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Clinical management of recurrent retinopathy of prematurity following intravitreal bevacizumab monotherapy

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Abstract

PURPOSE—To determine (1) incidence, (2) risk factors, (3) risk period, and (4) characteristics of recurrent retinopathy of prematurity (ROP) treated by intravitreal bevacizumab (IVB) monotherapy.

DESIGN—Retrospective case series.

PARTICIPANTS—Premature infants developing Type 1 ROP [subdivided into ROP stage 3+ and aggressive posterior ROP (APROP)] in zone I or zone II posterior, receiving IVB monotherapy, and followed for at least 65 weeks adjusted age (AA).

METHODS—Retrospective review of infants who developed recurrence of Type 1 ROP following IVB monotherapy was performed including examination of RetCam fundus photographs and fluorescein angiograms.

MAIN OUTCOMES MEASURES—Incidence, risk factors, risk period, and characteristics of recurrent ROP.

RESULTS—IVB monotherapy in 241 infants (471 eyes) was reviewed. (1) Recurrence incidence was 8.3% (20/241) for infants and 7.2% (34/471) for eyes. (2) Recurrence risk factors of greatest significance were appearance of neovascularization as APROP ($P=0.006$), extended duration of hospitalization ($P=0.01$), and lower birth weight ($P=0.024$). (3) Recurrence risk period was between ≈ 45 and ≈ 55 weeks AA [90.0% (18/20) for infants and 94.1% (32/34) for eyes] with mean recurrence of 51.2 weeks AA (± 4.6 ; range 45.7 to 64.9), and mean interval of 16.2 weeks (± 4.4) between treatments. (4) Recurrence characteristics included *plus disease*, (20/20 infants; 100%) and *neovascularization* appeared at the following sites: (i) ROP stage 3+ with confluent

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neovascularization recurred *both* at the advancing edge and at the initial ridge and extra-retinal fibrovascular proliferative complex (12/14 infants; 85.7%). However, (ii) APROP (6/6 infants; 100%) [and ROP stage 3+ with non-confluent neovascularization (2/14 infants; 14.3%)] recurred *only* at the advancing edge. Also, *the anterior extent of retinal vascularization* was decreased (mean 1.76 versus 4.48 disc diameters [DD]), and *the rate of retinal vascularization* was delayed (mean 0.11 versus 0.23 DD/week) in those with versus without recurrence, respectively. Following retreatment with IVB, plus disease persisted, neovascularization regressed, and retinal vascularization proceeded minimally and slowly.

CONCLUSIONS—Premature children developing severe ROP are being treated successfully with IVB monotherapy. However, recurrence is not uncommon, so vigilant follow-up is necessary to ensure timely re-treatment when needed. Knowledge of recurrence incidence, risk factors, risk period, and characteristics allows tailored clinical management.

Retinopathy of prematurity (ROP) is a vascular proliferative disease of the developing retina in premature infants and currently is the most common ocular cause of childhood blindness worldwide with more than 30,000 affected annually.¹ Historically, there have been two treatment modalities (first cryotherapy, then laser therapy)^{2, 3} that reduce the risk of blindness by ablating the peripheral retina. As early as 1978,⁴ an angiogenic factor was suggested to initiate the pathogenesis of ROP with later demonstration of angiogenic activity in ocular tissues.⁵ In 1984,⁶ electron microscopy was utilized to localize an unknown angiogenic factor to the peripheral retina in ROP. Vascular endothelial growth factor (VEGF) was discovered to be an important angiogenic factor in 1989⁷ and was later related to retinal neovascularization.⁸ Studies utilizing anti-VEGF substances, especially intravitreal bevacizumab (IVB) (Avastin, Genentech/Roche, San Francisco, CA), in the rat animal model of ROP have provided further insight into the mechanisms affecting retinal neovascularization.^{9, 10} IVB therapy for ROP in preterm infants was first published in 2007,¹¹ and multiple case reports and small case series of IVB use for ROP appeared thereafter. Since 2011, utilization of IVB monotherapy for severe ROP has gained popularity, following publication of IVB efficacy in a prospective, stratified, randomized, controlled, multi-center, clinical trial, **Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP)**,¹²

Some practitioners are implementing IVB as part of a dual therapy with laser, rather than as monotherapy; however, this combination may have ramifications. Laser may cause more recurrences due to breakdown of the blood-retinal barrier perhaps allowing more escape of IVB from the eye. Especially in zone I cases and when near confluent laser therapy is performed, *unavoidable consequences* frequently occur with clinical implications including loss of visual field,¹³ increased myopia,¹⁴ and development of late angle closure glaucoma.^{15,16} Other potential complications of laser therapy include posterior synechiae, irregular pupils with inability to completely dilate, cataracts, development of early angle closure glaucoma, phthisis, leakage from choroidal vessels, and retinal detachment. Most of these consequences and complications (especially the increased myopia^{17–20} related to altered anterior segment development)^{19, 20} may be decreased by IVB monotherapy.²¹

Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)² and Early Treatment for Retinopathy of Prematurity (ETROP)³ both suggest that recurrence following peripheral retinal ablation for Type 1 ROP generally occurs before 54 weeks adjusted age (AA). However, IVB causes a delay in retinal vascularization, which is especially concerning if recurrence develops.²² The appropriate time to perform and to suspend follow-up examinations to allow timely diagnosis and treatment of recurrence following IVB monotherapy must be properly structured and extended until retinal vascularization is “complete”,²² which may not necessarily reach the ora serrata in the most immature infants.^{23, 24}

Cases of late recurrence following anti-VEGF monotherapy or combined with laser therapy have been reported in the literature with seemingly minimal lapses in follow-up. Thus, the apprehension of not knowing how frequently recurrence occurs (incidence of recurrence), which infants are at greatest risk for recurrence (risk factors), when the period of risk for recurrence finally ends (risk period), and where in the retina to concentrate follow-up examinations (clinical characteristics), causes many physicians to be very hesitant to treat ROP with IVB monotherapy.

Participants and Methods

Two cohorts were reviewed in this large retrospective case series: 1) Seventy-five infants treated with IVB in the BEAT-ROP clinical trial (Clinicaltrials.gov trial registration number NCT00622726) from March 13, 2008 to August 4, 2010;¹² and, 2) 218 infants treated consecutively with IVB (by HMH) following the BEAT-ROP clinical trial, who were treated and followed at the Memorial Hermann Hospital System in Houston, TX, and at the hospitals in Webster, Corpus Christi and El Paso, TX from August 5, 2010 to December 31, 2014. The Committee for the Protection of Human Subjects (the Institutional Review Board at The University of Texas Health Science Center) approved the study. All research adhered to the tenants of the Declaration of Helsinki and was HIPAA compliant.

