumab injection and subsequent laser treatment. Bevacizumab injection could work as either the primary treatment (Fig 2A, B) or salvage treatment after previously failed laser treatment (Fig 2C, D).

In eyes with stage 4 or 5 ROP, the injection was performed within the week before vitrectomy. The mean injection time was 36.8±3.1 weeks postmenstrual age. After the injection, the plus sign was alleviated in all eyes (Fig 3A, B). However, fibrotic traction on the retina increased in 2 eyes (Fig 4A–C). Two eyes (33%) with stage 4A ROP regressed after bevacizumab injection without the need for subsequent vitrectomy. Four eyes (67%) regressed after bevacizumab injection and subsequent vitrectomy. We did not encounter hemorrhage in the vitreous or the proliferative fibrovascular membranes during vitreous shaving in those patients. Two eyes with stage 5 ROP displayed decreased vascular tortuosity after bevacizumab injection, but the retina failed to reattach after multiple vitrectomy surgeries. Mean follow-up in this group of patients was 8.3±2.7 months.

Major ocular complications associated with bevacizumab injection included vitreous or pre-retinal hemorrhage in 4 eyes (8%) (Fig 5A, B), as well as transient vascular sheathing in the inferior venous branch in 2 eyes (4%) (Fig 6A, B). Vitreous or pre-retinal hemorrhage later resolved in all eyes. The eyes with sheathed vessels had reperfused at the subsequent follow-up after vitrectomy surgery for stage 4A ROP. No noticeable systemic complications related to the injection of bevacizumab were observed during follow-up.

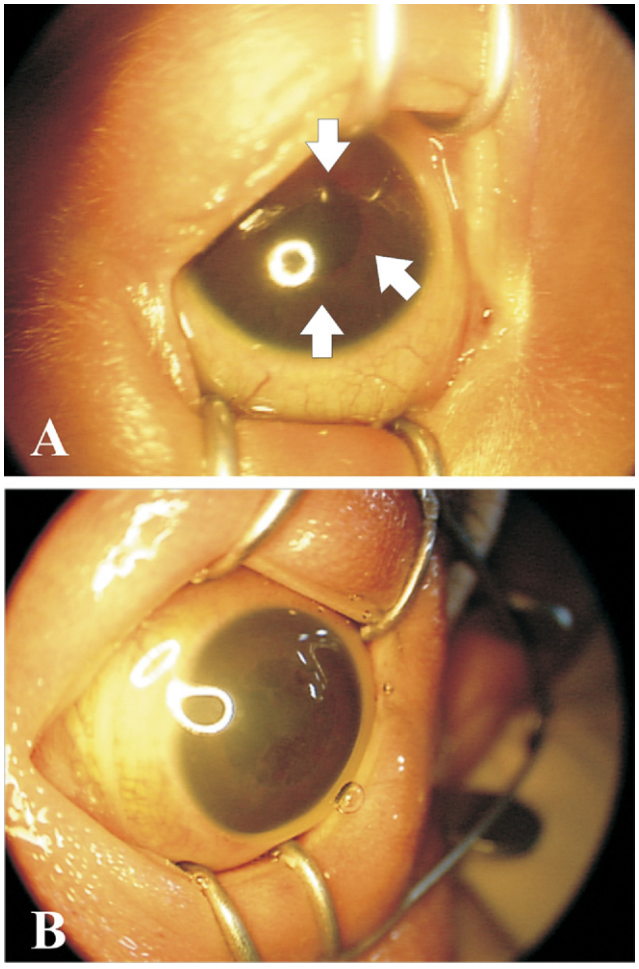

Figure 1. Regression of tunica vasculosa lentis in the left eye of a patient with stage 3 ROP after injection of bevacizumab. **A,** Before injection of bevacizumab, the pupil was fixed and the prominent vessels were seen along the papillary margin (*arrows*). **B,** Two days after bevacizumab injection, the pupil was fully dilated and tunica vasculosa lentis had disappeared. ROP = retinopathy of prematurity.

