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Intravitreal bevacizumab for retinopathy of prematurity in infants ineligible for laser therapy*

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Background/aim: To evaluate refractive and strabismic results and the efficacy of intravitreal bevacizumab in retinopathy of prematurity (ROP) ineligible for laser therapy.

Materials and methods: Thirty-nine eyes of 20 consecutive infants with high-risk prethreshold ROP (11 infants with Zone I and 9 infants with Zone II disease) who were ineligible for laser therapy due to systemic and/or ocular conditions were treated with intravitreal bevacizumab. Recurrent retinopathy was treated with laser ablation. The final follow-up examination was performed at 29.8 ± 6.0 months of corrected age.

Results: All eyes responded to the initial treatment with intravitreal bevacizumab. ROP recurred in 8 eyes (36%) with initial Zone I disease and in only 2 eyes (11%) with initial Zone II disease, which were successfully treated with laser ablation. No eye developed myopia higher than 5.0 diopters. At 2.5 years, the Zone I eyes that had received laser treatment appeared to be more myopic than the Zone I eyes treated only with intravitreal bevacizumab (P = 0.038). A tendency for a higher incidence of strabismus after additional laser therapy was also noted, but was not significant (P = 0.22).

Conclusion: Avoidance or even deferral of laser ablation with intravitreal bevacizumab may lead to less myopization in ROP compared with conventional laser treatment.

Key words: Bevacizumab, myopia, retinopathy of prematurity, strabismus, vascular endothelial growth factor.

1. Introduction

Retinopathy of prematurity (ROP) is a neovascular retinal disorder in premature infants that can lead to devastating vision complications. The role of vascular endothelial growth factor (VEGF) in the pathogenesis and progression of ROP has been well documented (1,2). The beneficial effects of intravitreal anti-VEGF agents in ROP management have been shown in previous studies (3–14). In a randomized and controlled multicenter study of stage 3 ROP with plus disease, intravitreal bevacizumab therapy appeared to excel conventional laser therapy for Zone I disease, and had comparable results with laser therapy for Zone II disease (8).

The major significant disadvantage of intraocular anti-VEGF therapy is the possibility of long-term systemic side effects in infants; even randomized trials do not have adequate power to provide an evidence-based answer to this concern. On the other hand, a major advantage of anti-VEGF agents over conventional laser is the avoidance of permanent destruction of the peripheral retina. It provides a chance for vascularization and salvaging the peripheral retina and the visual field. The prevalence of high myopia and strabismus was reported to be higher in premature infants who develop ROP and was correlated with ROP severity (15,16). A recent clinical trial has shown less myopization following intravitreal anti-VEGF treatment compared with laser treatment for ROP (17). In the present study, we aimed to report the results of intravitreal bevacizumab specifically in premature infants ineligible for laser therapy, with particular emphasis on refractive and strabismic outcomes. To the best of our knowledge, strabismic results after intravitreal anti-VEGF treatment in ROP have not been reported before.

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2. Materials and methods

The study protocol was approved by the Institutional Ethics Board. Consecutive premature infants with high-risk prethreshold (type 1) ROP (18) who were ineligible for conventional laser therapy in two major centers were enrolled and treated with intravitreal injection of bevacizumab (Avastin; Genentech Inc, San Francisco, CA, USA). These infants were either systemically too sick to receive general anesthesia for laser treatment or unable to undergo laser treatment due to ocular conditions such as corneal edema, a miotic pupil, or hazy media.

The revised guidelines set forth by the International Classification for Retinopathy of Prematurity were used to classify ROP (19). The criterion for enrollment and treatment was the presence of high-risk prethreshold (type 1) ROP, including stage 3 retinopathy and/or plus disease in Zone I or stage 2 or 3 retinopathy with plus disease in Zone II (18). The investigational nature of the treatment and off-label use of bevacizumab were clearly explained. In addition, written informed consent was obtained from the parents of all infants in the study.

Intravitreal injection of bevacizumab was performed under sterile conditions in the operating room, unless the general health status of the baby precluded transfer to the operating room. In such cases, treatment was carried out in the newborn intensive care unit. All treatments were performed 1 day after the diagnosis of high-risk prethreshold disease. After topical anesthesia, a drop of 5% povidone-iodine was placed into the conjunctival sac. Following treatment of the eyelids with 10% povidone-iodine, a pediatric lid speculum was inserted. The eye was stabilized with a cotton tip applicator, following which 0.5–0.625 mg of bevacizumab (0.02–0.025 mL) was injected intravitreally with a 30-gauge needle 0.5 to 1 mm posterior to limbus in the superior temporal quadrant. Following the injection, a drop of antibiotic (0.3% moxifloxacin) was applied and continued 4 times daily for 3 days.