All infants received IVB monotherapy for Type 1 ROP in zone I or zone II posterior with plus disease (published in ETROP³ in 2003) {subdivided in this study into ROP stage 3+ and aggressive posterior ROP (APROP) (included in the International Classification of ROP revisited (ICROP-R)^{25, 26} in 2005). Stage 3+ (defined as “extraretinal fibrovascular proliferation [EFP] or neovascularization that went through stages 1 and 2 to 3 that extends from the ridge into the vitreous”); and APROP (defined as an aggressive form of ROP typically seen in the posterior pole vessels that “show increased dilation and tortuosity in all 4 quadrants that is out of proportion to the peripheral retinopathy”...and...“may appear as only a flat network of neovascularization [FNV] at the deceptively featureless junction between vascularized and nonvascularized retina”) (as defined by ICROP-R).^{25, 26} All infants included in the study and its analysis had follow-up examinations extending to 65 weeks. All infants were treated with IVB monotherapy using the standard protocol as described in the BEAT-ROP clinical trial.¹² Both the first (initial treatment for Type 1 ROP) and the second (treatment for recurrence of Type 1 ROP) IVB injections given to patients were the same dose (0.625 mg; 0.025 mL). All bilateral treatments and retreatments were performed on the same day, rather than as a staged procedure. RetCam fundus photography

(Clarity Medical Systems, Inc., Pleasanton, CA) was used prior to the first IVB injection in all infants (241) to document Type 1 ROP, prior to the second IVB injection in all infants (20) with recurrent ROP to document recurrence characteristics, and in follow-up as needed for clinical management. Fluorescein angiography was performed on infants (9) at the time of recurrence and, when possible, to document the final extent of retinal vascularization in infants with and without recurrence. The final extent of retinal vascularization was measured, and the rate of retinal vascularization was calculated in eyes (25) without and (25) with recurrence. The non-recurrent eyes were selected from the 104 non-recurrent eyes of the BEAT-ROP clinical trial because these had been photographed (as per protocol) at the time of initial treatment and at approximately 54 weeks.⁽¹²⁾ Zone I ROP cases were selected to be measured so that final extent was clear. The final extent of zone II ROP cases was not always clear and measurable. The recurrent eyes were selected from 34 eyes (recurrences from both cohorts (the six recurrent eyes of BEAT-ROP clinical trial and the 28 recurrent eyes following the end of that clinical trial treated with bevacizumab monotherapy). Of these 34 eyes, 18 had ROP in zone I and 16 had ROP zone II, initially. The zone I and II eyes with the clearest final extent were selected to be measured. The selected photographs were printed and assembled from the optic nerve through the macula to the advancing edge. The disc diameter was measured. This measurement was used to calculate the extent of progression of retinal vascularization from the initial treatment site to the final extent of the retina in disc diameters (non-recurrent eyes) or from the initial to the second treatment sites in the retina in disc diameters (recurrent eyes). Dates of the photographs were used to calculate the rate of progression of retinal vascularization.

The study unit for all data analyses was infant, not eye, thus any unilateral recurrence was considered a recurrence. Any infants with asymmetric zones of ROP between the two eyes were classified as the smallest of the two zones. Demographic and baseline clinical data were summarized by mean (\pm standard deviation) for continuous variables or frequency (percentage) for discrete variables. Univariate analysis, two-sample *t*-test or the Fisher Exact test was used to compare each demographic, health status, and characteristic of initial treatment variable between infants without and with recurrence. Due to the correlation among the potential risk factors, a multivariate analysis with bidirectional stepwise logistic regression was used to identify and assess any potential risk factors for recurrence of ROP, including birth weight (BW), gestational age (GA), APGAR score at 1 and 5 minutes, initial location of ROP (zone I or zone II posterior), initial appearance of Type 1 ROP (subdivided into ROP stage 3+ or APROP), duration of hospital stay, and other systemic conditions including necrotizing enterocolitis (NEC) requiring surgery, sepsis proven by positive blood culture, patent ductus arteriosus (PDA) requiring surgery, and intraventricular hemorrhage (IVH). The odds ratio and associated *P* value (with a *P* value of <0.05 indicating significance) for each risk factor were determined. All statistical analyses were performed using SAS for Windows v9.4 (SAS, Inc., Cary, NC).

The characteristics of ROP were recorded at the first (for initial Type 1 ROP) and the second (for recurrent ROP) treatment (whether unilateral or bilateral) as follows:

1. At first (initial) treatment: (a) Type 1 ROP: (ROP stage 3+ or APROP); (b) the location (zone) of the ROP; and (c) the timing of the development of

ROP (as postnatal age [PNA] and as adjusted age [AA] = GA + PNA) were recorded.

2. At second (recurrent) treatment: (a) the site of re-appearance of neovascularization (NV) at the advancing edge and at the original site of the ridge and EFP complex [R+EFP] with return of plus disease; (b) the location (zone: now distance from original location of ROP) of the advancing edge of retinal vascularization; and (c) the timing (PNA, and AA) of the recurrence of ROP, and interval between treatments (weeks) were recorded.
3. The number of weeks from the initial treatment to the last follow-up examination and AA at the last follow-up examination for all infants (without or with recurrence) were also recorded.
4. Fundus photographs and fluorescein angiograms were reviewed to observe the location of neovascular changes at first treatment (for initial Type 1 ROP), at second treatment (for recurrent ROP), and after stabilization of these changes:
 - i. In a sample of eyes either with or without recurrence, the extent of retinal vascularization at the first treatment with IVB was measured in number of disc diameters (DD, measured from the temporal edge of the optic nerve through the fovea to the advancing edge) (MMG).
 - ii. In those eyes with recurrence, the extent of vascularization at the location of the second treatment for recurrence was measured in number of DD (MMG). The difference between the first and second IVB treatments (exact dates used) was calculated as the extent of progression of retinal vascularization.
 - iii. In those eyes without recurrence, the extent of vascularization at their location at 54 weeks AA was measured in number of DD as was part of the initial BEAT-ROP protocol¹² (MMG). The difference between IVB treatment and the extent of vascularization at 54 weeks AA (exact dates used) was calculated as the extent of progression of retinal vascularization.
 - iv. The rate of vascular progression for eyes with recurrence was then calculated by the number of DD radial progression between the first and second IVB treatments divided by number of weeks between the IVB treatments (exact dates used).
 - v. The rate of vascular progression for eyes without recurrence was then calculated by the number of DD radial progression between the IVB treatment and 54 weeks AA

divided by number of weeks between the IVB treatment and 54 weeks AA (exact dates used).

