Intravitreal Bevacizumab for Zone II Retinopathy of Prematurity

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Abstract

PURPOSE:
To evaluate the treatment outcomes of intravitreal bevacizumab injections as monotherapy in type 1 retinopathy of prematurity (ROP).

METHODS:
A retrospective chart review was performed for patients with type 1 ROP who had intravitreal bevacizumab injections between November 2013 and January 2015 at La Paz University Hospital in Madrid, Spain. Gestational age at birth, birth weight, sex, ROP zone, ROP stage, mean age at treatment, and follow-up period were recorded. The final clinical status of the retina was noted for each patient. The primary outcome measures included ROP recurrences requiring re-treatment, complete or incomplete peripheral vascularization, mean age at complete vascularization, and refractive errors.

RESULTS:
From 14 patients enrolled with type 1 ROP, 28 eyes were included. The mean gestational age at birth was 25.9 ± 2.34 weeks (range: 23.6 to 32.4 weeks) and the median birth weight was 694 g (range: 487 to 1,740 g). All eyes showed zone II ROP: 18 eyes (64.3%) had anterior zone II ROP and 10 eyes (35.7%) had posterior zone II ROP. One week after intravitreal bevacizumab injection, 14 eyes (50%) had achieved complete regression of ROP, and a partial regression of ROP was observed in 10 eyes (35.7%). Twenty-two eyes (78.6%) obtained complete vascularization during the follow-up. The median time to complete vascularization was 134 ± 21.45 days. The mean spherical equivalent at last visit was 1.99 diopters.

CONCLUSIONS:
Intravitreal bevacizumab injection used as a monotherapy is an effective treatment approach in patients with zone II ROP.

Introduction

Retinopathy of prematurity (ROP) remains one of the leading causes of childhood blindness in the world, despite advances in treatment.\(^1\) ROP is a vasoproliferative retinopathy that involves premature infants' developing retinas, in which abnormal angiogenesis can lead to devastating consequences as a result of vitreal bleeding and tractional retinal detachment.\(^2\)

The pathophysiology is not well understood, but the dysregulation of vascular endothelial growth factor (VEGF) is thought to be one of the primary causative factors. VEGF production is triggered by the avascular part of the retina, and the accumulation of VEGF eventually leads to neovascularization and retinal detachment if not treated in time.\(^3\)

Anti-VEGF therapies such as bevacizumab are emerging as successful treatments for ROP.\(^4\)–\(^6\) Recently, the BevacizumabEliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study compared the effectiveness of intravitreal bevacizumab with the use of panretinal photocoagulation for treating stage 3+ retinopathy. The study demonstrated intravitreal bevacizumab's greater effectiveness compared with panretinal photocoagulation, showing fewer recurrences than with laser in zone I ROP, but was not significant for zone II ROP.\(^7\) Other authors have confirmed the effectiveness of intravitreal bevacizumab, although questions remain regarding safety and anatomic outcomes.

One of the reported benefits of intravitreal bevacizumab is that the development of peripheral retinal vessels continues after treatment, whereas conventional laser therapy would lead to permanent destruction of the peripheral retina.\(^7\) However, few reports have evaluated the terms of vascularization as an important goal of treatment.\(^8\),\(^9\)

The aims of this study were to analyze the effectiveness of intravitreal bevacizumab in zone II ROP in a tertiary center in Spain and to outline the timing of complete vascularization, if achieved, and the anatomical outcome.

Patients and Methods

We conducted a retrospective chart review of infants who underwent treatment for type 1 ROP with intravitreal bevacizumab injection (Avastin; Genentech Inc., San Francisco, CA). Included in the study were consecutive infants with type 1 ROP who received intravitreal bevacizumab injection between November 2013 and January 2015 at La Paz University Hospital in Madrid, Spain, and who had at least 3 months of follow-up.