Each eye was examined daily after treatment until regression of neovascularization and plus disease was determined. Thereafter, eyes with Zone I and II disease were examined weekly and fortnightly, respectively, until complete vascularization was achieved or a decision for further treatment with laser was made. No eye received more than one injection. Recurrent cases of ROP were treated with near confluent laser ablation.

Follow-up visits included cycloplegic retinoscopy and evaluation of visual alignment, anterior segment, and retina. Cycloplegic retinoscopy was conducted approximately 30 min after two drops of 1% cyclopentolate hydrochloride were administered 10 min apart. Mean spherical equivalent refraction was compared using the Mann–Whitney U test and the proportion of cases with strabismus was compared using Fisher's exact test.

3. Results

The study involved 40 eyes of 20 infants (9 girls and 11 boys) with a mean birth weight of 809.2 ± 189.0 g (with a range of 570–1300 g) and a mean gestational birth age of 25.9 ± 1.7 weeks (with a range of 23–29 weeks). Twenty-two eyes of 11 infants presented with Zone I disease at 33.6 ± 1.5 weeks and 18 eyes of 9 infants presented with Zone II retinopathy at 34.6 ± 2.3 weeks (Table). All eyes had plus disease. Following intravitreal bevacizumab injection, the plus disease disappeared in 1 to 3 days and disease stage regression was documented at 1 or 2 weeks. No intravitreal bevacizumab injection was performed to the second eye of 1 infant with Zone I disease as retinopathy in this eye regressed after injection to the first eye. This eye was excluded from the study.

No injury to the lens or retina, retinal detachment, vitreous hemorrhage, or intraocular inflammation occurred following the injection. Five infants, all except one with initial Zone I disease, experienced ROP recurrence, requiring treatment in Zone II at 49.9 ± 7.9 weeks. The general health and ophthalmological status of these infants had improved and permitted laser treatment. Following laser treatment of these 10 eyes, no other complication occurred and disease regression was documented in these eyes. The final follow-up examination was performed at 29.8 ± 6.0 months of corrected age (with a range of 12–37 months).

No eye developed myopia higher than 5.0 D. Zone I and II eyes that had received only intravitreal bevacizumab treatment did not show any difference in terms of refractive error during the final visit ($P = 0.29$). Zone I eyes that had received the additional laser treatment appeared to be more myopic than Zone I eyes treated with only intravitreal bevacizumab ($P = 0.037$) (Table).

A lower proportion of the cases that received only intravitreal bevacizumab (2 of 15 cases: 13%) developed strabismus compared with the cases that received the additional laser treatments (2 of 5 cases: 40%). However, the difference was not significant ($P = 0.22$). The difference of the proportion of strabismus in cases with Zone I versus Zone II disease was also insignificant (3 cases (27%) versus 1 case (11%), respectively, $P = 0.31$). In addition, more cases with Zone I disease had additional systemic pathologies that can be related to strabismus (Table).

4. Discussion

In infants with high-risk prethreshold ROP ineligible for laser treatment intravitreal bevacizumab appeared to be effective for both Zone I and Zone II disease. The process also exhibited favorable refractive results compared with conventional laser treatment. The beneficial effect of intravitreal bevacizumab was noted in a few days with the resolution of plus disease, which was followed by

Table. Clinical data of the infants.

	Eyes with Zone I ROP			Eyes with Zone II ROP
	Laser treated	No laser treatment	Total	(Total)
Number of cases (eyes)	4 (8)	7 (13)	11 (21)	9 (18)
Gestational age	25.5 ± 2.5 weeks	26 ± 1.0 weeks	25.4 ± 2.1 weeks	26.1 ± 1.8 weeks
Birth weight	807.5 ± 290.9 g	803.5 ± 96.1 g	805.0 ± 175.8 g	814.4 ± 214.9 g
Corrected age at ROP diagnosis	32.2 ± 1.5 weeks	34.4 ± 0.9 weeks	33.6 ± 1.5 weeks	34.6 ± 2.3 weeks
Cases with additional systemic pathology				
Hydrocephaly	2	-	2	-
Intracranial hemorrhage	-	2	2	-
Bronchopulmonary dysplasia	1	2	3	1
Sepsis	-	2	2	-
SE refractive error* (final visit)	–1.2 ± 2.5 D	0.8 ± 1.1 D	0.1 ± 2.0 D	0.4 ± 0.9 D**
Cases with strabismus	2	1	3	1†

SE: spherical equivalent; D: Diopter; *: Mean ± standard deviation; **: The laser-treated 2 eyes of a single infant were excluded; †: In an infant who did not receive laser treatment.

regression of the disease stage. For Zone II disease, a single injection seemed to be effective for almost all cases in this study. However, among eyes with Zone I disease, 8 eyes (38%) required additional laser treatment about 18 weeks later. In these eyes, intravitreal bevacizumab served as a temporizing treatment, giving an opportunity for further development of the retina into Zone II, and hence allowing salvaging of more retinal tissue and a larger visual field. In addition, it gave an opportunity for the general and ocular health of the infants to improve, which made them eligible for laser treatment. Overall, 29 eyes (74%) achieved complete cure with only a single injection of intravitreal bevacizumab.