- vi. Any difference in extent of vascular progression (in number of DD) or in rate of vascular progression (in number of DD/week) between eyes with or without recurrence was evaluated by a mixed effect model. In the model, the subject unit was infant, the correlation structure between eyes was compound symmetric, and the fixed effect was without and with recurrence.

Results

A total of 241 infants (471 eyes, i.e., 11 unilateral cases) treated with IVB monotherapy for ROP in zone I or zone II posterior were eligible for review in this study (55 infants from the BEAT-ROP clinical trial and 186 infants treated following the BEAT-ROP clinical trial). Thirty-one infants without follow-up examinations extending to 65 weeks were excluded from analysis, as well as 21 infants who had died prior to 65 weeks.

The demographics, infant characteristics, and initial treatment information are summarized for all infants and subdivided between those without and with recurrence (Table 1). The recurrences were further subdivided between those with ROP stage 3+ and APROP at initial treatment (Table 1). Of all 241 study infants, the average BW was 714 grams (± 200 confidence interval [CI], ranging from 340 to 1590), the average GA was 24.7 weeks (± 1.7 CI, ranging from 22 to 32), 131 (54.4%) were male, and 136 (56.4%) were Hispanic. Most of the infants (230 [95.4%]) had bilateral ROP; 222 (92.1%) had ROP stage 3+, and 181 (75.1%) had ROP in zone II posterior (all ROP stage 3+), while 60 (24.9%) had ROP in Zone I (41 with ROP stage 3+ and 19 with APROP). The average AA at the initial treatment was 35.9 weeks (± 2.6 CI, ranging from 31 to 49). These 241 infants were followed after the initial treatment for an average of 132.6 weeks (± 90.2 CI, ranging from 19 to 384) with the last follow-up examination at an average of 168.5 weeks AA (± 89.9 CI, ranging from 66 to 417). For those without recurrent ROP, the average follow-up was for 131.2 weeks (± 89.7 CI, ranging from 19 to 370), while for those infants with recurrent ROP, the average follow-up was for 148.4 weeks (± 95.9 CI, ranging from 39 to 384).

Incidence of Recurrence

Twenty of 241 infants (8.3%) with 34 of 471 eyes (7.2%) had recurrent ROP (see Table 1). Figure 1 shows the Kaplan-Meier survival curve subdivided by initial appearance (ROP stage 3+ compared to APROP). Infants treated for APROP had significantly greater recurrences following initial treatment (31.6% recurrence incidence in those with APROP, versus 6.3% recurrence incidence in those with ROP stage 3+, $P < 0.001$). Details of recurrence for each infant are given in Table 2.

Risk Factors for Recurrence

Six baseline characteristics, including *immaturity factors* (BW [$P < 0.001$], GA [$P < 0.001$], zone [$P = 0.003$]); *initial treatment appearance* (APROP [$P = 0.002$]); and *health risk factors*

(single risk factor of NEC [$P=0.035$] and cumulative health issues noted by duration of hospitalization [$P<0.001$]), were significantly different between infants without and with recurrence of ROP (see Table 1).

Infants with ROP recurrence were significantly more immature at birth than those without ROP recurrence. Average BW of recurrent ROP infants (600 grams [± 113]) was significantly lower than the non-recurrent ROP infants (724 grams [± 203]), $P<0.001$. Average GA was significantly lower in recurrent ROP group (23.9 weeks [± 0.9]) compared to non-recurrent ROP infants (24.8 weeks [± 1.8]), $P<0.001$. Eleven of 60 zone I infants recurred (18.3%), while nine of 181 zone II posterior infants (5.0%) recurred, $P=0.003$. Additionally, in the recurrent ROP infants, the BW of APROP infants (512 grams [± 73]) was significantly lower than the ROP stage 3+ infants (638 grams [± 107]), $P=0.017$.

The results of stepwise logistic regression analysis with bidirectional elimination of all clinical and demographic data identified three risk factors for developing recurrent ROP: 1) the initial Type1 ROP appearance of APROP ($P=0.006$); 2) increased duration of hospital stay ($P=0.010$); and 3) decreased BW ($P=0.024$). Infants initially treated for APROP were found to have a 5-fold increased risk of developing recurrent disease than those infants treated for ROP stage 3+ (95% CI, ranging from 1.59 to 16.4). An average of one week increase in hospital stay increased the risk of recurrence by a factor of 1.04 (95% CI, ranging from 1.01 to 1.07). Every 100 grams of BW decrease was associated with an increased risk of recurrence by a factor of 1.56 (95% CI, ranging from 1.06 to 2.30).

Risk Period of Recurrence

Recurrent ROP was seen in 20 infants between 45.7 and 64.9 weeks AA (mean 51.2 weeks ± 4.6). Eighteen of 20 infants (90.0%) and 32 of 34 eyes (94.1%) developed recurrence within a 10-week window from ≈ 45 to ≈ 55 weeks AA. There were 2 infants treated initially for APROP who developed recurrence at 57.9 weeks AA and 64.9 weeks AA (see Figure 1 and Table 2).

Patient # 5 developed ROP stage 4A temporal retinal detachment in the right eye and received a second IVB injection with final outcome of macular dragging, but resolution of the ROP stage 4A detachment. Patient #13 returned for follow up with ROP stage 5 right eye and ROP stage 4B left eye and was referred for vitrectomies, which were unsuccessful, and did not receive a second injection of IVB (Table 2). Both of these patients were previously detailed in the BEAT-ROP clinical trial.¹²⁾

Clinical Characteristics of Recurrence

Clinical characteristics of recurrence included return of *plus disease* (in 20/20 (100%) infants [and 34/34 (100%) eyes] with recurrence) and *neovascularization* (seen clinically, but best seen by fluorescein angiography, which was performed on 9 infants at the time of recurrence) at one or two specific sites in 12/14 (85.7%) infants [and 22/26 (84.6%) eyes] with ROP stage 3+ recurred at *both* the initial ridge and extraretinal fibrovascular proliferative complex (R+EFP) as well as at the advancing edge. The only exceptions to this were 2/14 (14.3%) infants [and 4/26 (15.4%) eyes], which had non-confluent neovascularization initially and recurred only at the advancing edge (see Table 2). However,

6/6 (100%) infants [and 8/8 (100%) eyes] with APROP recurred *only* at the advancing edge. Following the second IVB treatment, plus disease did not decrease, but neovascularization resolved in all cases.

