Continuing Medical Education:

Involution patterns of retinopathy of prematurity after treatment with intravitreal bevacizumab: implications for follow-up

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Assess early regression rates after treatment with intravitreal bevacizumab for retinopathy of prematurity
2. Determine the degree of regression in the short term after treatment with intravitreal bevacizumab for retinopathy of prematurity
3. Evaluate patterns of revascularization after treatment with intravitreal bevacizumab for retinopathy of prematurity
4. Distinguish long-term outcomes after treatment with intravitreal bevacizumab for retinopathy of prematurity

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Involution patterns of retinopathy of prematurity after treatment with intravitreal bevacizumab: implications for follow-up

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Abstract

Purpose To describe involution patterns following monotherapy with intravitreal bevacizumab injection (IVB) for type 1 retinopathy of prematurity (ROP) in zone I or zone II posterior.

Methods A retrospective chart review of infants treated with IVB from January 2010–April 2014. Infants with minimum of 82 weeks postmenstrual age at last follow-up were included. Primary outcome was timing of involution of type 1 ROP for the first 12 weeks post treatment. Secondary outcomes were development of any recurrence and structural outcome at last follow-up. Retinal examination records, fundus, and fluorescein angiography images were reviewed.

Results Twenty-eight eyes were included. Average follow-up post treatment was 33.9 ± 9.7 months (range 21.4–61.9). Cumulative frequency of regression of plus disease was seen in 73.3, 86.7, and 100% of eyes by days 3, 5, and 8, respectively. Regression of both stage 3 and plus disease was observed in 29, 82, 88, and 100% by weeks 1, 2, 3, and 4, respectively. Within the first 3 months, 17/28 eyes developed recurrence to stage 1 or 2 after regression. None developed recurrence of plus disease. By the end of 3 months 18% of eyes vascularized into zone III. At a mean of 24 ± 17.3 months, 39% of eyes were not vascularized into zone III as seen on fluorescein angiography with scleral indentation.

Conclusion Our experience suggests regression of plus disease and stage 3 are

expected within the first 4 weeks after bevacizumab treatment. Recurrence may occur despite initial regression and requires careful follow-up.

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Introduction

Anti-vascular endothelial growth factors are increasingly used in the management of retinopathy of prematurity (ROP).¹ Off label use of bevacizumab has been shown to be an effective treatment for type 1 ROP.^{2–5}

Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) randomized trial reported significant treatment benefit with bevacizumab over laser for stage 3 plus ROP in zone I.² However, reports of late recurrence and development of retinal detachment necessitate frequent follow-up for an extended time period post treatment.^{6,7} Information on involution patterns following this treatment modality is not available.

Involution patterns for non-threshold ROP were studied previously.^{8–10} In addition, the process of involution of threshold disease after treatment with diode laser photocoagulation was described.¹¹ There is scarcity of evidence to guide clinicians on forms of recurrence, frequency and length of follow-up, and involution patterns that may lead to unfavorable structural outcomes following treatment with intravitreal bevacizumab (IVB). The purpose of this study is to describe timing of regression following monotherapy with IVB for type 1 ROP

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in zone I or zone II posterior and its relationship to structural outcomes.

Materials and methods

We performed a retrospective chart review of all infants with ROP treated at our institution with intravitreal bevacizumab injection (Avastin; Genentech Inc, San Francisco, CA, USA) from January 2010 to April 2014. The study was approved by the hospital's research ethics board. At this institution, we now offer treatment with IVB as an alternative treatment to laser for type 1 ROP in zone I or zone II posterior. Since the use of IVB for anterior disease has not been subjected to randomized controlled trials, this treatment was only offered for sick infants that would not tolerate laser treatment under general anesthesia. These infants were not included in this study. An informed consent was obtained for each treated infant as described by our group previously.^{12,13} Bevacizumab 0.625 mg/0.025 ml was injected into the vitreous cavity with a 30-gauge needle at 1.0 mm posterior to the corneoscleral junction. All injections were performed in the neonatal intensive care unit under topical anesthesia. All infants received a single injection of bevacizumab.

To capture theoretical recurrences and the latest reported recurrence of treatable ROP in the literature, a minimum of 82 weeks post-menstrual age (PMA) at last follow-up was required for inclusion in this study.^{6,7,14} Demographic data on gestational age, birth weight and PMA at time of treatment and at last follow-up were collected.

The primary outcome of the study was time to involution of type 1 ROP in the first 3 months post treatment. Secondary outcomes were development of any recurrence and structural outcome at last follow-up. Structural outcome was defined as in the Early Treatment for Retinopathy of Prematurity.¹⁵ Results of fundus examination for each visit were collected. Consensus by the two treating ophthalmologists (NT, KM) was sought for retinal examination findings including stage, zone and the presence or absence of plus disease as stated in the

ROP examination record, fundus images, and fluorescein angiography (FFA) (RetCam Clarity Medical Systems, Pleasanton, California). Follow-up was performed at day one post injection, then once more during the first week as per clinical need, then weekly until resolution of neovascularization. Longer term follow-up was according to response based on the follow-up screening guidelines.¹⁶ Beyond 45 weeks of PMA follow-up was individually tailored based on extent of retinal vascularization. Involution of ROP in this study was defined as regression of disease severity by at least one stage and absence of plus disease.