The favorable efficacy of intravitreal bevacizumab therapy for ROP in this patient group is mostly in accordance with previous reports. However, our success rate with only a single injection of intravitreal bevacizumab appears to be lower compared with most previous studies (3,6,9–12). On the other hand, a few studies have reported lower success rates comparable with our results (13,14). Differences in patient characteristics, neonatal intensive care, study protocol, and reactivation criteria may be responsible for these dissimilarities. A significant difference of this study, in terms of patient characteristics, was the inclusion of only infants ineligible for laser treatment. The results may be different in the cases of optional intravitreal bevacizumab treatment for infants suitable for laser treatment or intravitreal bevacizumab as salvage treatment when laser treatment has failed.

Another important point to consider in terms of success after intravitreal anti-VEGF treatment is the duration of follow-up. Studies with shorter follow-up may report higher success rates since eyes that appear to respond initially may subsequently develop recurrent disease. Such a phenomenon typically occurs quite late in the disease course and can progress to retinal detachment without treatment. Therefore, a prolonged follow-up for late peripheral retinal changes and reactivation appears to be mandatory until complete vascularization is achieved or laser ablation of avascular peripheral retina is performed (20–22).

Myopia in infants with ROP tends to correlate with early gestational age, low birth weight, and disease severity (16,23). In our study, Zone I and II eyes receiving only intravitreal injection did not reveal any difference in refraction. Although Zone I eyes would be expected to have higher myopia, a contradicting outcome was also observed in a recent report of refractive outcomes of the BEAT-ROP trial (17). These results may imply that severity of retinopathy may not be the most important determinant of myopia in ROP.

Previous studies have also demonstrated that myopia in ROP correlates with application of ablative treatment. In the ETROP study, approximately 70% of high-risk prethreshold ROP eyes were myopic in early childhood (16,23). In addition, myopization was more significant in children receiving an invasive cryotherapy than in children treated with the less invasive laser ablation (24). Less myopization following intravitreal bevacizumab compared with laser ablation in ROP was first reported by Harder et al. (9). In a recent randomized clinical trial,

intravitreal bevacizumab treatment resulted in about 6.0 and 4.5 D lower myopia compared with conventional laser treatment in Zone I and II eyes, respectively (17). In our study, avoidance of laser treatment also appeared to offer a refractive benefit of less myopization in Zone I eyes (P = 0.038). However, we could not perform such a refractive comparison for Zone II eyes because only 1 infant with Zone II disease required laser treatment. In addition, the refractive benefit of avoiding laser treatment was only about 2.0 D lower myopia in our study, far less than that reported in the BEAT-ROP trial (17). However, our study had a different design: laser ablation was used as a salvage treatment for recurrent disease and at a later gestational age. In addition, no eye developed high myopia (higher than 5.0 D) and even the myopia in Zone I eyes that received laser was much lower compared with that following primary laser ablation in other studies (8,17). This could be due to laser ablation being performed much later compared with primary laser therapy, thus possibly salvaging some extent of anterior segment development in the intervening time (17).

Avoidance of laser treatment did not offer a significant benefit in terms of strabismus in the present study (P = 0.22). However, a trend in favor of only anti-VEGF treatment (13% versus 40%) was observed. A greater proportion of cases with Zone I disease suffered from strabismus compared with cases with Zone II disease. However, this difference was not significant either (P = 0.31). In addition, central nervous system (CNS) pathologies, namely hydrocephalus and intracranial hemorrhage, were more frequent in infants with Zone I disease and could have a greater effect on strabismus than ROP itself. On the other hand, less myopization may provide secondary beneficial outcomes such as a lower possibility of anisometropia and amblyopia, which are known risk factors for strabismus in patients with ROP (15). Further research with a greater number of cases may reveal a beneficial effect of avoiding laser in terms of strabismus. Nevertheless, the disclosure of a favorable effect on strabismus appears to be challenging because CNS pathologies, which are frequent in infants with ROP, also appear to play an important role in pathogenesis of strabismus.

In conclusion, intravitreal bevacizumab was an effective treatment for ROP in infants ineligible for laser therapy. A single injection seemed to be almost completely sufficient for eyes with Zone II disease, while in some eyes with Zone I disease additional laser treatment was necessary. Nevertheless, intravitreal bevacizumab served as a temporizing treatment in the eyes that required laser treatment and gave an opportunity for further development of the retina and visual field into Zone II. Avoidance or deferral of laser ablation with intravitreal bevacizumab treatment seemed to provide less myopization in this patient group.

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