A third characteristic of recurrence was a decreased extent of retinal vascularization as evidenced by progression of the advancing edge only a mean of 1.76 DD (± 1.0 CI; range 0.48 to 4.75DD; n=25 eyes) from its location at time of initial treatment to that at the time of recurrence. This was significantly less ($P=0.024$) than the extent of progression of retinal vascularization seen in eyes without recurrence mean of 4.48 DD (± 1.46 CI, range 1.41 to 7.60 DD; n=25 eyes). Similarly, there was also a significantly decreased rate of retinal vascularization in eyes with ROP recurrence mean of 0.11 DD/week (± 0.05 CI, range 0.03 to 0.20; n=25 eyes) versus in those without ROP recurrence mean of 0.23 DD/week (± 0.07 CI, range 0.07 to 0.36; n=25 eyes; $P=0.032$).

Figures 2C and 2D show an eye that recurred and required *a second* injection to induce regression for ROP stage 3+ with 2 recurrence sites. Figure 3C and 3D show an eye that recurred and required *a second* injection for APROP with 1 recurrence site. Figures 4A and 4B show an eye that required only *one* injection to induce regression for ROP stage 3+. Figures 4C and 4D show an eye that required only *one* injection to induce regression for APROP. Figures 4E and 4F show an eye that required *no* injection (for ROP stage 2) and spontaneously regressed, for comparison. These five infants (in Figures 2 to 4) were selected because they had similar BW (BW ranging from 450 to 510 grams) and GA (GA ranging from 23 to 24 weeks).

Discussion

There have been several case reports of late recurrence following treatment of ROP stage 3+ or APROP with IVB monotherapy^{27, 28} and following combined treatment utilizing laser therapy with intravitreal ranibizumab²⁹ or with IVB.^{27, 30–32} In each of these reports, close follow-up (every 1 or 3 weeks) was not performed beyond 55 weeks AA; however, standard follow-up recommendations have not been established by ophthalmologic studies reviewing prospective data. Also, not surprisingly, there are reports of failure following use of IVB monotherapy for ROP stages 4B and 5 because treatment was performed too late and membrane formation was too extensive.^{33–35}

Of greatest interest in the literature is a case series of 9 patients (17 eyes) treated initially with IVB monotherapy for ROP stage 3+ or APROP at a mean of 34.1 weeks AA with recurrences developing at mean of 49.3 weeks AA. Thus, they found an interval between initial IVB monotherapy and recurrence with a mean of 15.2 weeks.²² Authors of this case series discussed the return of plus disease and the re-appearance of neovascularization at one or two sites: at the R+EFP and/or at the advancing edge of retinal vascularization. This is identical to our findings.

From these previous reports of recurrence and the results of this study, several clinical management issues can be recognized: IVB monotherapy is a very effective recent addition to the treatment armamentarium for ROP with <8% incidence of recurrence in infants or

eyes requiring a second IVB treatment. There is only one case series from Turkey, which reports need of a third injection of IVB;³⁶ however, there are no published cases of infants requiring a third administration of IVB in developed nations, to our knowledge. If an infant has identified risk factors (APROP at the time of initial treatment, extended duration of hospitalization due to multiple clinical risk factors, or very low BW) this should cause clinicians to be more vigilant and to examine more frequently and possibly longer.

Clinical characteristics of return of plus disease and re-appearance of neovascularization [at either the original site of the ridge and extraretinal fibrovascular proliferative complex \pm at the advancing edge of retinal vascularization²² (\pm at other currently unknown sites)] are required to diagnose the need for re-treatment of recurrent Type 1 ROP following IVB monotherapy. Additionally, a small extent and a slow rate of advancement of retinal vascularization is noted (see Figures 2 and 3), which is especially noticeable in zone I cases, and should be considered a warning sign of possible imminent recurrence. When an infant was initially treated for ROP stage 3+ with **confluent** EFP, recurrence was observed and documented at two distinct sites: at the original R+EFP and at the advancing edge of retinal vascularization (see Figure 2). In comparison, when an infant was initially treated for APROP or ROP stage 3+ with only **nonconfluent** EFP, recurrence was observed and documented at only one site: at the advancing edge of retinal vascularization (see Figure 3). While the location of the neovascularization could be seen with the indirect ophthalmoscope with a 20 or 28 Diopter lens and with fundus photography, it was best documented by fluorescein angiography with the RetCam imaging system (see Figure 2C and 2D and Figure 3C and 3D). Although we were unable to perform fluorescein angiography in all cases of recurrence, based on the photographs taken in all recurrences and the available fluorescein angiograms (9 infants), it is our impression that Figures 2 and 3 are representative of the two common patterns of recurrence.

Since there is a virtual cessation of retinal vessel advancement following the second IVB injection, there is often a large avascular peripheral area of retina that remains undeveloped, especially in former zone I and APROP cases. Successful IVB treatment (inducing *regression* of ROP) is usually recognized before 65 weeks AA by a rapid advancement of retinal vascularization from the original R+EFP in ROP stage 3+ (see Figures 4A and 4B) or from the original FNV in APROP (see Figures 4C and 4D), toward, but not necessarily to, the ora serrata in the most immature infant eyes.^{23, 24} Anecdotally, *spontaneous regression* of ROP is also accompanied by rapid advancement of retinal vascularization before 65 weeks AA (see Figures 4E and 4F) toward, but not necessarily to, the ora serrata in the most immature infant eyes.^{23, 24} In all cases of regressed ROP, whether following two, one, or no IVB injections, it is our experience and belief that unless extensive tractional elements are present, no further intervention, such as laser ablation, is indicated for the remaining permanently undifferentiated, peripheral, avascular retina.