Before obtaining informed consent from the parents, we emphasized that intravitreal bevacizumab injection was an experimental, off-label therapy with no long-term results as of yet. The diagnosis of ROP was based on the revisited guidelines of the International Committee for the Classification of Retinopathy of Prematurity (ICROP).\(^10\)
The injection procedure was planned in collaboration with the Department of Neonatology. The surgery was performed under light sedation with topical anesthesia, using oxybuprocaine hydrochloride/tetracaine hydrochloride eye drops (Colircusi Anestésico Doble; Alcon-Cusi, Barcelona, Spain). All of the infants were continuously monitored during and after the procedure.

The intravitreal bevacizumab injection was performed under sterile conditions using sterile gloves, drapes, and speculum after rigorous flushing of the conjunctival cul-de-sac with povidone-iodine 5%. The dosage of bevacizumab was 0.375 mg in 0.03 mL. At 1.5 mm posterior to the limbus in the nasal inferior quadrant, a 30-gauge needle was passed through the sclera in an oblique manner to minimize a reflux. After the injection, posterior pole revision using an indirect ophthalmoscope confirmed the absence of central artery occlusion to plan an anterior paracentesis if needed. Postoperatively, antibiotic drops (polymyxin/neomycin) were administered four times a day for 5 days. The surgical procedure was performed by two experienced surgeons (JP, PL-F). The postoperative follow-up was performed 1 week after the procedure and every 2 weeks thereafter until complete dissolution of the retinopathy was obtained or complete vascularization was achieved.

The collected data included gestational age (GA) at birth, birth weight, sex, ROP zone, ROP stage, mean age at treatment, and follow-up period. The clinical status of the retina at the last dilated fundus examination was noted for each patient, and the status was classified as attached with no dragging or macular ectopia, attached with macular ectopia, attached with dragging, detached stage 4, detached stage 5, or other. The primary outcome measures included ROP recurrences requiring re-treatment, peripheral vascularization (complete or incomplete), regular retinal examination 1 week after treatment, mean age at complete vascularization, and refractive errors. We defined recurrence as any of the following: recurrent plus disease, recurrent neovascularization, or progression of traction despite treatment. Complete vascularization was defined as vessels reaching into the temporal ora serrata at one visit or vessels in zone III in the two following examinations. RetCam (Clarity Medical Systems, Inc., Pleasanton, CA) images were obtained during each visit to record the findings.

The refractive error data included spherical power, spherical equivalent, and age at last examination. Cycloplegic refractions were performed after instilling one drop of a mixture of 0.5% cyclopentolate and 5% phenylephrine in both eyes three times every 10 minutes, then waiting 30 to 40 minutes for complete cycloplegia to be achieved.

Statistical analysis of the data was performed using SPSS for MacIntosh software (version 21.0; IBM Corp., Armonk, NY). For the purpose of this study, the two eyes of the same patient were used as independent variables. The data are presented as mean and standard deviation. Kaplan–Meier survival curves were used to determine the probability of complete
vascularization. The comparison between the variables for complete vascularization was made using the Mantel–Cox test. *P* values of less than .05 were considered to be statistically significant.

### Results

This was a retrospective, noncomparative case series of 14 patients (28 eyes) treated with intravitreal bevacizumab injection between November 2013 and January 2015 at La Paz University Hospital in Madrid, Spain (Table 1).

<table>
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<th>Case</th>
<th>Gender</th>
<th>GA (wk)</th>
<th>Weight (g)</th>
<th>Time to Treatment (wk)</th>
<th>GA at Treatment (wk)</th>
<th>Zone</th>
<th>Stage</th>
<th>Plus</th>
<th>Regression Pattern*</th>
<th>Vascularization Time (days)</th>
<th>Sphere (D) OD/DI*</th>
<th>SE (D) OD/DI*</th>
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*GA = gestational age; D = distance; OD = right eye; OS = left eye; SE = spherical equivalent; IIA = zone II anterior; EP = zone II posterior; Plus disease 1 = mild; 2 = moderate; 3 = severe; CR = complete regression; PR = partial regression.

*At last visit.

*See Table 1: Patient Data and Intravitreal Bevacizumab Injection Results.

