Intravitreal bevacizumab as single drug therapy for retinopathy of prematurity in 12 patients

Aldo Bancalari M., M.D.,[a] Ricardo Schade Y., M.D.,[b] Rubén Peña Z., M.D.,[c] Nicolás Pavez P., M.D.[d]

ABSTRACT

Ophthalmological outcomes in a series of children with retinopathy of prematurity (ROP) in the threshold stage treated with intravitreal bevacizumab are reported.

Twelve very low birth weight (VLBW) preterm infants who were administered intravitreal bevacizumab as monotherapy for retinopathy of prematurity in the threshold stage and in whom standard laser photocoagulation therapy was contraindicated were evaluated. Ophthalmological examinations were carried out and response to treatment, second interventions, and complications were evaluated.

The gestational age of these patients was 26.3 ± 1.8 weeks and their birth weight was 845 ± 153 g. A good response was observed in eight cases, while four patients required to be reintervened with laser photocoagulation. No immediate complications were detected and there were no deaths.

Key words: *retinopathy of prematurity, intravitreal injections, bevacizumab.*

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INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retinal vasculature. It is the main cause of blindness in children, both in developed and developing countries.[1] In a study conducted in Chile, it was shown that ROP was the main cause of childhood blindness.[2] The lower the birth weight and the gestational age, the higher the incidence of this disorder.[3]

ROP pathogenesis occurs in two phases; phase I is characterized by hyperoxia in the retinal artery and low circulating levels of the vascular endothelial growth factor (VEGF), followed by phase II in which there is hypoxia-induced vascular proliferation, and high VEGF levels.[4] The use of VEGF inhibitors, like the monoclonal antibody bevacizumab, has shown promising results in the treatment of retinopathy in the threshold stage.[5]

Bevacizumab has been approved by the US Food and Drug Administration (FDA) for the treatment of some types of cancer; but it has not been approved for the treatment of ROP yet.[6] Given its mechanism of action, this drug has been used as monotherapy for ROP in the threshold stage or as adjuvant therapy in addition to laser photocoagulation (LPC).[5,6]

It is worth mentioning that the standard treatment for ROP is LPC, which might give rise to complications such as burns to the cornea or iris, retinal bleeding and hyphema.[7] This has led to the search of new treatment options in selected cases.

OBJECTIVE

To present the ophthalmological results related to the administration of intravitreal bevacizumab in a series of preterm newborn infants with retinopathy in the threshold stage.

MATERIAL AND METHODS

From January 2008 to December 2012, medical records of very low birth weight (VLBW) preterm infants to whom bevacizumab (Avastin®) had been administered were analyzed. This drug was used for the treatment of ROP in the threshold stage and for not being able to use the standard LPC in the first place because of the following conditions: incomplete dilation because of rubeosis iridis, disease in the posterior segment of the eye, and contraindication to general anesthesia due to instability of the premature infant. In our site, the use of bevacizumab has been approved by the Ethics Committee in the above mentioned selected cases of ROP. A written informed consent was obtained from all newborn infants' parents before starting treatment and the indication, administration route and potential drug complications were explained to them.

The eye examination was started at 4 weeks after birth, by indirect ophthalmology technique,

a. Neonatology Unit, Department of Pediatrics.
b. Department of Ophthalmology.
Hospital Guillermo Grant Benavente, Concepción, Chile.
c. Resident of Pediatrics.
d. Resident of Internal Medicine.
School of Medicine, Universidad de Concepción.

E-mail Address:
Aldo Bancalari Molina, M.D.: aldobancalari@gmail.com

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and check-ups were performed once a week. ROP was classified as per the International Classification of Retinopathy.[8] Candidates for treatment were those infants whose retinopathy was on stage 3 plus (+) and on stage 2 plus when there was posterior zone I or II involvement.

Newborn infants (NBIs) sedation was done with phentanile and a topical anesthetic, proparacaine hydrochloride, was used for the eyeball. The dosage of 0.625 mg bevacizumab was injected through the *pars plana* at 2 mm from the limbus (*Figure 1*). After the procedure, antibiotic prophylaxis with eye drops (tobramycin/dexamethasone) every 3 hours for 3 days was administered. Serial eye check-ups were done the day after and then on a weekly basis until 3 months of age, and on a monthly basis until reaching the adjusted age of 1 year old. The drug was administered in the Neonatology Unit and the overall and neurologic follow-up was done as per the national care plan for newborn infants.