Timing of the administration of IVB monotherapy is critical

IVB is an ideal treatment when ocular (and blood) VEGF levels are high with sufficient neovascularization (Phase 2) and rather than when VEGF levels are low with minimal neovascularization (before Phase 2).³⁷ IVB can inhibit normal development of the retina if

administered in Phase 1, and thus, IVB cannot be utilized as *prophylactic* treatment.³⁷ Similarly, IVB is ideally administered prior to the development of advancing retinal detachment (after Phase 2) as has been demonstrated by reports of accelerated retinal detachment following IVB treatment for ROP stages 4B and 5,^{33–35} and therefore, IVB cannot be utilized as *salvage* therapy. This is the clinical experience in diabetic patients who develop accelerated retinal detachment associated with IVB administration when tractional membranes are extensive.³⁸

Appropriate follow-up examinations are mandatory for successful clinical management. Recurrence of ROP following IVB monotherapy should now be more easily and promptly identifiable by treating ophthalmologists. Since the incidence of recurrence is <8%, most infants will demonstrate regression with rapid progression of retinal vessels toward the ora serrata. The risk factors for recurrence are known to be immaturity (lower BW and GA, and zone 1 ROP), APROP, and cumulative health issues (i.e. duration of hospital stay and NEC requiring surgery), which should heighten vigilance during follow-up examinations. The risk period of recurrence of ROP following IVB, although more delayed, is predictable with a critical 10-week recurrence window from ≈ 45 to ≈ 55 weeks AA, with recurrence developing at a mean of 51.2 weeks AA, and infrequently, as late as 65 weeks AA, as shown by this series of recurrences. We believe collaborative consensus groups should consider amending the current guidelines of weekly examinations until 70 weeks AA³⁹ in light of the knowledge of this report to better reflect the available evidence. We believe clinicians should be more vigilant in their examinations for recurrence during the 45 to 55 week AA “recurrence window” and should perform more frequent examinations during this time. Before and after this critical period of time, we believe examinations can be less frequent until retinal vascularization is completed. However, we believe those initially treated for APROP are at increased risk for recurrence and should be monitored closely until at least 65 weeks AA (as was the case of the delayed recurrences in this series).

There are several appearances of regressing ROP in the first few weeks following initial treatment with IVB, with the retinal vessels ranging from the appearance of vascular projections from the former R+EFP without a defined new ridge to an advancing edge with a defined ridge that may thicken. However, clinicians can easily distinguish these normal regression patterns from recurrence of ROP by the continued resolution of plus disease and the lack of continued progression of formation of dilated, hyperemic vessels (neovascularization) in the former R+EFP. Also, the appearance of these regression patterns is often much earlier than the time period in which recurrence usually occurs (≈ 45 to ≈ 55 weeks AA). Furthermore, it is our clinical impression from anecdotal experience that after treatment with IVB the plus disease resolves rather quickly, i.e., within a couple of days, while the R+EFP can take several weeks to resolve, depending on how extensive the neovascularization was prior to treatment and/or retreatment. However, it is our clinical impression that this delayed resolution of R+EFP can be discerned from early recurrence by the appearance of closed gray to white vessels at the site of the former R+EFP.

The strengths of this study are that the large sample size with all infants following the same examination, documentation, and treatment protocols utilized in the BEAT-ROP clinical trial, and that the same clinical information is available for all of these infants who are all

documented photographically, with last mean follow-up at age 148.1 weeks AA, over a period of almost 7 years.

The limitations of this study are that much of what we now recognize about recurrence has been learned after the initial documentation protocol was designed. Thus, patterns of recurrence were not known from the initial time that IVB monotherapy began to be utilized for treatment warranted ROP. Further, fluorescein angiography was not available at some of the centers, and the importance of doing fluorescein angiography at the time of recurrence was not known. Thus, fluorescein leakage at the 2 specific sites with recurrence was not documented for all infants. Fortunately, the changes in the critical sites of recurrence in the retina were observed by indirect ophthalmoscopy and were documented by fundus photography for all recurrences. Further, it would have been ideal to sample prospectively each infant's blood VEGF level before each IVB injection and the bevacizumab blood level for a few months after each IVB injection to establish any relationship to severity of initial disease and to the development of recurrence. Additionally, perhaps the screening and treatment of this study's population with more Hispanic patients than those of other published ROP clinical trials may have influenced the clinical findings to some degree.

As with any treatment involving injection of a drug not FDA approved for intravitreal use in premature infants for ROP, further investigation to determine the long-term safety concerns (both ocular and systemic) of IVB monotherapy should be systematically performed. More investigation into the most efficient drug and dose of an intravitreal anti-VEGF drug for ROP is also needed. Ultimately, a higher dose of an "ideal" anti-VEGF drug may be appropriate for those infants with higher risk of recurrence of ROP following anti-VEGF therapy. Conversely, a lower dose of an "ideal" anti-VEGF drug may be appropriate for those infants who have lower risk of recurrence of ROP following anti-VEGF therapy.

In summary, IVB is a very effective treatment modality for ROP. Recurrence is very important to recognize promptly, and infants should be followed closely until they are beyond the time period during which recurrence has been reported. We hope this report can help clinicians feel more comfortable treating with IVB monotherapy and following patients for recurrence with knowledge that (1) the incidence of recurrence is low (8.3% in this study); (2) some infants at increased risk for recurrence are identifiable (initial treatment for APROP, multiple ROP risk factors requiring prolonged hospitalization, especially if NEC requiring surgery has occurred, and extremely low BW); (3) recurrence risk period is limited, although extended compared to laser therapy, with the vast majority of cases recurring during a critical time period (≈ 45 to ≈ 55 weeks AA) and before 65 weeks AA; and 4) with the return of plus disease and lack of progression of retinal vascularization, there are two specific locations to re-examine for recurrent neovascularization. With this knowledge, we believe collaborative consensus groups may be able to amend the current screening guidelines to help the clinician more safely and efficiently monitor for recurrence following treatment with IVB.