The patients comprised 9 females and 5 males. The mean GA at birth was 25.9 ± 2.34 weeks (range: 23.6 to 32.4 weeks) and the median birth weight was 694 g (range: 487 to 1,740 g).

All eyes showed zone II ROP: 18 eyes (64.3%) had anterior zone II ROP and 10 eyes (35.7%) had posterior zone II ROP. Of all eyes, 21 (75%) presented ROP grade 2, and 7 (25%) presented ROP stage 3; 12 eyes (42.8%) had mild plus disease, whereas 16 (57.1%) had moderate to severe plus disease. The mean GA was 35.1 ± 1.94 weeks (range: 32.85 to 39.7 weeks).

One week after intravitreal bevacizumab injection, 14 eyes (50%) had achieved complete regression of ROP, and a partial regression of ROP was observed in 10 eyes (35.7%) (Figure 1). In 2 patients (*n* = 4), the regression pattern at the first week was not registered. All 28 eyes were treated successfully with intravitreal bevacizumab as monotherapy. No patients developed recurrent disease. All of the cases had attached retinas with no macular dragging.
In this series, 22 eyes achieved complete vascularization (78.6%) during the follow-up (Figure 2), with a mean time to complete vascularization of 144 ± 51 (−3 to +6.75) days. The median time to complete vascularization was 134 ± 21.45 days (Kaplan–Meier).

There was a trend toward a shorter time to full vascularization in the cases with complete regression during the first week compared with the cases of partial regression (164 vs 155.25 days, respectively) but it was not statistically significant (Mantel–Cox, \( P = .60 \)). We found no differences in the time to vascularization depending on the zone or the grade of ROP.

The mean GA at the last visit was 74.62 weeks (range: 43.43 to 108.57 weeks) and the mean follow-up time was 39.53 weeks (range: 9 to 73.14 weeks). The refraction measures were available for 15 of 17 patients. The mean spherical equivalent was 1.8 ± 2.3 (range: 71 to 231 days) diopters (D) at the last visit.
The neonatology team closely monitored each patient's vital signs immediately after the injection, and there were no reports of changes unrelated to the patients' preexisting complicated systemic conditions. There were no other ocular complications such as endophthalmitis, cataract, or ocular inflammation. Subsequent follow-up visits beyond the first 4 weeks after the injection revealed no unexpected untoward events such as cardiopulmonary distress, stroke, or renal insufficiency, as reported by the neonatologist. However, 1 patient died of complications from a previous respiratory condition 9 weeks after the procedure.

**Discussion**

In the current study, we found that intravitreal bevacizumab is an effective treatment for type 1 ROP in zone II, without any recurrence and with a rate of complete vascularization of 78.6% during a mean follow-up of 39.53 weeks. This is the first report of intravitreal bevacizumab injection for ROP in Spain. In this series, our infants were more mature and had greater weight compared with infants in previous studies. The infants also had less severe ROP, without ROP in zone I.

In addition, it appears that a regression pattern 1 week after the treatment could be a good indicator of the time required to complete vascularization. These data would be valuable to program an adequate scheduled revision in patients. However, the results did not reach significance.

To date, many studies have been published regarding the good results of intravitreal bevacizumab for ROP; however, concerns remain about the development of the immature retina of these eyes.

The BEAT-ROP study showed a 100% rate of complete vascularization at the endpoint of 19.5 weeks of follow-up at 54 weeks' GA. However, other authors have observed complete vascularization in 90% of patients at 37.8 weeks of follow-up. Sahin et al. was the first group to study the length of time to vascularization. They found a 100% vascularization rate with a mean full retinal vascularization time of 136.6 ± 26.6 days. In our series, we observed a 76% rate of full vascularization at a mean endpoint of 39.53 weeks. The median time to vascularization was 134 ± 21.45 days. This result concurs with that of Sahin et al. regarding the mean time to full vascularization, although during the follow-up time we had 3 cases who had not achieved complete vascularization. This fact could be explained by the shorter follow-up of 2 patients and the early death of another (9 weeks).

