Low-dose ranibizumab administration in retinopathy of prematurity

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Abstract

Purpose To evaluate the efficiency of low-dose intravitreal ranibizumab therapy in the treatment of aggressive retinopathy of prematurity (A-ROP).

Methods A total of 124 eyes of 62 patients who underwent intravitreal ranibizumab after an A-ROP diagnosis between January 2015 and January 2021 were evaluated retrospectively. After receiving family-approved informed consent, low-dose intravitreal ranibizumab was administered, and regular follow-ups were performed.

Results Patients included in the study had a mean birth week of 26.6 (23–33 weeks), a mean birth weight of 905 (450–1970) grams, and an average injection postnatal time of 9.1 (4–19) weeks. The mean follow-up period was 63 (24–250) weeks. In all eyes, ROP regressed in the first week after injection, and no asymmetrical response was observed in the eyes of any baby. A total of 58 eyes recovered with a single dose of intravitreal injection therapy, and peripheral retinal vascularization was completed. A second injection was required in 38 eyes. Rescue treatment was applied in addition to intravitreal ranibizumab treatment in 22 eyes of 11 babies. None of the patients had any ocular or systemic side effects.

Conclusion Low-dose intravitreal ranibizumab injection with close follow-up and appropriate timing is an effective treatment modality in A-ROP. Even among patients undergoing rescue laser treatment, the treatment can be completed with a wide visual field.

Keywords Aggressive retinopathy of prematurity · Ranibizumab · Low-dose intravitreal injection · Recurrence

Introduction

Retinopathy of prematurity (ROP) is the most common cause of bilateral blindness in early infancy. Aggressive retinopathy of prematurity (A-ROP) is rarely seen, and it is a rapidly progressing, severe form [1]. A-ROP, seen in zone 1 and posterior zone 2, may progress rapidly regardless of stage and result in retinal detachment and blindness unless diagnosed and treated early [2, 3]. In the Early Treatment for Retinopathy of Prematurity (ETROP) study, it was reported that poor outcomes might occur even if it is treated early [4].

Both physiological and pathological vascular processes in the retina are mediated by angiogenic growth factors, especially vascular endothelial growth factor...
VEGF has been shown to play a key role in the pathogenesis of ROP. The basic pathophysiology of ROP is the cessation of physiological retinal vascularization and the formation of pathological neovascularization. Therefore, the main purpose of ROP treatments is to prevent and reverse the development of pathological neovascularization and to promote the continuation of physiological retinal vascularization. Although laser photocoagulation is applied as the gold standard treatment method for ROP, its visual and anatomical results do not seem to be positive in severe diseases such as A-ROP in zone 1 and posterior zone 2 [6–12]. Thus, anti-VEGF treatments aiming to inactivate VEGF by blocking it in the vitreous have been widely applied. In the Bevacizumab Eliminates the Angiogenic Treat of Retinopathy of Prematurity (BEAT-ROP) study, which is the largest anti-VEGF study in ROP to date, bevacizumab, a full-size anti-VEGF antibody, can stop the progression of severe ROP, reverse the pathological angiogenic changes, and promote physiological retinal vascularization [13].

However, there are some concerns regarding anti-VEGF therapy in ROP. For example, it is known that when bevacizumab is administered intravitreally it passes into the systemic circulation. In a study of intravitreal bevacizumab (IVB), it was shown that serum VEGF levels were suppressed for approximately two months in infants [14]. In our experimental study in sheep eyes, IVB was detected in the milk of the sheep and in the blood of the milk-fed lambs. However, in the ranibizumab group, drug concentrations in the sheep blood and milk and drug concentrations in the lamb blood were below the limit of the ELISA kit [15].

As organogenesis continues in premature babies, unlike adult patients, it is not clear what negative effects VEGF suppression will have on organogenesis. The other question concerns the dose titration of anti-VEGF. It remains unknown which dose is the most ideal in terms of curability and the spectrum of side effects. In many studies, including the BEAT-ROP study, half of the adult dose is applied [13, 16–19]. However, new studies have shown that lower doses of anti-VEGF are also effective in the treatment of ROP [20, 21].