Discussion

This study found that IVB (0.625 mg), used either as a primary treatment or salvage treatment after laser treatment, caused neovascularization to regress and resulted in full retinal vascularization in the majority of patients with stage 3 ROP. In advanced ROP with retinal detachment, the treatment benefits of bevacizumab are less evident than in stage 3 ROP. The plus sign decreased after injection, and no active bleeding was noted during vitrectomy surgery. However, fibrotic traction on the retina increased in some eyes after the injection. Ocular complications did occur, but no apparent systemic adverse effects related to the injection were found up to the date of the last follow-up. Because VEGF is highly elevated in advanced ROP and has been found to play a central role as the driving force for neovascularization,[18,19,30] blocking VEGF with anti-VEGF agents seems to be a reasonable approach. These results are encouraging because they suggest the potential of a new treatment for ROP.

Bevacizumab seems to work best in stage 3 ROP, including zone 1 ROP. None of the eyes progressed to stage 4 ROP after a single injection of bevacizumab. However, some patients also received laser treatment if positive symptoms or neovascularization persisted or worsened over the course of 2 to 3 weeks. Bevacizumab injection neutralizes the VEGF already present in the vitreous cavity, but it does not inhibit continued production of VEGF in the avascular area. Laser treatment in the avascular retina further decreased VEGF production by destroying VEGF expression in the avascular retina. In addition, VEGF is not the only growth factor up-regulated in the eye. Insulin-like growth

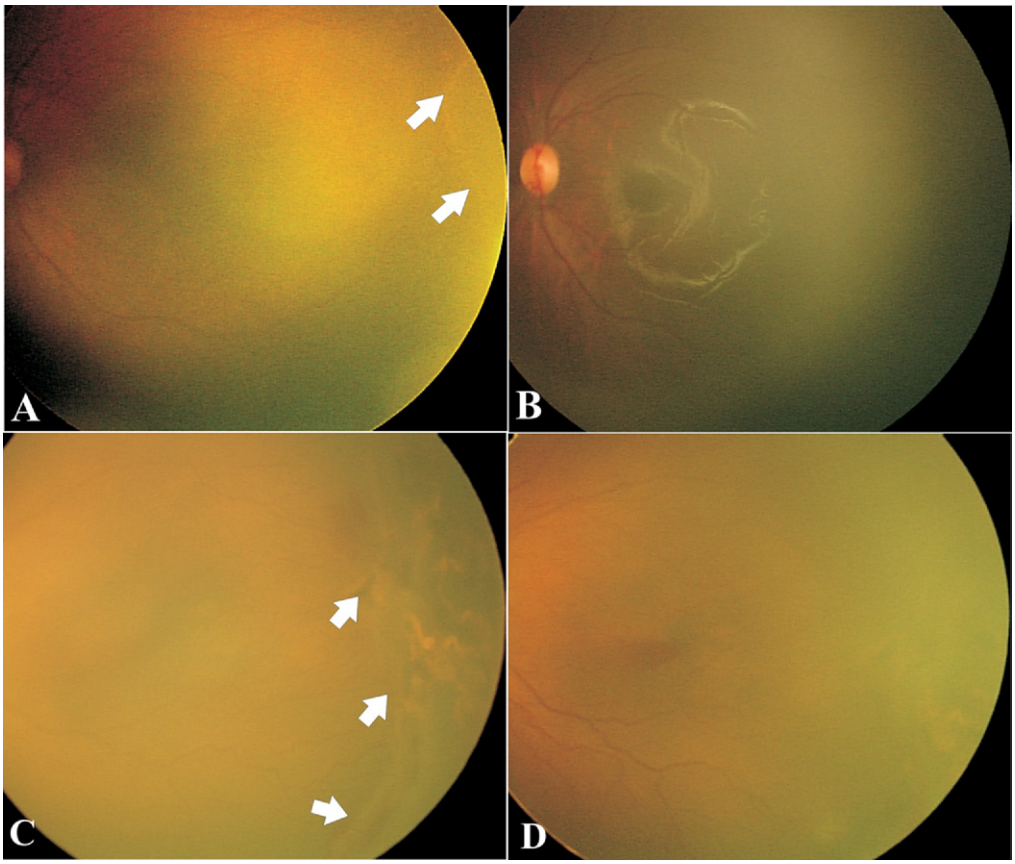

Figure 2. Full vascularization and the regression of stage 3 ROP in patients who received bevacizumab as the primary treatment **(A, B)** or salvage treatment **(C, D)**. **A,** Before injection of bevacizumab, neovascularization was seen at the border of the vascular and avascular retina (*arrows*). **B,** After injection of bevacizumab, the retinal vessel continued to grow and the ROP regressed. **C,** In the left eye of a patient with stage 3 ROP, neovascularization was still persistent (*arrows*) 3 weeks after laser treatment. **D,** After bevacizumab injection, the ROP regressed with full retinal vascularization. ROP = retinopathy of prematurity.

factor-1 and other growth factors may also play some role in the pathogenesis of ROP.[18,19,30–33] Inhibition of VEGF by bevacizumab may not be able to induce regression in all ROP cases. However, the majority of eyes responded well to this treatment alone, and only 10% of ROP eyes required additional laser treatment. Because the effects of bevacizumab injection in ROP eyes remain to be fully elucidated, standard laser treatment could serve as a backup in those cases that are nonresponsive.