Another important concern is the actual retinal vascularization status. In the report by Tahija et al., fluorescein angiography was performed to accurately visualize the extent of peripheral retinal vessel growth in the eyes treated with intravitreal bevacizumab injection. They found an incomplete vascularization rate in 55% of the eyes in 259 weeks of follow-up. Based on this outcome, we might be overestimating the rate of complete vascularization; therefore,
more angiographic evidence is required. According to the available data to date, we find that the BEAT-ROP postmenstrual age of 54 weeks is a short time to achieve complete vascularization in 100% of patients.

To our knowledge, most of the intravitreal bevacizumab treatments for ROP studies have used the BEAT-ROP criteria for ROP treatment (patient with ROP in zone I and III plus disease in posterior zone II). In contrast, the Early Treatment for Retinopathy of Prematurity (ETROP) study group emphasized the treatment of all type 1 ROP (zone I any grade with plus disease; zone II grade 2 or 3 with plus disease).18

In this study, we performed intravitreal bevacizumab injection in stage 2 and 3 in cases of anterior and posterior zone II ROP in which disease progression was observed, following ETROP criteria. Eight patients (16 eyes) were successfully treated with intravitreal bevacizumab in anterior zone II.

Despite most ROP data coming from highly developed countries, the increasing problem of ROP in middle-income countries (called the “third epidemic of ROP”) has been well documented.19,20 In these countries, infants with ROP are typically larger and more mature than those from highly developed countries and do not have ROP in zone I; therefore, the indications from clinical trials such as the BEAT-ROP might not extrapolate to these areas. Furthermore, although this disease is potentially preventable with current knowledge, the health systems of developing countries, including ophthalmologists who are well trained to examine infants at risk and to treat them with laser therapy, are not often available to deliver the high level of neonatal care required. Due to the available data and the excellent outcomes in the current study, and if we also consider bevacizumab as an inexpensive, readily available, and easy-to-administer drug, we propose that intravitreal bevacizumab injection would be a reasonable option to treat ROP in our country and in middle-income countries, even if BEAT-ROP criteria are not met.

In our study, the refractive outcome at last visit was a mean sphere of 2.46 D and a mean spherical equivalent of 1.99 D. New reports on the refractive outcome of intravitreal bevacizumab are currently being published. The BEAT-ROP study showed a mean spherical equivalent of −1.51 D for zone I ROP treated with intravitreal bevacizumab and −0.58 D for zone II ROP after intravitreal bevacizumab. This was considerably less compared with conventional laser treatment (−8.44 D for zone I and −5.83 D for zone II).21 Recent reports have shown a mean spherical equivalent at a 2-year end point of −0.98 D.22 Our follow-up time is too short to compare with this series, but in one study by Harder et al. with a follow-up time of 0.88 years, they obtained a mean spherical equivalent of 1.04 D.14 Our patients at their last visit had a follow-up time of 43 weeks (0.81 years), and presented a mean spherical equivalent of 1.99 D, which is slightly more hypermetropic than in the series by Harder et al.
The nature of premature myopia has been studied; nevertheless, its exact mechanism is not well understood. In the recent BEAT-ROP study, the authors suggest the possibility that based on their results, treatment with laser panretinal photocoagulation is more important in the genesis of myopia than the severity of ROP alone.\textsuperscript{21}

Although our study was not powered to evaluate safety, we did not find any effect attributable to the intravitreal bevacizumab. In a necropsy study, the histopathological analysis did not reveal any local inflammation, retinal degeneration, or necrosis after the use of intravitreal bevacizumab.\textsuperscript{23} Nevertheless, VEGF is a ubiquitous molecule implicated in the development of the brain, lungs, and kidneys; therefore, the safety data sought should include specific ocular, neurological, pulmonary, renal, and bone complications.\textsuperscript{24} Recent studies have shown that systemic VEGF levels remain inhibited for 8 weeks after intravitreal bevacizumab injection.\textsuperscript{25} Therefore, it is mandatory to establish that the treatment is safe and well tolerated.

