The Journal of Maternal-Fetal and Neonatal Medicine, 2012; 25(11): 2194–2197

ISSN 1476-7058 print/ISSN 1476-4954 online
DOI: 10.3109/14767058.2012.684109

informa
healthcare

Intravitreal bevacizumab for retinopathy of prematurity as first line or rescue therapy with focal laser treatment. A case series

Carlo Dani[1], Saverio Frosini[2], Pina Fortunato[3], Giovanna Bertini[4], Simone Pratesi[4], Liliana Pollazzi[5], Roberto Caputo[3] & Agostino La Torre[2]

[1]Department of Surgical and Medical Critical Care, Section of Neonatology, Careggi University Hospital of Florence, Florence, Italy, [2]Department of Specialised Surgical Sciences, University of Florence, Florence, Italy, [3]Department of Pediatric Ophthalmology, Meyer Hospital of Florence, Florence, Italy, [4]Division of Neonatology, Careggi University Hospital of Florence, and [5]Orthoptist Ophthalmology Assistant, Florence, Italy

Objectives: **Laser therapy is effective in the treatment of severe forms of retinopathy of prematurity (ROP), and aggressive posterior ROP (APROP), but always damages the retina. We report our preliminary findings in seven premature infants with complicated ROP or APROP who were treated with intravitreal bevacizumab (IVB) as first line monotherapy or rescue therapy combined with laser treatment.** ***Methods:*** **We studied retrospectively seven preterm infants, who were affected by APROP (*n* = 4) or pre-threshold ROP (*n* = 3). Infants were treated with IVB (0.625 mg; Avastin®, Roche, Basel, Switzerland) monotherapy (*n* = 2) when they were too sick to undergo lengthy laser treatment.** ***Results:*** **Monotherapy IVB (*n* = 3 eyes) and IVB combined with laser therapy (*n* = 3 eyes) of APROP cases were followed by regression of the ROP and complete peripheral vascularization. The combined therapy with IVB and laser therapy of pre-threshold ROP (5 eyes) produced a regression of neovascularization and good retinal anatomical outcome.** ***Conclusions:*** **In our series, IVB was successful in treating ROP in a small cohort of extremely preterm infants with APROP or pre-threshold ROP, both as monotherapy or rescue treatment after laser therapy, without the development of ocular and systemic short- and long-term adverse effects.**

Keywords: bevacizumab, retinopathy of prematurity, anti-VEGF, preterm infant

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder, which is the main cause of visual impairment and blindness in preterm infants [1]. It occurs in 65% of infants with birth weight <1250 g [2,3], but decreases to 35% when considering the more severe stages [4].

The pathogenesis of ROP is multi-factorial and the main risk factors are prematurity, low birth weight, respiratory distress syndrome (RDS) and oxidative stress favored by oxygen-therapy and blood transfusions [5,6]. Recently, the pivotal role of oxygen-regulated vascular endothelial growth factor (VEGF) in the pathogenesis of ROP has been demonstrated. The retinas of infants born prematurely are incompletely vascularized with a peripheral avascular zone, the area of which depends on the gestational age [7]. With maturation of the infant the resulting non-vascularized retina becomes increasingly hypoxic and this induces an increase in the expression of VEGF which promotes new blood vessel growth that is the typical retinal neovascularization of ROP [7].

The early treatment for retinopathy of prematurity (ETROP) study demonstrated that laser or cryotherapy was successful in improving outcome in approximately 50% of cases with stage 3+ROP; however approximately 10% of the patients, even with timely treatment of threshold or high-risk pre-threshold ROP, still may have severe vision loss [8]. Moreover, these treatments actually destroy approximately two-thirds of the retina [9–11]. Therefore, the development of treatment that could decrease the need for laser treatment or vitreoretinal surgery or improve their success rate would be valuable. This explains the rapid diffusion of anti-VEGF agents and publication of a number of reports on the off-label use of intravitreal bevacizumab (IVB) for ROP. Recently, a randomized clinical trial demonstrated that IVB monotherapy gives significant benefit in zone I stage 3+ROP in comparison with laser therapy [12], but many questions remains unanswered, such as the effectiveness of IVB in the treatment of advanced ROP (stage 4 and 5) and aggressive posterior ROP (APROP).