The original purpose of bevacizumab use in stage 4 or 5 ROP was to reduce the plus sign to help reduce hemorrhage during the subsequent vitrectomy. Stage 4A ROP regressed after bevacizumab injection without the need for subsequent vitrectomy in 2 eyes (33%). Neovascularization and retinal detachment regressed after bevacizumab injection and subsequent vitrectomy in 4 eyes (66%). Quiroz-Mercado et al[23] also reported 1 case of resolution of stage 4A ROP after bevacizumab injection. However, caution is necessary when bevacizumab is used in ROP with retinal detachment. While angiogenesis is inhibited, the fibrotic component of ROP may accelerate and retinal detachment might worsen.[34,35] Thus, we suggest that vitrectomy surgery should be performed within 1 week of bevacizumab injection, which is similar to the use of bevacizumab in proliferative diabetic retinopathy with retinal detachment in adult patients.[36,37]

Two eyes (1 case) with stage 4A ROP in our study developed transient retinal vessel sheathing after intravitreal injection. Whether the vessel sheathing was due to increased intraocular pressure after intravitreal injection or to the anti-VEGF agent remains unknown. Because the fundus was checked immediately after intravitreal injection in every patient, it is more likely that transient retinal vessel sheathing was due to delayed effects of the injected agent rather than the immediate increase in intraocular pressure. A previous study suggested that VEGF is the primary growth factor for endothelial cells;[1,38,39] thus, blocking VEGF by administering anti-VEGF agents in the immature retina might result in vessel collapse or nonperfusion. In addition, inflammation or a tractional force induced by accelerated fibrosis may place traction on retinal vasculature in a way that might impede vascular flow. Notably, retinal vessel sheathing in this case disappeared after vitrectomy. Various factors could contribute to the restoration of retinal vessel configuration. No long-acting gas was used after the surgery, and a lower target intraocular pressure was set for pediatric retinal surgery. In addition, vitrectomy could re-

