Low-Dose Ranıbızumab Admınıstratıon in Retınopathy of Prematurıty

Levent Tök (dr.leventtok@yahoo.com.tr)
Suleyman Demirel University: Suleyman Demirel Universitesi
Lütfi Seyrek
Konya Private Hospital
Özlem Tök
Suleyman Demirel University: Suleyman Demirel Universitesi

Research Article

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Abstract

Purpose: To evaluate the efficiency of low dose intravitreal ranibizumab therapy in the treatment of aggressive posterior premature retinopathy (APROP).

Methods: A total of 124 eyes of 62 patients who underwent intravitreal ranibizumab with APROP diagnosis between January 2015-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, an average injection week post-natal 9.1 (4-19) weeks. The mean follow-up period was 63 (24-250) weeks. In all eyes, it was observed that ROP was regressed in the first week control after injection and no asymmetrical response was observed in the eyes of any baby. A 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.

Conclusıon: Low-dose intravitreal ranibizumab injection with close follow-up and appropriate timing is an effective treatment modality in APROP. Even in patients undergoing rescue laser treatment, the treatment can be completed with a wider visual field.

Introduction

Retinopathy of prematurity (ROP) is the most common cause of bilateral blindness in early infancy. Aggressive posterior retinopathy of prematurity (APROP) is a rarely seen, rapid progressing, severe ROP form [1]. APROP, 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 may occur even if treated early [4].

Both physiological and pathological vascular processes in the retina are mediated by angiogenic growth factors, especially vascular endothelial growth factor (VEGF) [5]. VEGF has been shown to play a key role in the pathogenesis of ROP. The basic pathophysiology of ROP is the stoping of physiological retinal vascularization due to these factors and the formation of pathological neovascularizations. Therefore, the main purpose of ROP treatments is; to prevent and reverse the development of pathological neovascularization, as well as to promote the continuation of physiological retinal vascularization. Although laser photocoagulation is applied as the gold standard treatment method in the treatment of ROP, its visual and anatomical results do not seem to be positive in severe diseases such as APROP seen 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; It has been shown that bevacizumab, a full-size anti-VEGF antibody, can stop the progression of severe ROP, reverse 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 the drug administered intravitreally passes into the systemic circulation. In a study using 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, intravitreal bevacizumab was also detected in the milk of sheep and in the blood of milk-fed lambs; In the ranibuzumab group, drug concentrations in sheep blood and milk and drug concentrations in lamb blood were below the limit determined by the ELISA kit [15].

As organogenesis continues in premature babies, unlike adult patients, it is not known what negative effect VEGF suppression will have on organogenesis. The other question concerns dose titration of anti-VEGF. It remains unknown that which dose is the most ideal dose in terms of curability and 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 is 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 APROP.

Methods

This is a retrospective study evaluating the results of patients diagnosed with APROP in our clinic and treated with 0.01/0.01 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 APROP was made according to the criteria of the International Classification of Retinopathy of Prematurity (IC-ROP) which is last revised in 2005. Patients with bilateral APROP in zone I were included in the study. 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 additional diseases of the patients were recorded.

Treatment Application

Injections were given to all patients under topical anesthesia provided with proparacaine in 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 minutes. 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 SanFrancisco, CA, USA) was injected 1.5 mm posterior to the corneal limbus using a 30 Gauge needle. After IV ranibizumab injection, antibiotic and steroid eye drops were used 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, patients were consulted and followed up in the pediatrics clinic in terms of systemic side effects in the neonatal intensive care unit in the perioperative and postoperative periods. In addition, clinical follow-ups were made by pediatricians in terms of 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.

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

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

Rescue Treatment:

The infants whose plus disease did not regress, or whose preretinal ridge line and ROP stages did not regress, or who had significant pallor in the peripheral avascular retina were considered as 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 APROP.

The criteria for terminating the follow-up period were completion of retinal vascularization. Life-long 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 program was used in the analysis of the data. Continuous variables were expressed as mean ± SD and

categorical variables as percentages. Group comparisons were made with the independent t test. For $P < 0.05$, the results are statistically significant.

Results

A total of 62 infants (124 eyes) were included in the study. Thirty two of the patients were female. 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 week of the first intravitreal injection for treatment was 9.1 (4–19) weeks, and the mean follow-up time was 63 (24–250) weeks.

In the first examination of all patients after the first injection in the treatment, regression of APROP findings and response to treatment were observed. Response to treatment after injections was similar between both eyes in all patients.