The aim of the present study was to report our preliminary findings in seven premature infants with complicated ROP or APROP who received IVB injections either as first line monotherapy or as rescue therapy following laser therapy.

Methods

This retrospective study was performed at the Neonatal Intensive Care Unit of the Careggi University Hospital of Florence from 2007 to 2009. Bevacizumab was given as compassionate treatment to extremely preterm infants who failed laser therapy for ROP or were too ill to undergo a lengthy laser treatment. Before drug administration, the parents received a thorough explanation of the off-label use of bevacizumab and its possible short- and long-term complications and signed an informed consent form.

Two categories of patients were consecutively enrolled: (1) infants with APROP, which is a severe form of ROP with posterior

Correspondence: Carlo Dani, Division of Neonatology, Careggi University Hospital, University of Florence School of Medicine, Viale Morgagni, 85 Firenze, Italy. Tel.: +39 055 7947428. Fax : +39 055 7947425. E-mail: cdani@unifi.It

(Received 23 January 2012; revised 15 March 2012; accepted 06 April 2012)

location, prominence of plus disease, and ill-defined nature of retinopathy which if left untreated usually progresses to stage 5 ROP [13]; (2) infants with pre-threshold ROP defined as (1) any ROP in zone I, (2) ROP in zone II with plus disease, (3) zone II with stage 3 ROP and no plus disease, or (4) zone II with plus disease and stage 3 ROP but with less than the five contiguous or eight cumulative clock hours of stage 3 ROP required for diagnosis of threshold ROP [4].

Serial eye examinations were performed by board-certified consultant ophthalmologists according to a standard schedule suggested by the Italian Society of Neonatology. The first examination was made at 4–6 weeks of life but not later than the 29th week of post-conceptional age. When examination was normal the next controls were scheduled every 2 weeks until complete retinal vascularization; if the vascularization was limited to zone 1 or in case of stage 1 and 2 the next ROP controls were weekly; in case of more severe forms of ROP (stage ≥3 or plus diseases) the eye examinations were performed several times a week at the discretion of the ophthalmologist. Eye examination was performed through indirect ophthalmoscopy. The RetCam Imaging System II (Clarity Medical Systems, Pleasanton, CA, USA) was used to confirm diagnosis, monitor disease and treatment, evaluate retinal neovascularization, and fundus photography in any grade ROP.

Laser photocoagulation was performed under general anesthesia by a diode laser (Ophthalas 532 Eyelite® Laser System, Alcon, Irvine, CA, USA). The eyes were treated with a double line of confluent laser spots in avascular retina anterior and posterior to the ridge including vascular nets up to the clear retina. In case of intensive vascular activity around the avascular retina, laser treatment was directed also posterior to the ROP ridge on retinal ischemic areas surrounded by intensive vascular activity, because this finding is a feature of severe ROP [14]. After laser therapy, patients were examined by RetCam II and indirect video ophthalmoscopy at least the next day and weekly thereafter for 3 weeks. If there was any recurrence, insufficient regression with or without hyphema, or vitreous and retinal hemorrhage, IVB injection was planned.

Intravitreal bevacizumab was given in the Neonatal Intensive Care Unit: after pupil dilatation with 3 instillations of tropicamide drops, the eyelids were cleaned with povidone–iodine (5%) ophthalmic solution and draped. A lid speculum was placed, and the conjunctiva was prepared with three instillations of povidone–iodine (5%) ophthalmic solution. Approximately 0.025 mL (0.625 mg) of bevacizumab (Avastin®, Roche, Basel, Switzerland) were injected with a 30-gauge needle 1 mm posterior to the limbus in the inferior temporal quadrant. The injections were performed under sedation with ketamine (1 mg/kg i.v.). Indirect ophthalmoscopy was also performed after injection to ensure adequate blood flow. When necessary both eyes were treated during the same session. Local antibiotic drops were administered six times a day for 1 week postoperatively. Two infants received IVB as monotherapy because they were too sick to undergo lengthy laser treatment. After IVB each infant was examined by RetCam II every day during the first week and once a week during the first month to evaluate the progression of the disease and possible complications of injection.