SAS for Windows software version 9.4, (SAS Institute, Cary, NC, USA) was used for statistical analysis. PROC MIXED with RANDOM and REPEATED statement was used for the correlation calculations between the two eyes in bilateral treated cases. Interclass correlation (ICC) was estimated using an unconditional random effect model. Findings on time to regression were described in frequency tables and cumulative frequency curves.

Results

A total of 26 infants were treated with IVB. Three were excluded because they had not reached follow-up of 82 weeks of PMA. Four had treatment for disease in anterior zone II and therefore were excluded. Two infants were excluded because we did not have complete data on each visit post treatment. Twenty eight eyes of 17 patients fulfilled the inclusion criteria and were analyzed for involution of ROP. Baseline characteristics of included infants are shown in Table 1.

ROP was diagnosed in zone I in 10 eyes and in zone II posterior in 18 eyes. All eyes had stage 3 plus ROP, except for three in zone I that had stage 3 with preplus disease.

High correlation was found between the two eyes with an ICC of 0.9 (95% CI: 0.85, 0.99). Because of high correlation, we included the eye that took longer to regress in the time to involution analysis. Cumulatively, regression by at least one stage and absence of plus disease was observed in 29%, 82%, 88%, and 100% of eyes by weeks 1, 2, 3, and 4 post treatment, respectively.

Table 1 Baseline characteristics of infants with type 1 retinopathy of prematurity treated with intravitreal injection of bevacizumab

Number of patients	17
Number of eyes	28
Male/Female	11/6
BW, mean $\pm$ SD (median, range)	727 $\pm$ 117 g (750,540-920)
GA, mean $\pm$ SD (median, range)	25.2 $\pm$ 1.3 weeks (25.1,23.3-27.6)
PMA at treatment, mean $\pm$ SD (median, range)	37.4 $\pm$ 1.8 weeks (37.2,35.3-41.7)
PMA at last follow-up, mean $\pm$ SD (median, range)	184.4 $\pm$ 42.1 weeks (173.1,127.9-304.2)

Abbreviations: BW, Birth weight; GA, Gestational age; PMA, post menstrual age.

Mean number of days to regression was 11 ± 5.8 (median 8, range 3–23). Regression of plus disease was observed in 73.3%, 86.7%, and 100% of eyes by days 3, 5, and 8 post treatment, respectively. The mean number of days to regression of plus disease was 3.0 ± 2.0 (median 2, range 1–8). Figure 1 shows the cumulative frequency curves for involution by more than 1 stage and by plus disease.

Twenty out of 28 eyes (71%) regressed to no ROP (Figure 2), while 29% regressed to stage 1 or 2. 17/28 eyes (61%) developed recurrence of stage 1 or 2 after regression. None developed recurrence of plus disease. At 3 months post-treatment, 32%, 61%, and 7% of the eyes had no ROP, stage 1, and stage 2, respectively. Five eyes (18%) had vascularized into zone III whereas the majority (82%) remained in zone II. No eye with zone I ROP before treatment had vascularized into zone III.

At a mean final follow-up of 33.9 ± 9.7 months (range 21.4–61.9) all recurrences of stage 1 or 2 had regressed, none of the eyes required retreatment or had unfavorable structural outcome. 15 out of 17 infants (25 eyes) had at least 1 examination under anesthesia (EUA) (range 1–4) with indented peripheral retinal exam and FFA study over the course of follow-up. These examinations were coordinated with other surgical procedures that infants were booked for ($n=9$) or performed specifically for the eye examination ($n=6$). Additional 12 eyes (43%) were documented to have vascularized into zone III (total of 61%) as seen on fluorescein angiography with scleral indentation performed at a mean of 24 ± 17.3 months (range of 8–55) post treatment (Figure 3). Of the four infants (8 eyes) who did not fully vascularize, all had reached anterior zone II on indented examination and FFA and had no unfavorable structural outcomes at 2–3.1 years post injection. The two infants (3 eyes) who did not have an EUA, had vascularized into anterior zone II at last indented scleral exam 4 and 6 months post treatment and have remained well at 2.3 and 4 years of follow-up, respectively.

Discussion

This paper describes patterns of involution of type 1 ROP following treatment with IVB. Regression of plus disease occurred earlier than regression of stage 3 ROP.

All eyes showed involution by 4 weeks after treatment. Vascularization into zone III occurred in 18% of the eyes by the end of 3 months. Additional 43% of eyes (total 61%) vascularized into zone III by an average follow-up of 34 months post treatment. Although two thirds of the eyes developed stage 1 or 2 after involution, all eyes regressed to no ROP, and none required retreatment or developed unfavorable structural outcome at last follow-up.