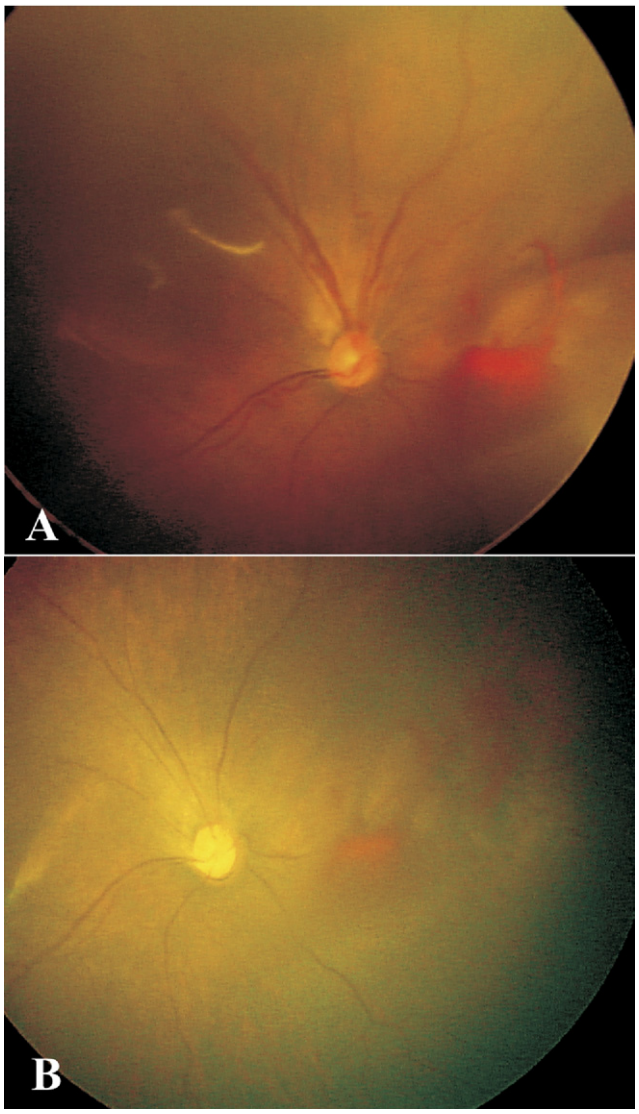

Figure 3. Plus sign decreased in the right eye of a patient with stage 4 A ROP after injection of bevacizumab. **A,** Before injection of bevacizumab, prominent retinal vessel tortuosity and some pre-retinal hemorrhage were seen. **B,** After injection of bevacizumab, the retinal vessels were less congestive and torturous. Pre-retinal hemorrhage had decreased after injection of bevacizumab. ROP = retinopathy of prematurity.

move the majority of bevacizumab in the vitreous cavity if it contributed to retinal vessel sheathing.

Some patients experienced pre-retinal or vitreous hemorrhage after the injection of bevacizumab. Advanced ROP has been found to be associated with both of these conditions. On the other hand, IVB itself could also lead to these complications, as reported previously.[40] Bevacizumab could lead to the resolution of new vessels. These forces exerted on the neovascularization could lead to bleeding. However, the hemorrhage observed did not cause significant damage to the eye and was typically reabsorbed a few weeks later.

Mintz-Hittner and Kuffel[24] showed that a single injection of bevacizumab prevented the progression to retinal detachment in all eyes with posterior zone 1 ROP, without the

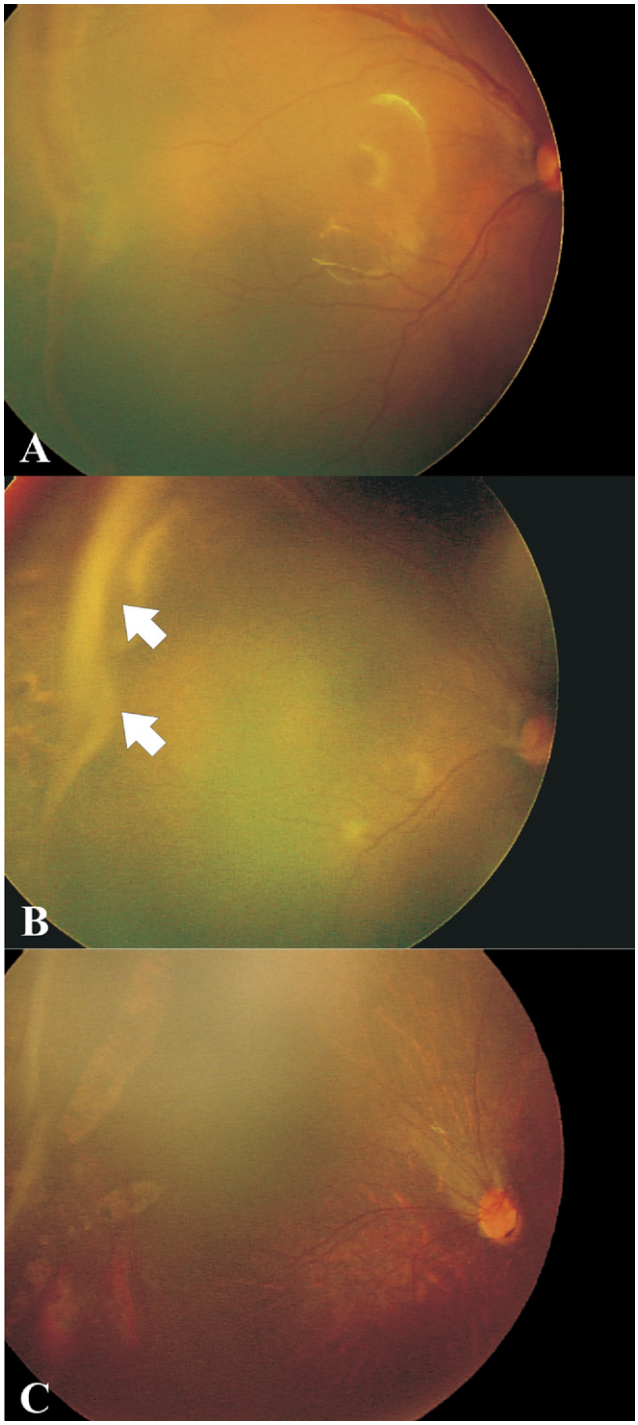

Figure 4. Plus sign decreased but fibrotic traction increased in the right eye of a patient with stage 4 A ROP after injection of bevacizumab. **A,** Before injection of bevacizumab, prominent retinal vessel tortuosity and focal retinal detachment were seen. **B,** After injection of bevacizumab, the retinal vessels were less congestive and torturous, but the fibrotic traction seemed to increase (*arrows*) and some disc dragging was noted. **C,** After vitrectomy, the retina was fully attached with some laser scarring. ROP = retinopathy of prematurity.