The aim of this study was to evaluate the efficacy of low-dose administration of 0.1 mg ranibizumab, an anti-VEGF antibody fragment with a systemic half-life of hours, in the treatment of A-ROP.

Methods

This is a retrospective study evaluating the results of patients diagnosed with A-ROP in our clinic and treated with 0.1/0.01 mg/ml intravitreal ranibizumab (IVR) between January 2015 and January 2021. Written informed consent was signed by the patients’ parents before treatment. The study was approved by the Ethics Committee of our hospital and was performed in accordance with the Declaration of Helsinki.

The diagnosis of A-ROP was made according to the criteria of the International Classification of Retinopathy of Prematurity (IC-ROP), which was last revised in 2005. Patients with bilateral A-ROP in zone I were included in this study. The stages of ROP were graded according to the international classification of retinopathy of prematurity [1].

Demographic data such as gestational age, birth weight, postnatal week, and other conditions were recorded.

Treatment application

Injections were given to all patients under topical anaesthesia provided by proparacaine under operating room conditions. Tropicamide 0.25% (Tropamide ®; Bilim Ilac, Istanbul, Turkey) was used for pupil dilation in the preoperative period. After instillation of 5% povidone iodine into the conjunctival sac, the eyelids and periorbital area were cleaned with gauze moistened with 10% povidone iodine for a period of 3 min. A sterile drape was then applied, and the conjunctival sac was rinsed with saline solution before injection. A lid speculum was placed, and 0.1 mg (0.01 ml) of ranibizumab (Lucentis®; Genentech Inc., South San Francisco, CA, USA) was injected 1.5 mm posterior to the corneal limbus using a 30 gauge needle. After IVR injection, antibiotic and steroid eye drops were applied 4 times daily for 7 days. The patients were followed up for ocular side effects such as postoperative ocular inflammation, endophthalmitis, increased intraocular pressure and secondary cataract development. In addition, the patients were followed up in the neonatal intensive care unit and the
paediatrics clinic in the perioperative and postoperative periods for systemic side effects. In addition, clinical follow-ups were made by paediatricians to evaluate their neurological and motor development.

Follow-up and treatment criteria

Patients were followed up on the first day, third day, first week, and first month after injection every week and then monthly until peripheral retinal vascularization was complete. Vascular termination closer than 2 disc diameters to the ora serrata was accepted as complete peripheral retinal vascularization.

All patients were examined under topical anaesthesia following appropriate pupil dilatation. Fundus examination was performed with indirect ophthalmoscopy in all patients. The severity, location, extent, and presence of plus disease were recorded at each examination.

An early response after injection was accepted as regression of the retinal neovascularization and plus disease. Re-emergence of the preretinal ridge line after anti-VEGF treatment, recurrence of plus disease, and recurrence of active proliferation were considered reactivation. Reinjection was planned for patients who responded to treatment but developed reactivation.

Rescue treatment

Infants whose plus disease did not regress, whose preretinal ridge line and ROP stages did not regress, or who had significant pallor in the peripheral avascular retina were considered to have an inadequate response to anti-VEGF treatment, and laser photocoagulation was applied as a salvage treatment.

Table 1 shows the treatment algorithm of patients diagnosed with A-ROP.

The criterion for terminating the follow-up period was the completion of retinal vascularization. Lifelong follow-up at regular intervals was recommended for babies in whom zone 3 was not vascularized.

Statistical analysis

The SPSS (Statistical Package for Social Sciences, Inc., Chicago, IL) for Windows 20.0 package was used for analysis of the data. Continuous variables are expressed as the mean ± SD, and categorical variables are expressed as percentages. Group comparisons were made with the independent t test. When \( P < 0.05 \), the results were statistically significant.

Results

A total of 62 infants (124 eyes) were included in this study. Thirty-two of the patients were girls. The mean gestational age of the patients included in the study was 26.6 (23–33) weeks, and the mean birth weight was 905 (450–1970) grams. The mean postnatal timing of the first intravitreal injection for treatment was 9.1 (4–19) weeks, and the mean follow-up time was 63 (24–250) weeks.