This study has several limitations. First, it was a retrospective study and non-comparative. Moreover, the follow-up period was short and variable. Second, the sample size was small, limiting the power of the findings. Finally, at the time of this study, we did not routinely perform fluorescein angiography.

Intravitreal bevacizumab injection might be a reasonably effective and safe treatment option for zone II ROP. There might be a relationship between the time of full retinal vascularization achieved and retinal regression pattern 1 week after treatment.

References


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The authors have no financial or proprietary interest in the materials presented herein.

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METHODS:
A retrospective chart review was performed for patients with type 1 ROP who had intravitreal bevacizumab injections between November 2013 and January 2015 at La Paz University Hospital in Madrid, Spain. Gestational age at birth, birth weight, sex, ROP zone, ROP stage, mean age at treatment, and follow-up period were recorded. The final clinical status of the retina was noted for each patient. The primary outcome measures included ROP recurrences requiring re-treatment, complete or incomplete peripheral vascularization, mean age at complete vascularization, and refractive errors.

RESULTS:
From 14 patients enrolled with type 1 ROP, 28 eyes were included. The mean gestational age at birth was 25.9 ± 2.34 weeks (range: 23.6 to 32.4 weeks) and the median birth weight was 694 g (range: 487 to 1,740 g). All eyes showed zone II ROP: 18 eyes (64.3%) had anterior zone II ROP and 10 eyes (35.7%) had posterior zone II ROP. One week after intravitreal bevacizumab injection, 14 eyes (50%) had achieved complete regression of ROP, and a partial regression of ROP was observed in 10 eyes (35.7%). Twenty-two eyes (78.6%) obtained complete vascularization during the follow-up. The median time to complete vascularization was 134 ± 21.45 days. The mean spherical equivalent at last visit was 1.99 diopters.

CONCLUSIONS:
Intravitreal bevacizumab injection used as a monotherapy is an effective treatment approach in patients with zone II ROP.


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Introduction

Retinopathy of prematurity (ROP) remains one of the leading causes of childhood blindness in the world, despite advances in treatment.\(^1\) ROP is a vasoproliferative retinopathy that involves premature infants' developing retinas, in which abnormal angiogenesis can lead to devastating consequences as a result of vitreal bleeding and tractional retinal detachment.\(^2\)

The pathophysiology is not well understood, but the dysregulation of vascular endothelial growth factor (VEGF) is thought to be one of the primary causative factors. VEGF production is triggered by the avascular part of the retina, and the accumulation of VEGF eventually leads to neovascularization and retinal detachment if not treated in time.\(^3\)

Anti-VEGF therapies such as bevacizumab are emerging as successful treatments for ROP.\(^4\)–\(^6\) Recently, the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study compared the effectiveness of intravitreal bevacizumab with the use of panretinal photocoagulation for treating stage 3+ retinopathy. The study demonstrated intravitreal bevacizumab's greater effectiveness compared with panretinal photocoagulation, showing fewer recurrences than with laser in zone I ROP, but was not significant for zone II ROP.\(^7\) Other authors have confirmed the effectiveness of intravitreal bevacizumab, although questions remain regarding safety and anatomic outcomes.

One of the reported benefits of intravitreal bevacizumab is that the development of peripheral retinal vessels continues after treatment, whereas conventional laser therapy would lead to permanent destruction of the peripheral retina.\(^7\) However, few reports have evaluated the terms of vascularization as an important goal of treatment.\(^8\)–\(^9\)

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We conducted a retrospective chart review of infants who underwent treatment for type 1 ROP with intravitreal bevacizumab injection (Avastin; Genentech Inc., San Francisco, CA). Included in the study were consecutive infants with type 1 ROP who received intravitreal bevacizumab injection between November 2013 and January 2015 at La Paz University Hospital in Madrid, Spain, and who had at least 3 months of follow-up.
Before obtaining informed consent from the parents, we emphasized that intravitreal bevacizumab injection was an experimental, off-label therapy with no long-term results as of yet. The diagnosis of ROP was based on the revisited guidelines of the International Committee for the Classification of Retinopathy of Prematurity (ICROP).10

The injection procedure was planned in collaboration with the Department of Neonatology. The surgery was performed under light sedation with topical anesthesia, using oxybuprocaine hydrochloride/tetracaine hydrochloride eye drops (Colircusi Anestésico Doble; Alcon-Cusi, Barcelona, Spain). All of the infants were continuously monitored during and after the procedure.