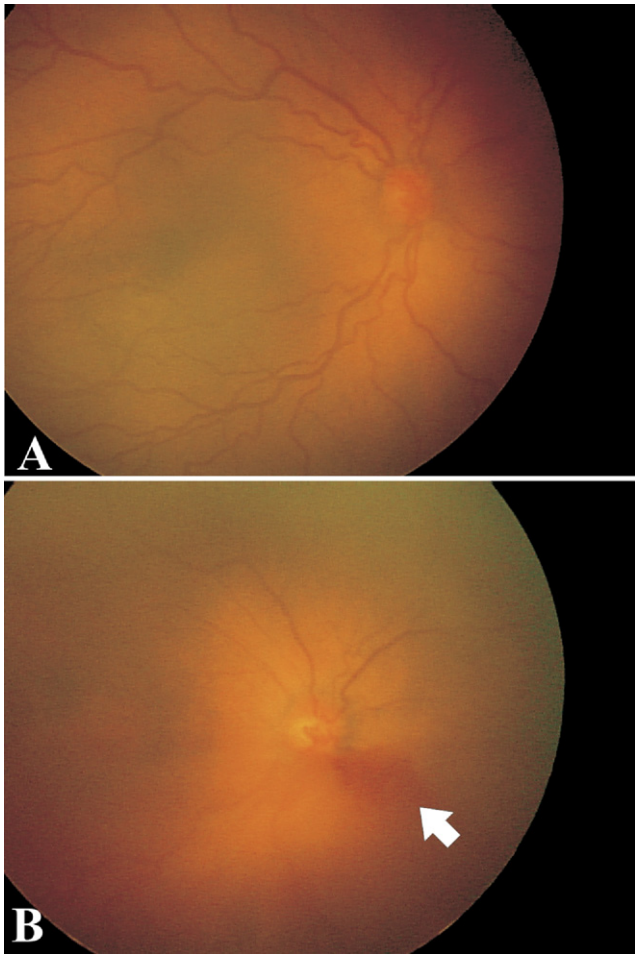

Figure 5. Pre-retinal hemorrhage after injection of bevacizumab in the right eye of a patient with stage 3 ROP. **A,** Before injection of bevacizumab, the retinal vessel was torturous but no preretinal hemorrhage was noted. **B,** After injection of bevacizumab, the retinal vessel tortuosity decreased but some retinal hemorrhage was present (*arrow*). ROP = retinopathy of prematurity.

need for laser ablation. These results are encouraging because approximately 27% to 47% of posterior zone 1 cases progress to retinal detachment, even after peripheral retinal ablation.[41–43] In our case series, 9 eyes (22%) were classified as zone 1 ROP. None of these eyes progressed to retinal detachment after bevacizumab treatment; therefore, bevacizumab treatment seems to be better than laser treatment for zone 1 ROP. However, this study is only a small case series report, and no definite conclusions can be drawn. The other potential benefits of anti-VEGF therapy in comparison with ablative treatment include the ease of the procedure, the reduced operating time, and no need for equipment related to laser or cryotherapy. Bevacizumab is also less destructive to the retina. Furthermore, tunica vasculosa lentis regression and pupil dilation facilitate further follow-up or subsequent treatments. Finally, the technique eliminates complications associated with ablative treatments, such as refractive errors or visual field loss.[44–46] However, long-term study is needed to substantiate this result.