During the first examination of all patients after the first injection, regression of the A-ROP findings and the response to treatment were observed. The response to treatment after the injections was similar in both eyes in all patients. Intravitreal injection treatment was applied to 78 eyes of 39 infants. Of these, 58 eyes of 29 infants recovered with a single-dose intravitreal injection treatment, and peripheral retinal vascularization was completed at an average of 20.6 ± 3.75 postnatal weeks (16–30). After a single injection, zone 1–2 was vascular in 6 eyes of 3 babies, while zone 3 was avascular. No additional treatment was applied, because no ROP findings or additional pathology were detected in the follow-ups. In 14 eyes of 7 infants who received a single-dose injection, rescue laser photocoagulation therapy was performed, considering the inadequate response to anti-VEGF therapy, approximately 3.85 (2–6) weeks after the injection.

A second injection was applied to 46 eyes of 23 babies 4 weeks after the first injection. Of these, 38 eyes of 19 infants recovered with reinjection, and peripheral retinal vascularization was completed at an average postnatal week of 25.6 ± 4.75 (20–36). Eight eyes of 4 babies were reinjected and rescue argon laser photocoagulation therapy was applied approximately 9.2 (7–11) weeks after the start of treatment.

Rescue treatment was needed in addition to intravitreal ranibizumab treatment in 22 eyes (17.74%) of 11 infants in total. Rescue treatment was administered at a mean postnatal week of 5.7 (2–11). When we compared the birth weight and gestational age of the babies who received only intravitreal injection treatment with the rescue treatment group, the birth weight and gestational age of the group that received rescue
treatment were found to be significantly lower than those of the other group (birth weight: 740 ± 172 g vs 950 ± 121 g, \( p: 0.01 \); gestational age 25.6 ± 1.63 weeks vs 27.8 ± 3.86 weeks, \( p: 0.005 \)), respectively.

During the follow-up period, no per-postoperative ocular side effects were detected. No additional systemic developmental pathology was observed in the infants during the clinical follow-ups in the neonatal intensive care unit and afterwards.

**Discussion**

In this study, we presented the results of patients diagnosed with A-ROP and treated with 0.1 mg ranibizumab. ROP control was achieved in 102 eyes.
of 51 infants without the need for salvage therapy. The dose we used in this study was lower than the 50% adult dose of bevacizumab used most frequently in the off-label treatment of ROP and the doses of ranibizumab used in most studies. It is 20% of the adult ranibizumab dose.

In the treatment of ROP, the main purpose of applying anti-VEGF drugs is to control the ROP while maximizing the retinal area that will contribute to visual function by providing full retinal vascularization. In cases where there is a large avascular retinal area, such as in A-ROP, and a high VEGF concentration in the vitreous [22–24], anti-VEGF treatments are superior to laser treatment. In A-ROP patients who had laser photocoagulation as their first treatment option in the past, retinal vascularization was not in question, and the peripheral visual field was also very narrow after the treatment. With the increase in knowledge and experience with anti-VEGF treatments, the first treatment option in patients diagnosed with A-ROP in our clinic and in most parts of the world is intravitreal anti-VEGF.

There are many studies in the literature showing that bevacizumab, ranibizumab, aflibercept and conbercept treatment, which have all been applied at different doses since 2012, are effective in the regression of ROP [13, 16–21, 25–27], but there is no consensus on which anti-VEGF should be administered at which dose. In the BEAT-ROP study, in which approximately 300 eyes with stage 3 ROP in zone 1 and posterior zone 2 or A-ROP were evaluated, an IVB dose of 0.625 mg was administered, and recurrence was reported in 6 of 140 eyes [13]. Chen et al. [18] and Castellanos et al. [19] reported that vascularization was completed without recurrence in all patients who were administered 0.25 mg IVR. Menke et al. [17] reported that vascularization was completed in 6 eyes without recurrence when they applied 0.3 mg IVR. On the other hand, Baumall et al. [20] applied 0.2 mg IVR to 8 eyes of 4 patients with type 1 ROP and reported that recurrence was observed in all patients. Wong et al. [16] reported that they observed recurrence in 5 of 6 eyes with 0.25 IVR.