Infants were followed up for at least 1 year with the assessment of anterior segment, fundus, ocular motility, and refraction and evaluation of neuro–psycho-motor development.

Treatment success was defined as the disappearance of tunica vasculosa lentis, disappearance or decrease in retinal vessel tortuosity and neovascularization, vascularization beyond the ridge to the periphery, and elimination of vitreous hemorrhage or hyphema. No second IVB was given to patients.

Results

We reviewed the medical charts of seven consecutive neonates who underwent treatment with IVB and whose main clinical characteristics are detailed in Table I. The mean gestational age and birth weight were 23.9 ± 0.7 weeks (range 23–25) and 680 ± 120 g (range 550–820), respectively. Laser therapy and IVB were performed at the mean post-conceptional age of 33.8 ± 1.3 weeks (range 32–36) and 33.5 ± 1.2 weeks (range 32–36), respectively.

Four patients were affected by APROP [six eyes; two monolateral (in two patients only one eye developed ROP)]: three eyes were treated with IVB, as monotherapy, and three were treated with IVB after laser treatment, as rescue therapy. Both first-line and rescue therapy IVB were followed by regression of the ROP and complete peripheral vascularization within 2 months of bevacizumab treatment.

Three patients were affected by pre-threshold ROP [five eyes; one monolateral (in one patient only one eye developed ROP)]: all eyes were treated with IVB after laser treatment, as rescue therapy. Intravitreal bevacizumab was always effective in promoting the regression of neovascularization and plus condition and was followed by complete peripheral vascularization within 1 months of bevacizumab treatment. However, one patient with a bilateral ROP had only partial resolution of vitreous hemorrhage in the left eye.

Table I. Clinical characteristics of patients with retinopathy of prematurity (ROP) who were treated with intravitreal bevacizumab (IVB).

Patient	GA (weeks)	BW (g)	Main pathologies	Sex	Indication	Stage	Zone	Treatment	Age at treatment (weeks)	Outcome of ROP
1	24	770	RDS	M	APROP	2	2	IVB	33	Regression, complete retinal vascularization
2	23	550	RDS, BPD, IVH	M	APROP	3	1	Laser + IVB	33	Regression, complete retinal vascularization
3	24	820	RDS, IVH	F	APROP	3	1	Laser + IVB	34	Regression, complete retinal vascularization
4	25	580	RDS, BPD	F	APROP	3	1	IVB	32	Regression, complete retinal vascularization
5	24	720	RDS, BPD	F	Pre-threshold	3	2	Laser + IVB	35	Regression, complete retinal vascularization
6	23	650	RDS	M	Pre-threshold	2 plus	2	Laser + IVB	32	Regression, complete retinal vascularization
7	24	690	RDS, PVL	F	Pre-threshold	3	2	Laser + IVB	34	Regression, complete retinal vascularization[a]

RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; GA, gestational age; BW, birth weight.
[a]This patient had only a partial resolution of vitreous haemorrhage in the left eye.

The procedures were well tolerated without local or systemic complications. No infants showed recurrence of intraocular hemorrhage and/or neovascularization. No cataract, retinal detachment, and endophthalmitis occurred in these patients, but two patients developed moderate myopia (one with previous APROP and one with previous pre-threshold ROP) and one patient (with previous APROP) developed moderate myopia plus strabismus.

Discussion

In this study, we found that IVB was successful in treating ROP in a small cohort of extremely preterm infants with APROP or pre-threshold ROP, both as first intention or rescue treatment after laser therapy. Moreover, all infants developed normal retinal vascularization without recurrence of the disease. This approach was safe without the development of short- or long-term adverse effects attributable to bevacizumab on visual and/or neuro–psycho-motor development in treated patients.