Study Limitations

The limitations of this study include its retrospective nature and the lack of a concomitant control group. Also, fundus photographs were not available in all study centers. Finally, laser treatment was allowed if a response was not observed in 2 to 3 weeks. Nonetheless, to our knowledge, this study is the largest case series of bevacizumab use in the treatment of ROP ever reported. Data were collected from multiple centers all over the country, and all of the patients were followed up for at least 6 months. However, many questions remain to be answered regarding the optimal dosing of bevacizumab for ROP, optimal injection time, value of combination treatment, and long-term safety and efficacy

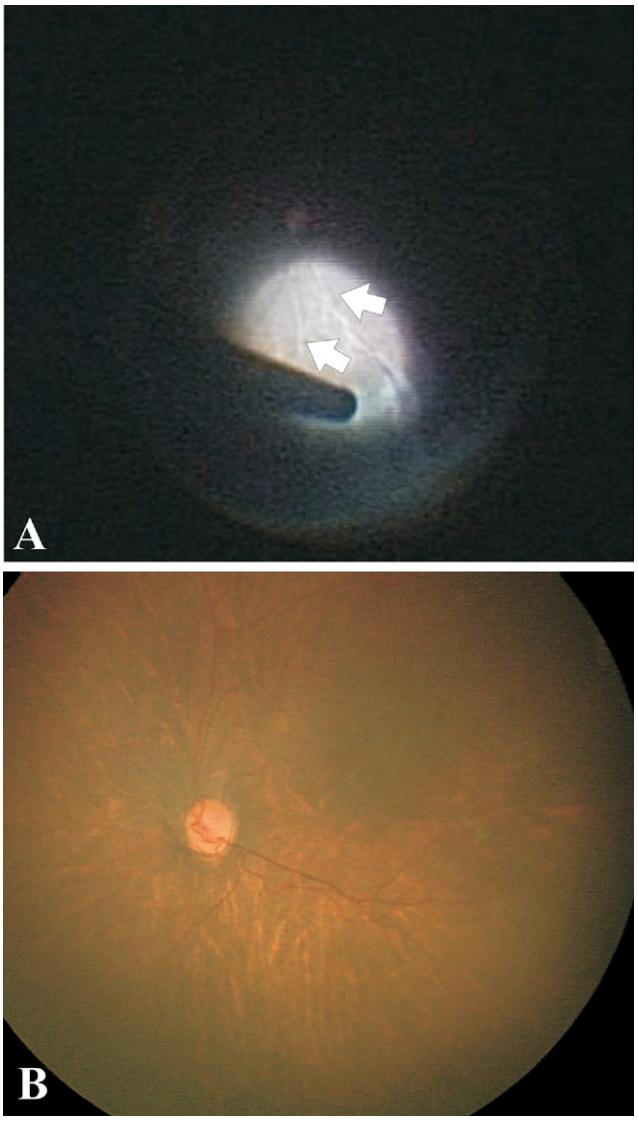

Figure 6. Transient retinal vessel sheathing after injection of bevacizumab in a patient with stage 4 A ROP. **A,** Three days after injection of bevacizumab, inferior retinal vein sheathing (*arrows*) was noted during the vitrectomy surgery. **B,** After the vitrectomy, the retinal vessel sheathing disappeared with the regression of ROP. ROP = retinopathy of prematurity.

of bevacizumab use in the eyes of children. Further randomized, prospective studies with a concurrent control group are urgently needed to provide evidence-based answers to these questions.

In conclusion, 90% of stage 3 eyes regressed after a single bevacizumab injection, either primarily or after failing laser treatment, whereas the remaining 10% regressed when laser ablation was performed secondarily. Vasculosa lentis and plus sign responded quickly to treatment with bevacizumab. For stage 4 ROP, bevacizumab use before vitrectomy decreased vessel activity and the incidence of retinal hemorrhage during surgery. Bevacizumab could even lead to the resolution of stage 4A ROP in some cases, making vitrectomy unnecessary. Although our initial experience using bevacizumab to treat ROP seems promising, some ocular complications do occur after the use of bevacizumab. Longer follow-up of these patients is necessary to determine the long-term ocular and systemic safety of this anti-VEGF agent when used in the rapidly developing pediatric eye.