Single dose 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 postnatal week 20.6 ± 3.75 (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 finding and 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 inadequate response to anti-VEGF therapy, approximately 3.85 (2–6) weeks after 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 re-injection, peripheral retinal vascularization was completed at an average of postnatal week 25.6 ± 4.75 (20–36). eight eyes of 4 babies who were re-injected; 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 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; birth weight and gestational age of the group that received rescue treatment were found to be statistically significantly lower than the other group (birth weight: 740 ± 172 g- 950 ± 121 g, p: 0.01; gestational age 25.6 ± 1.63–27.8 ± 3.86, p:0.005).

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

Discussion

In this study, the results of patients diagnosed with APROP and treated with 0.1 mg ranibizumab were presented. ROP control was achieved in 102 eyes of 51 infants without the need for salvage therapy. The

dose we used in the study is lower than the 50% adult dose of bevacizumab used most frequently in the treatment of off-label 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 Anti-VEGF is to control the ROP, while to maximize 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 APROP, and high VEGF concentration in the vitreous [22–24], anti-VEGF treatments have become superior to laser treatment. In APROP patients, who had laser photocoagulation as the 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 about anti-VEGF treatments, the first treatment option in patients diagnosed with APROP in our clinic and all over the world is intravitreal anti-VEGF.

There are many studies in the literature showing that bevacizumab, ranibizumab,aflibercept and conbercept treatment, which has 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 APROP is evaluated, an IVB dose of 0.625 mg was administered and in 6 of 140 eyes recurrence was reported [13]. Chen et al.[18] and Castellanos et al.[19] reported that vascularization was completed without recurrence in all patients who administered 0.25 mg IVR. Menke et al.[17] reported that vascularization was completed in 6 eyes without recurrence, in another study in which they performed 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 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. 46 eyes of 23 infants (37%) showed reactivation of ROP requiring reinjection. Although the rate of reinjection in our study appears to be higher than 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 that these infants have a more premature retina than infants who do not need additional treatment reinjection is part of low-dose ranibizumab therapy. Contrary to laser photocoagulation, in anti-VEGF application, the ischemic 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 the adult, suppress all VEGF in the vitreous, suppressing both neovascularization and natural vascularization.

Tahija et al.[28] reported that after administering a single dose of intravitreal bevacizumab to 20 eyes of 10 patients with APROP, early regression was observed in all patients, avascular retinal area decreased, but retinal vascularization was not completed with RetCam Fluorescein angiography in 11 eyes. Sukgen

et al.[26] reported that retinal vascularization was not completed in 2 of 13 patients with APROP who administered 0.25 mg IVR. In the Care-ROP study, complete vascularization was reported as 55% in the 0.12 mg ranibizumab group and 16.7% in the 0.24 mg group[29]. In our study, it was observed that vascularization was completed in 77.4% (48/62) of them. Vascularization did not progress to zone 3 in 3 patients. These 3 patients, the youngest of which is 3 years old, are being followed up without any problems. Laser photocoagulation was performed as a rescue treatment in 22 eyes of 11 patients who showed inadequate response to ranibizumab treatment, did not progress in vascularization in repeated controls, recurred plus disease, active proliferations, and pallor in the avascular retina. Laser applications were performed on average postnatal 5.7 weeks. 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 the vascularization of the retina is allowed as much as possible during this period, enabling babies to have more 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. Sato et al. [30] serum VEGF and bevacizumab concentrations were measured pre-injection, first day, 1st week, 2nd week in infants treated with 0.25 mg or 0.5 mg IVB in both eyes. The serum concentration of bevacizumab before and 1 day, 1week, and 2 weeks after a total of 0.5 mg of intravitreal bevacizumab was 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 about 500 ng/mL of bevacizumab was able to completely block the VEGF activities [31}. It showed that after 0.5 mg of IVR treatment, serum VEGF levels decreased from 46 pg/ml to 11pg/ml and VEGF levels were suppressed for 1 week [32]. In the study of Sato et al.[30], it was shown that with a total of 0.5 mg intravitreal bevacizumab, serum VEGF levels decreased from 1628 pg/ml on day 1 to 427 pg/ml, 246 pg/ml at week 1 and 269 pg/ml at week 2. In a Canadian study involving 125 infants; neurological development of babies who received IVB and laser therapy because of ROP were evaluated at 18 months, according to gestational age and gender, and the rate of neurodevelopmental disability was found to be 3.1 times higher in the IVB group [33]. APROP 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 grams. 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 APROP patients, considering that ranibizumab is safer in such advanced 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 of average 63 weeks in the presence of a pediatrician. Although the oldest baby we are currently following up clinically is 5 years old and there is no systemic abnormality in the patients, it can not be said that systemic complications are absent in these patients. Follow-ups should be continued in long-term.