Our findings confirm the results of previous preliminary studies conducted in small series of patients which have evidenced good anatomical result in most cases [15–29], and are in agreement with Mintz-Hittner et al. who demonstrated in a randomized controlled study that IVB provides a significant benefit for stage 3+ROP in zone I in comparison to laser therapy and is followed by normal peripheral retinal vessel development [12].

With particular regard to the management of APROP, our cases show that IVB both as first line or rescue treatment is associated with regression of neovascularization and the following normal retinal vascularization. These results are in agreement with previous case series where is reported, that IVB is successful in the treatment of APROP both as mono therapy (10 overall patients) [15,21], and as combined therapy after laser photocoagulation (20 overall patients) [15–18,25]. However, IVB administered following laser therapy has been found to fail in one patient [25], and was followed by cataract in another [17]. Thus, although it is impossible to compare the effects of IVB monotherapy and its combination with laser therapy, due to lack of randomized controlled studies, the available data suggest that IVB as first-line could provide more benefit in infant with APROP than combined treatment. This later strategy could be negatively affected by the delay of IVB administration when it is given after laser failure and the inevitable retinal damage induced by photocoagulation.

This point is crucial because APROP is difficult to recognize and to treat, with many of these eyes quickly progressing to retinal detachment despite multiple treatments with laser or cryotherapy. These atypical features and its rapid worsening have spurred the quest for a less invasive and more effective approach to APROP, and we believe that monotherapy with antivascular endothelial growth factor agents goes in the right direction.

Recently, Sato et al. demonstrated that IVB administration in preterm infants with ROP is followed by bevacizumab escape from the eye into the systemic circulation and decrease in VEGF serum level [30]. Therefore, although no systemic adverse event has been reported after IVB in eyes with ROP, there are concerns about potential ocular and systemic adverse effects following IVB treatment especially in a growing infant in whom VEGF is required for normal vasculogenesis and organ development. However, in agreement with previous studies [15–29] we did not observe systemic adverse effects directly attributable to IVB in early or late follow-up, such as hypertension, cardiopulmonary distress, or renal insufficiency.

In conclusion, our series and the reports in the literature support the effectiveness of IVB, both as monotherapy and rescue therapy after laser photocoagulation, in the treatment of severe ROP and APROP. Randomized controlled studies are warranted to determine the optimal dose and timing of IVB, but we believe that they are mainly needed to evaluate the effectiveness of IVB monotherapy in the treatment of APROP due to its current poor outcome with laser or cryotherapy. However, it must be emphasized that the question of safety of IVB has not yet been definitively addressed and, although we did not find systemic or local toxic effects attributable to the administration of bevacizumab, careful follow-up of treated patients is necessary to exclude the development of long- term adverse effects.

Declaration of Interest: The authors declare that they did not receive any form of financial support in performing the present study and that they have not conflicts of interest.

References

1. Drack AV. Preventing blindness in premature infants. N Engl J Med 1998;338:1620–1621.
2. Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB, Tung B. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology 1991;98:1628–1640.
3. Hardy RJ, Good WV, Dobson V, Palmer EA, Phelps DL, Quintos M, Tung B; Early Treatment for Retinopathy of Prematurity Cooperative Group. Multicenter trial of early treatment for retinopathy of prematurity: study design. Control Clin Trials 2004;25:311–325.
4. Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Quintos M, Tung B; Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. Pediatrics 2005;116:15–23.
5. Dani C, Reali MF, Bertini G, Martelli E, Pezzati M, Rubaltelli FF. The role of blood transfusions and iron intake on retinopathy of prematurity. Early Hum Dev 2001;62:57–63.
6. Dani C, Martelli E, Bertini G, Pezzati M, Rossetti M, Buonocore G, Paffetti P, Rubaltelli FF. Effect of blood transfusions on oxidative stress in preterm infants. Arch Dis Child Fetal Neonatal Ed 2004;89:F408–F411.
7. Smith LE. Pathogenesis of retinopathy of prematurity. Growth Horm IGF Res 2004;14 Suppl A:S140–S144.
8. Repka MX, Tung B, Good WV, Shapiro M, Capone A Jr, Baker JD, Barr CC, et al. Outcome of eyes developing retinal detachment during the early treatment for retinopathy of prematurity study (ETROP). Arch Ophthalmol 2006;124:24–30.
9. Gilbert WS, Quinn GE, Dobson V, Reynolds J, Hardy RJ, Palmer EA. Partial retinal detachment at 3 months after threshold retinopathy of prematurity. Long-term structural and functional outcome. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Cooperative Group. Arch Ophthalmol 1996;114:1085–1091.
10. Wu WC, Drenser KA, Lai M, Capone A, Trese MT. Plasmin enzyme-assisted vitrectomy for primary and reoperated eyes with stage 5 retinopathy of prematurity. Retina (Philadelphia, Pa) 2008;28:S75–S80.
11. Chen J, Smith LE. Retinopathy of prematurity. Angiogenesis 2007;10:133–140.
12. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;364:603–615.
13. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;124:1669–1670.
14. Ng EY, Lanigan B, O'Keefe M. Fundus fluorescein angiography in the screening for and management of retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 2006;43:85–90.
15. Roohipoor R, Ghasemi H, Ghassemi F, Karkhaneh R, Riazi-Esfahani M, Nili-Ahmadabadi M. Intravitreal bevacizumab in retinopathy of prematurity: an interventional case series. Graefes Arch Clin Exp Ophthalmol 2011;249:1295–1301.