The intravitreal bevacizumab injection was performed under sterile conditions using sterile gloves, drapes, and speculum after rigorous flushing of the conjunctival cul-de-sac with povidone-iodine 5%. The dosage of bevacizumab was 0.375 mg in 0.03 mL. At 1.5 mm posterior to the limbus in the nasal inferior quadrant, a 30-gauge needle was passed through the sclera in an oblique manner to minimize a reflux. After the injection, posterior pole revision using an indirect ophthalmoscope confirmed the absence of central artery occlusion to plan an anterior paracentesis if needed. Postoperatively, antibiotic drops (polymyxin/neomycin) were administered four times a day for 5 days. The surgical procedure was performed by two experienced surgeons (JP, PL-F). The postoperative follow-up was performed 1 week after the procedure and every 2 weeks thereafter until complete dissolution of the retinopathy was obtained or complete vascularization was achieved.

The collected data included gestational age (GA) at birth, birth weight, sex, ROP zone, ROP stage, mean age at treatment, and follow-up period. The clinical status of the retina at the last dilated fundus examination was noted for each patient, and the status was classified as attached with no dragging or macular ectopia, attached with macular ectopia, attached with dragging, detached stage 4, detached stage 5, or other. The primary outcome measures included ROP recurrences requiring re-treatment, peripheral vascularization (complete or incomplete), regular retinal examination 1 week after treatment, mean age at complete vascularization, and refractive errors. We defined recurrence as any of the following: recurrent plus disease, recurrent neovascularization, or progression of traction despite treatment. Complete vascularization was defined as vessels reaching into the temporal ora serrata at one visit or vessels in zone III in the two following examinations. RetCam (Clarity Medical Systems, Inc., Pleasanton, CA) images were obtained during each visit to record the findings.

The refractive error data included spherical power, spherical equivalent, and age at last examination. Cycloplegic refractions were performed after instilling one drop of a mixture of 0.5% cyclopentolate and 5% phenylephrine in both eyes three times every 10 minutes, then waiting 30 to 40 minutes for complete cycloplegia to be achieved.
Statistical analysis of the data was performed using SPSS for MacIntosh software (version 21.0; IBM Corp., Armonk, NY). For the purpose of this study, the two eyes of the same patient were used as independent variables. The data are presented as mean and standard deviation. Kaplan–Meier survival curves were used to determine the probability of complete vascularization. The comparison between the variables for complete vascularization was made using the Mantel–Cox test. \( P \) values of less than .05 were considered to be statistically significant.

**Results**

This was a retrospective, noncomparative case series of 14 patients (28 eyes) treated with intravitreal bevacizumab injection between November 2013 and January 2015 at La Paz University Hospital in Madrid, Spain (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Patient Data and Intravitreal Bevacizumab Injection Results</th>
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GA = gestational age; OD = right eye; OS = left eye; SE = spherical equivalent; EA = zone I anterior; RP = zone I posterior; Plus disease 1 = mild; 2 = moderate; 3 = severe; CR = complete regression; RI = partial regression.
1 week after treatment.
*No last visit.

The patients comprised 9 females and 5 males. The mean GA at birth was 25.9 ± 2.34 weeks (range: 23.6 to 32.4 weeks) and the median birth weight was 694 g (range: 487 to 1,740 g).