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Abbreviations

ROP	retinopathy of prematurity
APROP	aggressive posterior retinopathy of prematurity
CRYO-ROP	cryotherapy for retinopathy of prematurity
ETROP	early treatment for retinopathy of prematurity
BEAT-ROP	bevacizumab eliminates angiogenic threat of retinopathy of prematurity
VEGF	vascular endothelial growth factor
ICROP-R	International Classification for Retinopathy of Prematurity-Revisited
FDA	federal drug administration
R+EFP	ridge and extraretinal fibrovascular proliferative complex
FNV	flat neovascularization
BW	birth weight
GA	gestational age
PNA	postnatal age
AA	adjusted age
APGAR	backronym for Dr. Virginia Apgar's score: appearance, pulse, grimace, activity, respiration
CI	confidence interval
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
PDA	patent ductus arteriosus
DD	disc diameters

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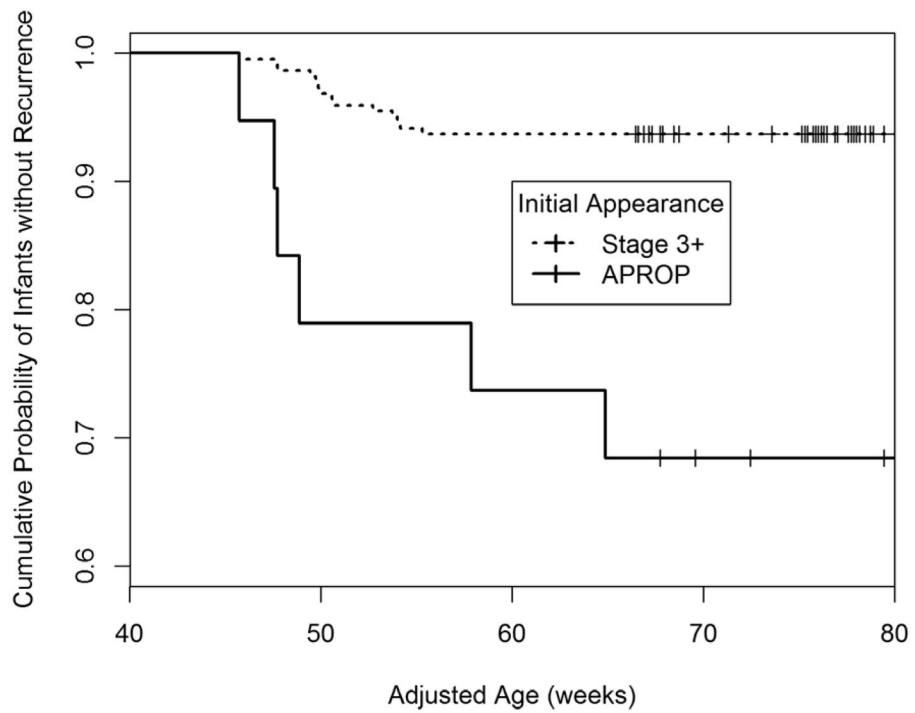


Figure 1. The Kaplan-Meier survival curve for the probability for **NO RECURRENCE** with Type 1 ROP was found for infants **Stage 3+** to be 93.7% (208/222) and for infants with **APROP** to be 68.4% (13/19).

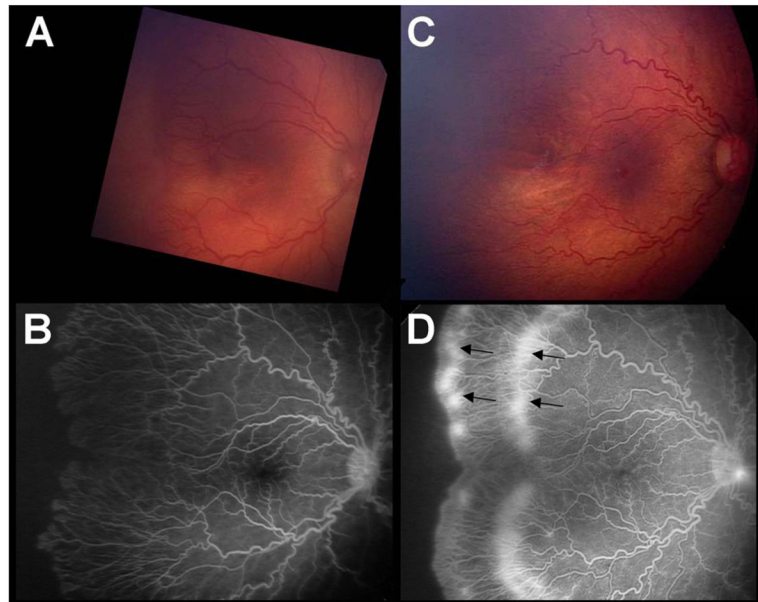


Figure 2.

The right eye of Patient 9 had **ROP stage 3+** requiring 2 injections of bevacizumab for initial and recurrent disease (470 grams, 24 weeks at birth). A. Photograph just prior to first injection for ROP stage 3+ ROP (35.1 weeks AA). B. Fluorescein angiogram of same eye (A) after completion of retinal vascularization (77.9 weeks AA). C. Photograph and D. Fluorescein angiogram just prior to second injection for recurrent ROP at two sites (52.7 weeks AA). (Arrows).

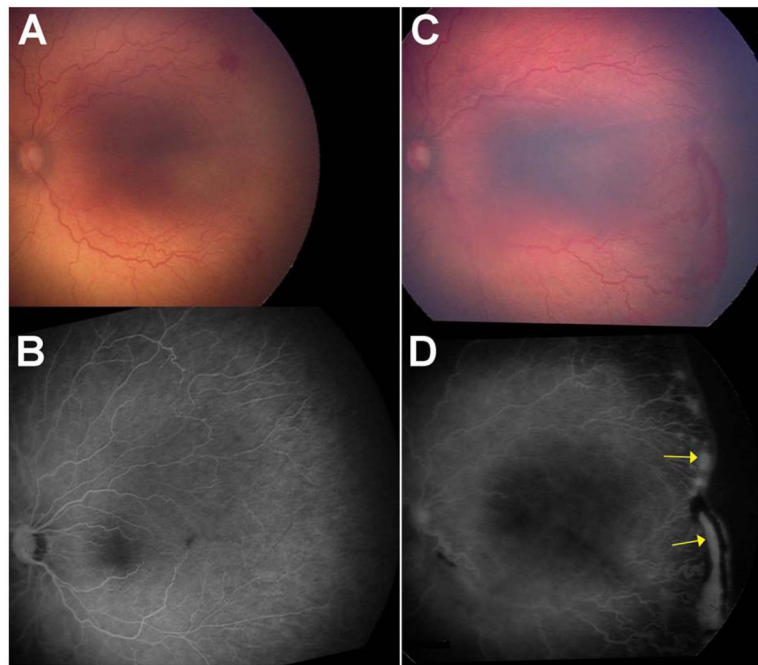


Figure 3.