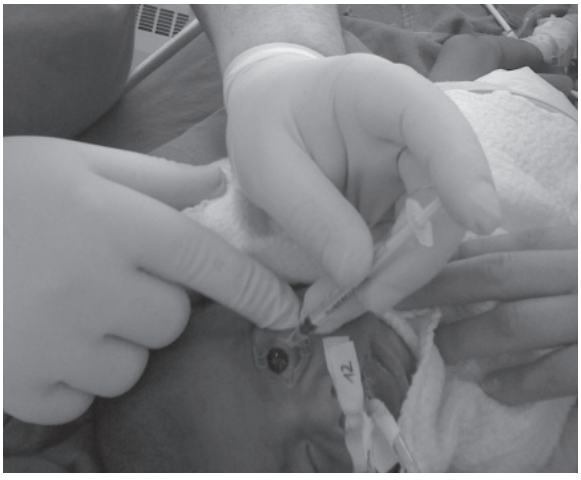
Response to treatment, complications related to treatment use, such as hyphema, endophthalmitis or retinal detachment, and the need to reintervene were evaluated in each patient.

Those patients whose condition worsened or who stayed on posterior stage 2+ or 3 after having administered intravitreal bevacizumab were considered candidates for reintervention with LPC.

RESULTS

Twelve VLBW infants with an average ± SD gestational age and birth weight of 26.3 ± 1.8 weeks and 845 ± 153 g, respectively, were treated. Average ± SD postnatal age at the time of bevacizumab administration was 7.8 ± 2.1 weeks. Sex distribution was similar. Individualized demographic data for each newborn infant are presented in *Table 1*. The earliest bevacizumab administration was at 4 weeks old, which corresponds to the heaviest NBI (1120 g), and the latest one was at 10 weeks old in the NBI whose birth weight was 680 g (patient 3).

FIGURE 1. *Intravitreal administration of bevacizumab in the Neonatology Unit*



At the time of administering bevacizumab, 8 of the 12 patients were on stage 3+ ROP *(Table 1)* and the remaining 4 were on stage 2+. One of the evaluated newborn infants developed retinal bleeding (patient 1). II was the most affected in 8 out of the 12 cases.

Of all newborn infants who were treated with bevacizumab, 4 required further treatment with LPC *(Table 1)*. Reinterventions were necessary because ROP progressed to stage 3, having previously documented a regression phase to stage 1. In the 8 remaining patients, progress was satisfactory and no further interventions were required.

When performing serial eye examinations, no complications like hyphema, endophthalmitis, retinal detachment nor cataracts were found. However, in the follow-up at one year, patient 10 *(Table 1)* showed vascular tortuosity with mild macular traction in the right eye. There were no deaths among studied children.

DISCUSSION

In our series, treatment with bevacizumab was started in 2008 with the purpose of treating patients diagnosed with ROP in the threshold stage who were not adequate to receive laser photocoagulation at the time it was indicated. It should be noted that the standard treatment for ROP in the threshold stage is LPC; however, the use of VEGF inhibitors, like bevacizumab, has shown promising results in selected cases.[9]

From a pathophysiological standpoint, retinopathy of prematurity is characterized by vascular proliferation promoted by high levels of VEGF; therefore, when using an inhibitor of this molecule, the aim is to conduct a treatment directed against the mechanism of disease production.[10] The intravitreal injection of bevacizumab is a less aggressive procedure on the retina since it prevents peripheral retinal destruction as the one that occurs with the use of laser.[11]

Recently, the first prospective multicenter randomized clinical trial was published in 150 patients, comparing the effectiveness of

TABLE 1. *Demographic characteristics and involvement of patients with retinopathy of prematurity treated with bevacizumab*

