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

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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 therapy 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...
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 1, (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 (Ophthalmics 532 Eyelit® 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%) ophthamlic solution and draped. A lid speculum was placed, and the conjunctiva was prepared with three instillations of povidone–iodine (5%) ophthamlic 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).

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

RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; GA, gestational age; BW, birth weight.

*This patient had only a partial resolution of vitreous hemorrhage 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 it is reported, that IVB is successful in the treatment of APROP both as monotherapy (10 overall patients) [15,21], and as combined therapy after laser photoagulation (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 photoagulation.

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 photoagulation, 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


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