All eyes showed zone II ROP: 18 eyes (64.3%) had anterior zone II ROP and 10 eyes (35.7%) had posterior zone II ROP. Of all eyes, 21 (75%) presented ROP grade 2, and 7 (25%) presented ROP stage 3; 12 eyes (42.8%) had mild plus disease, whereas 16 (57.1%) had moderate to severe plus disease. The mean GA was 35.1 ± 1.94 weeks (range: 32.85 to 39.7 weeks).

http://www.healio.com/ophthalmology/journals/jpos/2016-11-53-6%7B08e247d7-8eb2-41f1-ac5f-80cb56b0e317%7D/intravitreal-bevacizumab-for-zone-II...
One week after intravitreal bevacizumab injection, 14 eyes (50%) had achieved complete regression of ROP, and a partial regression of ROP was observed in 10 eyes (35.7%) (Figure 1). In 2 patients (n = 4), the regression pattern at the first week was not registered. All 28 eyes were treated successfully with intravitreal bevacizumab as monotherapy. No patients developed recurrent disease. All of the cases had attached retinas with no macular dragging.

In this series, 22 eyes achieved complete vascularization (78.6%) during the follow-up (Figure 2), with a mean time to complete vascularization of 144 ± 51 (−3 to +6.75) days. The median time to complete vascularization was 134 ± 21.45 days (Kaplan–Meier).

There was a trend toward a shorter time to full vascularization in the cases with complete regression during the first week compared with the cases of partial regression (164 vs 155.25 days, respectively) but it was not statistically significant (Mantel–Cox, \( P = .60 \)).
We found no differences in the time to vascularization depending on the zone or the grade of ROP.

The mean GA at the last visit was 74.62 weeks (range: 43.43 to 108.57 weeks) and the mean follow-up time was 39.53 weeks (range: 9 to 73.14 weeks). The refraction measures were available for 15 of 17 patients. The mean spherical equivalent was $1.8 \pm 2.3$ (range: 71 to 231 days) diopters (D) at the last visit.

The neonatology team closely monitored each patient's vital signs immediately after the injection, and there were no reports of changes unrelated to the patients' preexisting complicated systemic conditions. There were no other ocular complications such as endophthalmitis, cataract, or ocular inflammation. Subsequent follow-up visits beyond the first 4 weeks after the injection revealed no unexpected untoward events such as cardiopulmonary distress, stroke, or renal insufficiency, as reported by the neonatologist. However, 1 patient died of complications from a previous respiratory condition 9 weeks after the procedure.

**Discussion**

In the current study, we found that intravitreal bevacizumab is an effective treatment for type 1 ROP in zone II, without any recurrence and with a rate of complete vascularization of 78.6% during a mean follow-up of 39.53 weeks. This is the first report of intravitreal bevacizumab injection for ROP in Spain. In this series, our infants were more mature and had greater weight compared with infants in previous studies. The infants also had less severe ROP, without ROP in zone I.

In addition, it appears that a regression pattern 1 week after the treatment could be a good indicator of the time required to complete vascularization. These data would be valuable to program an adequate scheduled revision in patients. However, the results did not reach significance.

To date, many studies have been published regarding the good results of intravitreal bevacizumab for ROP; however, concerns remain about the development of the immature retina of these eyes.

The BEAT-ROP study showed a 100% rate of complete vascularization at the endpoint of 19.5 weeks of follow-up at 54 weeks' GA. However, other authors have observed complete vascularization in 90% of patients at 37.8 weeks of follow-up. Sahin et al. was the first group to study the length of time to vascularization. They found a 100% vascularization rate with a mean full retinal vascularization time of $136.6 \pm 26.6$ days. In our series, we observed a 76% rate of full vascularization at a mean endpoint of 39.53 weeks. The median time to vascularization was $134 \pm 21.45$ days. This result concurs with that of Sahin et al. regarding the mean time to full vascularization, although during
the follow-up time we had 3 cases who had not achieved complete vascularization. This fact could be explained by the shorter follow-up of 2 patients and the early death of another (9 weeks).

Another important concern is the actual retinal vascularization status. In the report by Tahija et al.,\(^9\) fluorescein angiography was performed to accurately visualize the extent of peripheral retinal vessel growth in the eyes treated with intravitreal bevacizumab injection. They found an incomplete vascularization rate in 55% of the eyes in 259 weeks of follow-up. Based on this outcome, we might be overestimating the rate of complete vascularization; therefore, more angiographic evidence is required. According to the available data to date, we find that the BEAT-ROP postmenstrual age of 54 weeks is a short time to achieve complete vascularization in 100% of patients.