The left eye of Patient 2 had **APROP** requiring 2 injections of bevacizumab for initial and recurrent disease (450 grams, 23 weeks at birth). A. Photograph just prior to first injection for APROP (34.0 weeks AA). B. Fluorescein angiogram of same eye (A) after completion of retinal vascularization (96.0 weeks AA). C. Photograph and D. Fluorescein angiogram just prior to second injection for recurrent ROP at a single site (48.9 weeks AA). (Arrows).

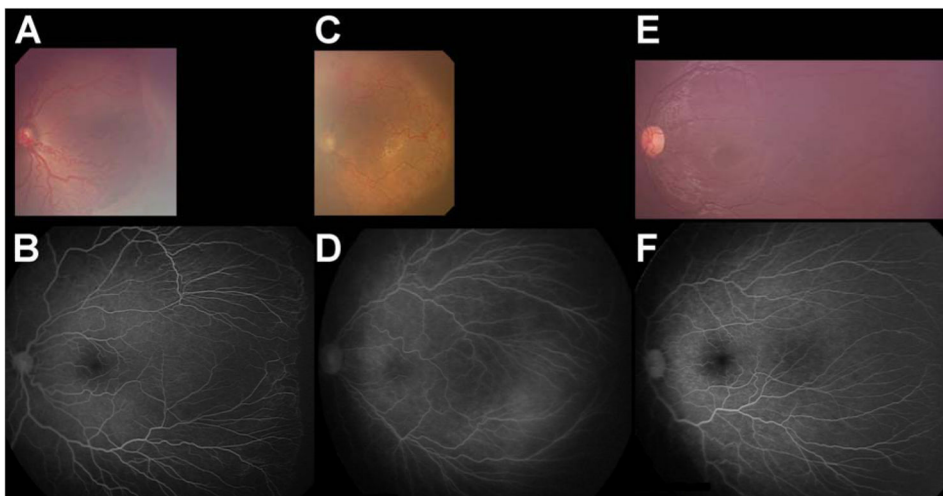


Figure 4.

The eyes of infants matched for BW (490 to 510 grams) and GA (23 to 24 weeks) at time of initial successful injection of bevacizumab (A) for **ROP stage 3+** or (C) for **APROP**, and (E) for no treatment for **spontaneously regressed ROP** compared to the same eyes when retinal vascularization reached the fullest extent possible based on GA²¹ in B, D, and F, respectively. A. Photograph of right eye treated for ROP Stage 3+ (495 grams, 23 weeks at birth) at 35.6 weeks AA. B. Fluorescein angiogram of same eye (A) after completion of retinal vascularization (79.6 weeks AA). C. Photograph of right eye treated for APROP (490 grams, 24 weeks at birth) at 34.6 weeks AA. D. Fluorescein angiogram of same eye (C) after completion of retinal vascularization (131.1 weeks AA). E. Photograph of right eye untreated (spontaneously regressed ROP stage 2) (510 grams, 23 weeks at birth) at 113.4 weeks AA. F. Fluorescein angiogram of same eye (E) after completion of retinal vascularization (113.4 weeks AA).

Table 1
 Summary: Demographics, infant characteristics, and initial treatment by recurrent status (N=241 Infants, 471 Eyes)

Variable	Demographics (N=241 Infants, 471 Eyes)				
	All ROP	Non-Recurrent ROP	All Recurrence	Recurrent ROP	
				Initial Type 1 ROP Appearance	APROP
Number of Infants (%)	241	221 (91.7%)	20 (8.3%)	14	6
Number of Eyes (%)	471	437 (92.8%)	34 (7.2%)	26	8
Treated Eye at the Initial (1 st) Treatment					
One Eye Only (%)	11 (4.6%)	10 (4.5%)	1 (5.0%)	1	0
Both Eyes (%)	230 (95.4%)	211 (95.5%)	19 (95.0%)	13	6
Infant Characteristics (N=241 Infants)					
Birth Weight (grams, mean ± SD, [min, max]) <i>P</i> <0.001	714 (± 200) [340 to 1590]	724 (± 203) [340 to 1590]	600 (± 113) [450 to 885]	638 (± 107) [470 to 885] <i>P</i> =0.017	512 (± 73) [450 to 640]
Gestational Age (weeks, mean ± SD, [min, max]) <i>P</i> <0.001	24.7 (± 1.7) [22 to 32]	24.8 (± 1.8) [22 to 32]	23.9 (± 0.9) [22 to 26]	24.1 (± 0.8) [23 to 26]	23.3 (± 0.8) [22 to 24]
Sex (Male, %)	131 (54.4%)	120 (54.3%)	11 (55.0%)	7	4
Race (%)					
White	56 (23.2%)	54 (24.4%)	2 (10.0%)	1	1
Black	35 (14.5%)	30 (13.6%)	5 (25.0%)	5	0
Hispanics	136 (56.4%)	124 (56.1%)	12 (60.0%)	8	4
Others	14 (5.8%)	13 (5.9%)	1 (5.0%)	0	1
APGAR Score (Missing 2 - born at home)					
At One Minute (score, mean ± SD, [min, max])	4.9 (± 2.4) [0 to 9]	5.0 (± 2.4) [0 to 9]	4.5 (± 2.0) [1 to 7]	4.5 (± 2.0) [2 to 7]	4.5 (± 2.3) [1 to 7]
At Five Minutes (score, mean ± SD, [min, max])	6.8 (± 1.8) [1 to 10]	6.8 (± 1.8) [1 to 10]	6.7 (± 1.9) [1 to 9]	7.0 (± 1.4) [4 to 9]	6.0 (± 2.7) [1 to 8]
Intra Ventricular Hemorrhage (%)					
0	152 (63.1%)	143 (64.7%)	9 (45.0%)	8	1
1	30 (12.5%)	267 (12.2%)	3 (15.0%)	1	2
2	18 (7.5%)	16 (7.2%)	2 (10.0%)	2	0
3	12 (5.0%)	11 (5.0%)	1 (5.0%)	0	1