In our study, we observed that acute ROP findings regressed within the first week in all eyes in which we applied 0.1 mg IVR. Thirty-two of 39 infants who received a single-dose injection recovered without any additional treatment. Forty-six eyes of 23 infants (37%) showed reactivation of ROP, requiring reinjection. As highlighted in the Rainbow study, the rate of elimination of ranibizumab from the eye was faster in infants with ROP than in adults [28]. The eye elimination rate of ranibizumab in infants in Xu et al. [29] was approximately 50% faster than that reported for adults (t1/2: 5.6 [infants] vs. 8.6 days [adults]). The faster elimination from the eye in preterm infants may be due to several factors, including structural differences in tissues, a shorter vitreous diffusion path in a smaller eye, and reduced blood-retina vessel barrier function in active ROP [30]. Although the rate of reinjection in our study appears to be higher than that in the BEAT-ROP study, it should be noted that reinjection is very different from salvage therapy. The reactivation in these patients is related to the level of VEGF released from the avascular retina, and these infants have a more premature retina than infants who do not need an additional reinjection and are basically receiving low-dose ranibizumab therapy. Contrary to laser photocoagulation, in anti-VEGF applications, the ischaemic retina that synthesizes VEGF is not destroyed. Only VEGF that accumulates in the vitreous is blocked. With low-dose anti-VEGF, VEGF in the vitreous is partially blocked, and physiological natural vascularization is maintained with the remaining unblocked VEGF. High doses, such as half that for the adult, suppress all VEGF in the vitreous, suppressing both neovascularization and natural vascularization.

Tahija et al. [31] reported that after administering a single dose of intravitreal bevacizumab to 20 eyes of 10 patients with A-ROP, early regression was observed in all patients, the avascular retinal area decreased, but retinal vascularization was not completed as shown by RetCam fluorescein angiography in 11 eyes. Sukgen et al. [26] reported that retinal vascularization was not completed in 2 of 13 patients with A-ROP who were administered 0.25 mg IVR. In the Care-ROP study, complete vascularization was reported for 55% in the 0.12 mg ranibizumab group and 16.7% in the 0.24 mg group [32].

In our study, vascularization was completed in 77.4% (48/62) of patients. Vascularization did not progress to zone 3 in 3 patients. These 3 patients, the youngest of whom is now 3 years old, are being followed up and not showing any problems. Laser photocoagulation was performed as a rescue treatment in 22 eyes of 11 patients who showed an inadequate response to ranibizumab treatment, did not progress in
vascularization despite repeated injections, had a recurrence of plus disease, active proliferation, and pallor in the avascular retina. Laser applications were performed 5.7 weeks postnatally. This period was 3.85 weeks on average after single-dose IVR treatment. The fact that the need for a second injection occurred one month after the first injection brings to mind the question of how many of these patients could have avoided rescue treatment if a second injection had been given instead. The peripheral avascular retinal appearance on the fundus examinations of the patients who were given rescue treatment was different from that of the patients who were given a second injection. Avascular retinal pallor and proliferation progressed more in favour of fibrosis in patients who were given rescue treatment. Despite everything, we observed that vascularization progressed to the middle of zone 2 in patients who underwent laser. In the treatment of aggressive ROP, even if the response to the treatment is insufficient with low-dose ranibizumab, time is gained for rescue treatment, and vascularization of the retina is allowed as much as possible during this period, enabling the babies to have a wider visual field after laser treatment.