References

1. Alon T, Hemo I, Itin A, et al. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. Nat Med 1995;1:1024–8.
2. 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. Arch Ophthalmol 2003;121:1684–94.
3. Repka MX, Tung B, Good WV, et al. Outcome of eyes developing retinal detachment during the Early Treatment for Retinopathy of Prematurity Study (ETROP). Arch Ophthalmol 2006;124:24–30.
4. Gilbert WS, Quinn GE, Dobson V, et al, Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Cooperative Group. Partial retinal detachment at 3 months after threshold retinopathy of prematurity: long-term structural and functional outcome. Arch Ophthalmol 1996;114:1085–91.
5. Wu WC, Drenser KA, Lai M, et al. Plasmin enzyme-assisted vitrectomy for primary and reoperated eyes with stage 5 retinopathy of prematurity. Retina 2008;28(suppl):S75–80.
6. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.
7. Bashshur ZF, Haddad ZA, Schakal AR, et al. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: the second year of a prospective study. Am J Ophthalmol 2009;148:59–65.
8. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006;26:383–90.
9. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006;113:1695–705.
10. Mason JO III, Nixon PA, White MF. Intravitreal injection of bevacizumab (Avastin) as adjunctive treatment of proliferative diabetic retinopathy. Am J Ophthalmol 2006;142:685–8.
11. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. Retina 2006;26:275–8.
12. Jonas JB, Libondi T, von BS, Vossmerbaeumer U. Intravitreal bevacizumab for vitreous haemorrhage [letter]. Acta Ophthalmol 2008;86:585–6.
13. Ruiz-Moreno JM, Montero JA, Lugo F, et al. Intravitreal bevacizumab in recurrent diabetic vitreous haemorrhage after vitrectomy [letter]. Acta Ophthalmol 2008;86:231–2.
14. Iliev ME, Domig D, Wolf-Schnurrbursch U, et al. Intravitreal bevacizumab (Avastin) in the treatment of neovascular glaucoma. Am J Ophthalmol 2006;142:1054–6.
15. Kriechbaum K, Michels S, Prager F, et al. Intravitreal Avastin for macular oedema secondary to retinal vein occlusion: a prospective study. Br J Ophthalmol 2008;92:518–22.
16. Prager F, Michels S, Kriechbaum K, et al. Intravitreal bevacizumab (Avastin) for macular oedema secondary to retinal vein occlusion: 12-month results of a prospective clinical trial. Br J Ophthalmol 2009;93:452–6.
17. Jaissle GB, Leitritz M, Gelisken F, et al. One-year results after intravitreal bevacizumab therapy for macular edema secondary to branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol 2009;247:27–33.
18. Sato T, Kusaka S, Shimojo H, Fujikado T. Simultaneous analyses of vitreous levels of 27 cytokines in eyes with retinopathy of prematurity. Ophthalmology 2009;116:2165–9.
19. Sato T, Kusaka S, Shimojo H, Fujikado T. Vitreous levels of erythropoietin and vascular endothelial growth factor in eyes with retinopathy of prematurity. Ophthalmology 2009;116:1599–603.
20. Kong L, Mintz-Hittner HA, Penland RL, et al. Intravitreous bevacizumab as anti-vascular endothelial growth factor therapy for retinopathy of prematurity: a morphologic study [letter]. Arch Ophthalmol 2008;126:1161–3.
21. Kusaka S, Shima C, Wada K, et al. Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: a pilot study. Br J Ophthalmol 2008;92:1450–5.
22. Chung EJ, Kim JH, Ahn HS, Koh HJ. Combination of laser photocoagulation and intravitreal bevacizumab (Avastin) for aggressive zone I retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol 2007;245:1727–30.
23. Quiroz-Mercado H, Martinez-Castellanos MA, Hernandez-Rojas ML, et al. Antiangiogenic therapy with intravitreal bevacizumab for retinopathy of prematurity. Retina 2008;28(suppl):S19–25.
24. Mintz-Hittner HA, Kuffel RR Jr. Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. Retina 2008;28:831–8.
25. Azad R, Chandra P. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity [letter]. Indian J Ophthalmol 2007;55:319; author reply 320.
26. dell'Omo R, Kulkarni A, Franks WA. Intravitreal and intracameral bevacizumab to treat neovascular complications of retinopathy of prematurity [letter]. Acta Ophthalmol 2008;86:698–700.
27. Travassos A, Teixeira S, Ferreira P, et al. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthalmic Surg Lasers Imaging 2007;38:233–7.
28. Rishi E, Rishi P, Ratra D, Bhende M. Off-label use of bevacizumab in retinopathy of prematurity [letter]. Retina 2009;29:284; author reply 284–5.
29. Lalwani GA, Berrocal AM, Murray TG, et al. Off-label use of intravitreal bevacizumab (Avastin) for salvage treatment in progressive threshold retinopathy of prematurity. Retina 2008;28(suppl):S13–8.
30. Smith LE. Through the eyes of a child: understanding retinopathy through ROP. The Friedenwald Lecture. Invest Ophthalmol Vis Sci 2008;49:5177–82.