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

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

Declarations

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Conflicts of interest/Competing interests: This study has no commercial or proprietary interest. The authors report no conflict of interest.

Authors' contributions

(I) Conception and design: Tök L, (II) Administrative support: Tök L; (III) Provision of study materials or patients: Tök L ; (IV) Collection and assembly of data: Seyrek L (V) Data analysis and interpretation: Tök L, Tök ÖY (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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

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

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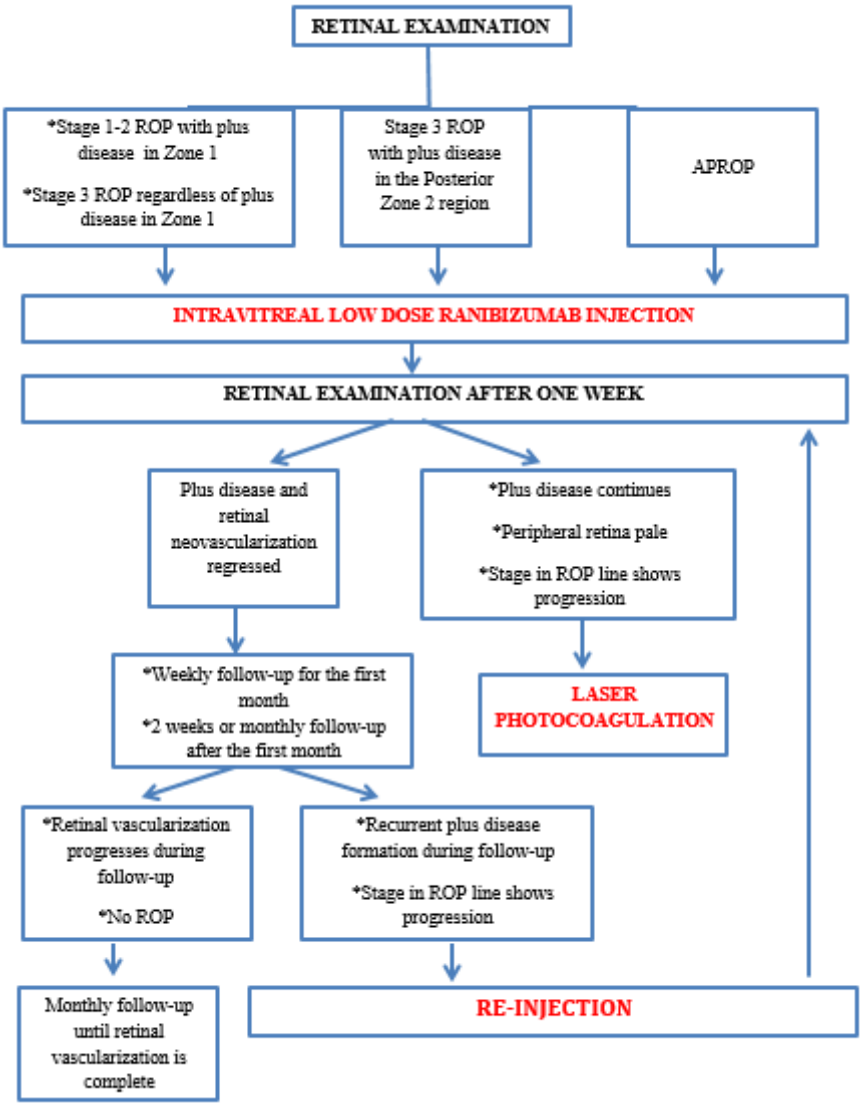
Tables

Table 1. Treatment algorithm in aggressive posterior premature retinopathy


RETINAL EXAMINATION
*Stage 1-2 ROP with plus disease in Zone 1
*Stage 3 ROP regardless of plus disease in Zone 1
Stage 3 ROP with plus disease in the Posterior Zone 2 region
APROP
INTRAVITREAL LOW DOSE RANIBIZUMAB INJECTION
RETINAL EXAMINATION AFTER ONE WEEK
Plus disease and retinal neovascularization regressed
*Plus disease continues
*Peripheral retina pale
*Stage in ROP line shows progression
*Weekly follow-up for the first month
*2 weeks or monthly follow-up after the first month
LASER PHOTOCOAGULATION
*Retinal vascularization progresses during follow-up
*No ROP
*Recurrent plus disease formation during follow-up
*Stage in ROP line shows progression
Monthly follow-up until retinal vascularization is complete
RE-INJECTION