16. Travassos A, Teixeira S, Ferreira P, Regadas I, Travassos AS, Esperancinha FE, Prieto I, et al. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthalmic Surg Lasers Imaging 2007;38:233–237.
17. Shah PK, Narendran V, Tawansy KA, Raghuram A, Narendran K. Intravitreal bevacizumab (Avastin) for post laser anterior segment ischemia in aggressive posterior retinopathy of prematurity. Indian J Ophthalmol 2007;55:75–76.
18. 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;245:1727–1730.
19. Lalwani GA, Berrocal AM, Murray TG, Buch M, Cardone S, Hess D, Johnson RA, Puliafito CA. Off-label use of intravitreal bevacizumab (Avastin) for salvage treatment in progressive threshold retinopathy of prematurity. Retina (Philadelphia, Pa) 2008;28:S13–S18.
20. Quiroz-Mercado H, Martinez-Castellanos MA, Hernandez-Rojas ML, Salazar-Teran N, Chan RV. Antiangiogenic therapy with intravitreal bevacizumab for retinopathy of prematurity. Retina (Philadelphia, Pa) 2008;28:S19–S25.
21. 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 (Philadelphia, Pa) 2008;28:831–838.
22. 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;246:1061–1063.
23. Kusaka S, Shima C, Wada K, Arahori H, Shimojyo H, Sato T, Fujikado T. Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: a pilot study. Br J Ophthalmol 2008;92:1450–1455.
24. Law JC, Recchia FM, Morrison DG, Donahue SP, Estes RL. Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. J AAPOS 2010;14:6–10.
25. Altinsoy HI, Mutlu FM, Güngör R, Sarici SU. Combination of laser photocoagulation and intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthalmic Surg Lasers Imaging 2010;:1–:5.
26. Lee JY, Chae JB, Yang SJ, Yoon YH, Kim JG. Effects of intravitreal bevacizumab and laser in retinopathy of prematurity therapy on the development of peripheral retinal vessels. Graefes Arch Clin Exp Ophthalmol 2010;248:1257–1262.
27. Dorta P, Kychenthal A. Treatment of type 1 retinopathy of prematurity with intravitreal bevacizumab (Avastin). Retina (Philadelphia, Pa) 2010;30:S24–S31.
28. Kychenthal A, Dorta P. Vitrectomy after intravitreal bevacizumab (Avastin) for retinal detachment in retinopathy of prematurity. Retina (Philadelphia, Pa) 2010;30:S32–S36.
29. Harder BC, von Baltz S, Jonas JB, Schlichtenbrede FC. Intravitreal bevacizumab for retinopathy of prematurity. J Ocul Pharmacol Ther 2011;27:623–627.
30. Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahashi-Shima C, Kusaka S. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol 2012;153:327–333.