Although neovascularization is stopped at high anti-VEGF doses, natural retinal vascularization also stops; in addition, the amount of anti-VEGF that escapes into the systemic circulation increases, and the risk of systemic complications also increases. With bilateral injection of IVR 0.1 or 0.2 mg (per eye), the systemic Cmax was 7.6 and 16.2 times higher in infants, respectively, than in adults who received 0.5 mg IVR in one eye. The median Cmax was approximately 11.5 and 24.3 ng/mL in infants who received 0.1 mg and 0.2 mg IVR, respectively, and 1.5 ng/mL in adults [28]. The elimination rate of ranibizumab from the serum of infants is approximately three times lower than that in adults (t1/2: 0.3 vs. 0.09 days) [29]. In the Rainbow study, after bilateral intravitreal administration, the estimated t1/2 in the eye was approximately 5.6 days, and the estimated t1/2 of ranibizumab in the systemic circulation was 0.3 days [28]. Sato et al. [33] measured serum VEGF and bevacizumab concentrations preinjection and on the first day, 1st week, and 2nd week in infants treated with 0.25 mg or 0.5 mg IVB in both eyes. The serum concentrations of bevacizumab before and 1 day, 1 week, and 2 weeks after a total of 0.5 mg of IVB were 0 ng/mL, 195 ng/mL, 946 ng/mL, and 1214 ng/mL, respectively. An in vitro experiment using human umbilical vein endothelial cells demonstrated that approximately 500 ng/mL bevacizumab was able to completely block the VEGF activity [34]. After 0.5 mg of IVR treatment, serum VEGF levels decreased from 46 pg/ml to 11 pg/ml, and VEGF levels were suppressed for 1 week [35]. In the study of Sato et al. [33], it was shown that with a total of 0.5 mg IVB, the initial serum VEGF level was 1628 pg/ml before the injection and it decreased to 427 pg/ml on day 1, 246 pg/ml at week 1 and 269 pg/ml at week 2. In a Canadian study involving 125 infants, the neurological development of babies who received IVB and laser therapy because of ROP were evaluated at 18 months according to gestational age and sex, and the rate of neurodevelopmental disability was found to be 3.1 times higher in the IVB group [36]. A-ROP is usually observed in extremely premature and low birth weight infants [1, 11]. The mean birth week of the babies in our study was 26.6 weeks, and the mean birth weight was 905 g. The dose of intravitreal anti-VEGF used in the treatment of these extremely premature babies becomes more of an issue in terms of systemic side effects. In addition, considering that the systemic half-life of bevacizumab is expressed in days and ranibizumab in hours in studies in adult patients, we prefer ranibizumab in A-ROP patients, considering that ranibizumab is safer in premature babies.

In our study, no ocular side effects were observed in any of the patients after low-dose IVR treatment, and no additional developmental abnormalities were observed in the infants during our clinical follow-ups at an average of 63 weeks. Although the oldest child we are currently following up clinically is 5 years old and there is no systemic abnormality apparent in any of the patients, it cannot be said for sure that systemic complications are absent in these patients. Follow-ups should be continued in the long term.

Serum VEGF and anti-VEGF levels were not evaluated in our study. We did not perform angiography to evaluate the retinal vascularization. All data were obtained with an indirect ophthalmoscope. These are limiting factors of this study.

With sensitive titrated low-dose IVR administration and more frequent follow-up, results that simulate physiological retinal vascularization can be obtained. Thus, especially in A-ROP, the undesirable results of laser photocoagulation, such as visual field narrowing,
myopia and anterior segment ischaemia, can be avoided, and a better visual field and a vascularization process that is more physiological can be achieved. We believe that the 0.1 mg IVR administered in this study is a dose that allows for natural retinal vascularization and it is safe in terms of systemic complications for the treatment of A-ROP. However, larger and longer follow-up studies are needed on this subject.

Authors’ contributions Tok L was involved in conception and design, administrative support and provision of study materials or patients. Seyrek L was involved in collection and assembly of data. Tok L and Yalcin Tok O were involved in data analysis and interpretation. All authors were involved in manuscript writing and final approval of manuscript.

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Declarations

Conflict of interest This study has no commercial or proprietary interest. The authors report no conflict of interest.

Ethical approval Ethical approval was given; the relevant judgement Suleyman Demirel University, reference number is 17/274.

Consent to participate Written informed consent for publication was obtained from all participants.

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