To our knowledge, most of the intravitreal bevacizumab treatments for ROP studies have used the BEAT-ROP criteria for ROP treatment (patient with ROP in zone I and III plus disease in posterior zone II). In contrast, the Early Treatment for Retinopathy of Prematurity (ETROP) study group emphasized the treatment of all type I ROP (zone I any grade with plus disease; zone II grade 2 or 3 with plus disease).\(^{18}\)

In this study, we performed intravitreal bevacizumab injection in stage 2 and 3 in cases of anterior and posterior zone II ROP in which disease progression was observed, following ETROP criteria. Eight patients (16 eyes) were successfully treated with intravitreal bevacizumab in anterior zone II.

Despite most ROP data coming from highly developed countries, the increasing problem of ROP in middle-income countries (called the “third epidemic of ROP”) has been well documented.\(^{19,20}\) In these countries, infants with ROP are typically larger and more mature than those from highly developed countries and do not have ROP in zone I; therefore, the indications from clinical trials such as the BEAT-ROP might not extrapolate to these areas. Furthermore, although this disease is potentially preventable with current knowledge, the health systems of developing countries, including ophthalmologists who are well trained to examine infants at risk and to treat them with laser therapy, are not often available to deliver the high level of neonatal care required. Due to the available data and the excellent outcomes in the current study, and if we also consider bevacizumab as an inexpensive, readily available, and easy-to-administer drug, we propose that intravitreal bevacizumab injection would be a reasonable option to treat ROP in our country and in middle-income countries, even if BEAT-ROP criteria are not met.

In our study, the refractive outcome at last visit was a mean sphere of 2.46 D and a mean spherical equivalent of 1.99 D. New reports on the refractive outcome of intravitreal bevacizumab are currently being published. The BEAT-ROP study showed a mean spherical equivalent of −1.51 D for zone I ROP treated with intravitreal bevacizumab and
−0.58 D for zone II ROP after intravitreal bevacizumab. This was considerably less compared with conventional laser treatment (−8.44 D for zone I and −5.83 D for zone II).21 Recent reports have shown a mean spherical equivalent at a 2-year end point of −0.98 D.22 Our follow-up time is too short to compare with this series, but in one study by Harder et al. with a follow-up time of 0.88 years, they obtained a mean spherical equivalent of 1.04 D.14 Our patients at their last visit had a follow-up time of 43 weeks (0.81 years), and presented a mean spherical equivalent of 1.99 D, which is slightly more hypermetropic than in the series by Harder et al.

The nature of premature myopia has been studied; nevertheless, its exact mechanism is not well understood. In the recent BEAT-ROP study, the authors suggest the possibility that based on their results, treatment with laser panretinal photocoagulation is more important in the genesis of myopia than the severity of ROP alone.21

Although our study was not powered to evaluate safety, we did not find any effect attributable to the intravitreal bevacizumab. In a necropsy study, the histopathological analysis did not reveal any local inflammation, retinal degeneration, or necrosis after the use of intravitreal bevacizumab.23 Nevertheless, VEGF is a ubiquitous molecule implicated in the development of the brain, lungs, and kidneys; therefore, the safety data sought should include specific ocular, neurological, pulmonary, renal, and bone complications.24 Recent studies have shown that systemic VEGF levels remain inhibited for 8 weeks after intravitreal bevacizumab injection.25 Therefore, it is mandatory to establish that the treatment is safe and well tolerated.

This study has several limitations. First, it was a retrospective study and non-comparative. Moreover, the follow-up period was short and variable. Second, the sample size was small, limiting the power of the findings. Finally, at the time of this study, we did not routinely perform fluorescein angiography.

Intravitreal bevacizumab injection might be a reasonably effective and safe treatment option for zone II ROP. There might be a relationship between the time of full retinal vascularization achieved and retinal regression pattern 1 week after treatment.

References


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The authors have no financial or proprietary interest in the materials presented herein.

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