Patient	GA* (weeks)	Sex	Weight (g)	Stage	Zone	GA at the time of treatment (weeks)	Treatment	Reintervention
1	26	F	850	3+	2	36	Bevacizumab	
2	27	F	900	3+	2	35	Bevacizumab	Laser
3	26	M	680	3+	3	36	Bevacizumab	
4	25	F	1120	2+	2	29	Bevacizumab	
5	26	F	900	2+	2	34	Bevacizumab	Laser
6	25	M	720	3+	2	35	Bevacizumab	
7	31	F	1020	2+	1	36	Bevacizumab	
8	24	F	610	3+	2	32	Bevacizumab	Laser
9	26	M	980	2+	1	35	Bevacizumab	
10	27	M	890	3+	2	32	Bevacizumab	Laser
11	25	M	780	3+	2	36	Bevacizumab	
12	28	M	680	3+	2	35	Bevacizumab	

* GA: gestational age; g: grams.

bevacizumab versus laser photocoagulation therapy in stage 3+ ROP.[5] This clinical trial showed a 4% recurrence rate with bevacizumab as single drug therapy and a 22% in the group treated with LPC, a statistically significant difference.[5] In this study, the dose of bevacizumab was similar to the one used in our series (0.625 mg).

Very few complications have been reported regarding the use of bevacizumab. Some of these complications include hyphema, endophthalmitis, retinal detachment, or cataracts.[12] Such complications were not observed in our patients.

Given the angiogenic role of VEGF, that is necessary for developing new structures, among which are the central nervous system and pulmonary alveolar development,[13] it is important to conduct new studies with the follow-up of these patients to favor the use of intravitreal bevacizumab in ROP.

In spite of not having enough information to recommend its use, intravitreal bevacizumab treatment for ROP in the threshold stage could be better than LPC.[5,14] This therapy would be more specific according to the disease pathogenesis, with less visual field loss and the ease to use only local anesthesia.[15] However, it is necessary to perform mid- and long-term follow-up of patients treated with bevacizumab so as to evaluate possible local and systemic effects.

CONCLUSIONS

In our cases, none of the patients treated with intravitreal bevacizumab developed immediate ocular complications. A satisfactory response to monotherapy was observed in 8 out the 12 infants.■

REFERENCES

1. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev* 2008;84:77-82.
2. Gilbert C, Cánovas R, Kocksch R, Foster A. Ceguera infantil en Chile: estudio de escuelas de ciegos. *Arch Chil Oftalmol* 1993;50:49-53.
3. Bancalari A, González R, Vásquez C, Pradenas I. Retinopatía del prematuro: incidencia y factores asociados. *Rev Chil Pediatr* 2000;71:114-21.
4. Chen J, Smith LE. Retinopathy of prematurity. *Angiogenesis* 2007;10:133-40.
5. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011;364:603-15.
6. FDA. Avastin Approval History. U.S. Food and Drug Administration. [Access: 22 de mayo de 2013]. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf.
7. Clark D, Mandal K. Treatment of retinopathy of prematurity. *Early Human Devel* 2008;84:95-9.
8. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol* 2006;124:1669-70.
9. Micieli JA, Surkont M, Smith AF. A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity. *Am J Ophthalmol* 2009;148:536-43.

10. Travassos A, Teixeira S, Ferreira P, Regadas I, et al. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. *Ophthalmic Surg Lasers Imaging* 2007;38:233-7.
11. The Early Treatment of Retinopathy Cooperative Group. Final visual acuity results in the Early Treatment for Retinopathy of Prematurity Study. *Arch Ophthamo*l 2010;128(6):663-71.
12. Jamrozy-Witkowska A, Kowalska K, Jankowska-Lech I, Terelak-Borys B, et al. Complications of intravitreal injections--own experience. *Klin Oczna* 2011;113:127-31.
13. Thébaud B, Abman S. Bronchopulmonary dysplasia. Where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med* 2007;175:978-85.
14. Darlow BA, Gilbert C, Quinn GE, Azad R, et al. Promise and potencial pitfalls of anti VEGF drugs in Retinopathy of Prematurity. *Br J Ophthalmol* 2009;93(7):986.
15. Castellanos MA, Schwartz S, Leal R, Chan RV, et al. Pain assessment in premature infants treated with intravitreal antiangiogenic therapy for retinopathy of prematurity under topical anesthesia. *Graefes Arch Clin Exp Ophthalmol* 2013;251:491-4.