31. Heidary G, Vanderveen D, Smith LE. Retinopathy of prematurity: current concepts in molecular pathogenesis. Semin Ophthalmol 2009;24:77–81.
32. Lashkari K, Hirose T, Yazdany J, et al. Vascular endothelial growth factor and hepatocyte growth factor levels are differentially elevated in patients with advanced retinopathy of prematurity. Am J Pathol 2000;156:1337–44.
33. Lofqvist C, Niklasson A, Engstrom E, et al. A pharmacokinetic and dosing study of intravenous insulin-like growth factor-I and IGF-binding protein-3 complex to preterm infants. Pediatr Res 2009;65:574–9.
34. Honda S, Hirabayashi H, Tsukahara Y, Negi A. Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol 2008;246:1061–3.
35. Mintz-Hittner HA, Best LM. Antivascular endothelial growth factor for retinopathy of prematurity. Curr Opin Pediatr 2009; 21:182–7.
36. Yeh PT, Yang CM, Lin YC, et al. Bevacizumab pretreatment in vitrectomy with silicone oil for severe diabetic retinopathy. Retina 2009;29:768–74.
37. Oshima Y, Shima C, Wakabayashi T, et al. Microincision vitrectomy surgery and intravitreal bevacizumab as a surgical adjunct to treat diabetic traction retinal detachment. Ophthalmology 2009;116:927–38.
38. Pierce EA, Avery RL, Foley ED, et al. Vascular endothelial growth factor/vascular permeability factor expression in a mouse model of retinal neovascularization. Proc Natl Acad Sci U S A 1995;92:905–9.
39. Stone J, Itin A, Alon T, et al. Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. J Neurosci 1995;15:4738–47.
40. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, et al, Pan American Collaborative Retina Group (PACORES). Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008;246:81–7.
41. Foroozan R, Connolly BP, Tasman WS. Outcomes after laser therapy for threshold retinopathy of prematurity. Ophthalmology 2001;108:1644–6.
42. Kychenthal A, Dorta P, Katz X. Zone I retinopathy of prematurity: clinical characteristics and treatment outcomes. Retina 2006;26(suppl):S11–5.
43. O'Keefe M, Lanigan B, Long VW. Outcome of zone 1 retinopathy of prematurity. Acta Ophthalmol Scand 2003;81: 614–6.
44. Davitt BV, Dobson V, Quinn GE, et al, Early Treatment for Retinopathy of Prematurity Cooperative Group. Astigmatism in the Early Treatment for Retinopathy Of Prematurity Study: findings to 3 years of age. Ophthalmology 2009;116:332–9.
45. Quinn GE, Dobson V, Davitt BV, et al, Early Treatment for Retinopathy of Prematurity Cooperative Group. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity Study: findings to 3 years of age. Ophthalmology 2008;115:1058–64.
46. Quinn GE, Dobson V, Hardy RJ, et al, CRYO-Retinopathy of Prematurity Cooperative Group. Visual fields measured with double-arc perimetry in eyes with threshold retinopathy of prematurity from the Cryotherapy for Retinopathy of Prematurity Trial. Ophthalmology 1996;103:1432–7.

Footnotes and Financial Disclosures

Originally received: November 3, 2009.
Final revision: April 8, 2010.
Accepted: April 9, 2010.
Available online: July 29, 2010. Manuscript no. 2009-1523.

[1] Department of Ophthalmology, Chang Gung Memorial Hospital, Taoyuan, Taiwan and Chang Gung University, College of Medicine, Taoyuan, Taiwan.

[2] Department of Ophthalmology, National Taiwan University Hospital, Taipei.

[3] Department of Ophthalmology, Changhua Christian Hospital, Changhua, Taiwan, and School of Medicine, Chung-Shan Medical University, Taichung, Taiwan.

[4] Department of Ophthalmology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, and Chang Gung University, College of Medicine, Kaohsiung, Taiwan.

Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

This study was partly supported by grants from the National Science Council, Taiwan (96-2314-B-182A-094).

Correspondence:
Hsi-Kung Kuo, MD, Department of Ophthalmology, Chang Gung Memorial Hospital, 123, Dapi Rd., Niaosong Township, Kaohsiung County 833, Taiwan (R.O.C.). E-mail: hsikung@adm.cgmh.org.tw.