Demographics (N=241 Infants, 471 Eyes)						
Variable	All ROP	Non-Recurrent ROP	All Recurrence	Recurrent ROP		
				Stage 3+	Initial Type 1 ROP Appearance	APROP
4	29 (12.0%)	24 (10.9%)	5 (25.0%)	3	2	2
Respiratory Distress Syndrome (%)	258 (100%)	238 (100%)	20 (100%)	14	6	6
Patent Ductus Arteriosus (%)	96 (439.8%)	87 (39.4%)	9 (45.0%)	5	4	4
Sepsis (%)	65 (27.0%)	59 (26.7%)	6 (30.0%)	3	3	3
Necrotizing Enterocolitis (%) P=0.035	48 (19.9%)	40 (18.1%)	8 (40.0%)	6	2	2
Hospital Duration (weeks, mean \pm SD, [min, max]) P<0.001	20.2 (11.9) [4 to 118]	19.2 (\pm 11.6) [4 to 118]	29.2 (\pm 13.5) [14 to 67]	29.9 (\pm 15.6) [14 to 67]	27.4 (\pm 7.4) [17 to 37]	
Initial Treatment (N=241 Infants)						
Initial Type 1 ROP Appearance P=0.002						
Stage 3+ (%)	222 (92.1%)	208 (94.1%)	14 (70.0%)			N/A
APROP (%)	19 (7.9%)	13 (5.9%)	6 (30.0%)			
Zone P=0.003						
I (%)	60 (24.9%)	49 (22.2%)	11 (55.0%)	5	6	6
Posterior II (%)	181 (75.1%)	172 (77.8%)	9 (45.0%)	9	0	0
Adjusted Age at the Initial Treatment (weeks, mean \pm SD, [min, max])	35.9 (\pm 2.6) [31 to 49]	36.0 (\pm 2.6) [31 to 49]	35.0 (\pm 2.1) [32 to 39]	35.5 (\pm 2.2) [32 to 39]	33.8 (\pm 1.4) [32 to 35]	
Weeks of Follow-up (Initial Treatment to Last Follow-up Visit (weeks, mean \pm SD, [min, max]))	132.6 (\pm 90.2) [19 to 384]	131.2 (\pm 89.7) [19 to 370]	148.4 (\pm 95.9) [39 to 384]	149.3 (\pm 88.7) [39 to 357]	146.3 (\pm 120.2) [59 to 384]	
Adjusted Age at Last Follow-up Visit (weeks, mean \pm SD, [min, max])	168.5 (\pm 89.9) [66 to 417]	167.1 (\pm 89.5) [66 to 405]	183.4 (\pm 95.2) [77 to 417]	184.8 (\pm 88.0) [77 to 391]	180.1 (\pm 119.4) [94 to 417]	

Table 2
 Details of ROP patients with recurrence following intravitreal bevacizumab monotherapy (N=20 Infants, 34 Eyes)

Patient	BW	GA	INITIAL (1 ST) TREATMENT				RECURRENCE (2 ND) TREATMENT				OUTCOME			
			Eyes	Type 1	Zone	PNA	AA	Eyes	NV Site(s)	Zone		PNA	AA	Interval
1	450	23	OU	APROP	1	8.7	31.7	OU	AE	2	22.7	45.7	14.0	Regressed
2	450	23	OU	APROP	1	11.0	34.0	OU	AE	2	25.9	48.9	14.9	Regressed
3	490	24	OU	APROP	1	10.6	34.6	OD	AE	2	23.7	47.7	13.1	Regressed
4	490	24	OU	APROP	1	10.3	34.3	OS	AE	2	40.9	64.9	30.6	Regressed
5	550	22	OU	APROP	1	10.6	32.6	OD	AE	2	35.9	57.9	25.3	OD 4A
6	640	24	OU	APROP	1	11.4	35.4	OS	AE	2	23.6	47.6	12.3	Regressed
Mean (APROP)	512	23.3				10.4	33.8				28.8	52.1	18.4	
7	605	24	OU	3+*	1	9.6	33.6	OU	AE	2	25.4	49.4	15.9	Regressed
8	750	24	OU	3+*	2	8.1	32.1	OU	AE	2	23.7	47.7	15.6	Regressed
9	470	24	OU	3+	1	11.1	35.1	OU	AE & R+EFP3	2	28.7	52.7	17.6	Regressed
10	515	24	OU	3+	2	10.4	34.4	OU	AE & R+EFP3	2	25.9	49.9	15.4	Regressed
11	550	23	OU	3+	1	15.9	38.9	OU	AE & R+EFP3	2	30.7	53.7	14.9	Regressed
12	580	24	OU	3+	2	13.4	37.4	OU	AE & R+EFP3	2	26.6	50.6	13.1	Regressed
13	590	24	OU	3+	2	11.4	35.4	OU	AE & R+EFP3	2	26.6	50.6	15.1	OD 5/OS 4B
14	590	23	OU	3+	1	9.4	32.4	OU	AE & R+EFP3	2	22.7	45.7	13.3	Regressed
15	650	24	OU	3+	1	9.7	33.7	OU	AE & R+EFP3	2	26.0	50.0	16.3	Regressed
16	660	25	OU	3+	2	12.1	37.1	OS	AE & R+EFP3	2	24.8	49.8	12.7	Regressed
17	660	24	OU	3+	2	11.0	34.0	OU	AE & R+EFP3	2	24.7	47.7	13.7	Regressed
18	700	26	OU	3+	2	11.1	37.1	OU	AE & R+EFP3	2	28.0	54.0	16.9	Regressed
19	730	24	OU	3+	2	14.1	38.1	OU	AE & R+EFP3	2	20.1	54.1	16.0	Regressed
20	885	25	OD	3+	2	12.1	37.1	OD	AE & R+EFP3	2	30.3	55.3	18.1	Regressed
Mean (Stage 3+)	638	24.1				11.4	35.5				26.0	50.8	15.3	
Overall Mean	600	23.9				11.1	35.0				26.8	51.2	16.2	

BW = Birth Weight (grams); GA = Gestational Age (weeks); PNA = Postnatal Age (weeks); AA = Adjusted Age (weeks); NV = Neovascularization; [1] AE = Advancing Edge; [2] R+EFP = Initial Ridge + Extraretinal Fibrovascular Proliferative Complex; Interval between 1ST and 2ND treatments (weeks);

non-confluent EFP Initially; 4A = partial retinal detachment, macula on; 4B = partial retinal detachment, macula off; 5 = total retinal detachment.

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