Figure 1 Cumulative frequency curves. Involution of retinopathy of prematurity by at least one stage and resolution of plus disease over time following monotherapy with intravitreal bevacizumab injection.

The involution process following treatment with diode laser has been described.¹¹ However, pattern of involution following treatment with IVB remains unknown. Coats *et al*¹¹ reported complete involution of neovascularization in threshold ROP in 43 and 73% of the eyes at 2 and 4 weeks following treatment with laser. Compared with these findings, more eyes showed earlier involution of neovascularization in our group after IVB (82 and 100% at 2 and 4 weeks) than what has been reported following treatment with diode laser. However, complete involution in the laser study was defined as 'absence of any active neovascular tissues and absence of residual dilatation and/or tortuosity of arterioles or venules in the posterior pole without development of retinal detachment'.¹¹ To minimize variability in the subjective interpretation of disease severity of a retrospective study, we defined involution as regression of disease severity by at least one stage and absence of plus disease. We also wanted strict criteria of involution by having both regression of disease stage and plus disease. As well, we assessed disease stage at all-time points to better understand the continuous nature of the involution process over 3 months post treatment. We were able to show that it is not uncommon to develop recurrence of stage 1 or 2 ROP after regression. Importantly, all eyes showed regression to no ROP and none of the eyes required retreatment or developed unfavorable structural outcomes at last follow-up.

Figure 2 Regression of Zone 1, stage 3 retinopathy of prematurity: (a) pretreatment color fundus images and fluorescein angiography showing new vessels, (b) color fundus image of the same eye 17 days post intravitreal injection with bevacizumab showing regression to no disease.

Coats *et al*¹¹ reported that the majority of retinal detachments (RD) were diagnosed three weeks after laser treatment and were not observed in the immediate post-operative period. They reported a cumulative diagnosis of RD in 14% of the eyes at week 9 ± 3 . On the basis of these findings, they recommended follow-up examinations should continue for at least 10 weeks post laser treatment. Currently, there are no such established guidelines for follow-up regimen following treatment with bevacizumab. Delayed recurrence of active ROP has been reported with high risk of development of RD following treatment with IVB.^{2,6,7,14} The BEAT-ROP study recommended careful follow-up after IVB treatment until there is no active disease. The primary outcome in the BEAT-ROP trial was recurrence of neovascularization arising from retinal vessels and requiring retreatment by 54 weeks PMA. They reported a recurrence rate of 6% at a mean of 16 weeks after treatment with IVB. RD developed in two eyes that had recurrence in zone II posterior. Their paper, however, did not address the problem of eyes that

are not fully vascularized. Our paper identified that 18% of eyes were fully vascularized at 3 months and the majority required careful follow-up for peripheral vascularization. Hu *et al* reported 17 eyes with recurrence of active disease following initial treatment with bevacizumab. Five cases progressed to develop RD. Mean time between initial treatment and recurrence requiring treatment was 14.4 weeks with a range of 4–35 weeks. Recurrence was defined as arrest of anterior progression of vascularization with the presence of a new demarcation line, ridge or extraretinal fibrovascular proliferation (EFP) or leakage on fluorescein angiography with or without plus disease.⁶ Their definition of recurrence includes a wide range of disease severity, some of which may not meet retreatment criteria. Indeed their retreatment was not standardized but mainly performed if plus disease was present with or without EFP or EFP present with or without plus disease. Whilst presence of EFP is a worrisome sign it is still not clear whether this should qualify for retreatment without simultaneous recurrence

Figure 3 Regression of stage 3 retinopathy of prematurity in zone II posterior with plus disease: (a) pretreatment color images of the right eye, (b) fluorescein angiography images 20 months post intravitreal injection of bevacizumab with vascularization into Zone III (peripheral indentation showing nasal ora).

of plus disease or at least evidence of focal traction on the retina. In this cohort, recurrence of disease did not go beyond stage 2 and there were no unfavorable structural outcomes with up to 5.0 years of follow-up. The small sample size in the current study may be one reason why we did not observe recurrence to more severe stages.

Wu *et al*¹⁷ reported retreating 9% of the eyes because of no response or worsening of disease at a mean of 6 ± 3.4 weeks after initial treatment with IVB. Two percent of the eyes in their study developed RD. In our cohort of infants, we did not observe any recurrence of neovascularization within the first 3 months after treatment. In addition, after an extended follow-up, none developed neovascularization or RD. None of the above studies provided similar detail of involution or progression patterns to our paper and hence it is difficult to draw any conclusions by comparing studies. Because our results showed that recurrence can occur despite initial regression, we advise prolonged follow-up as

recommended by the policy statement of the American Academy of Pediatrics until full retinal vascularization in close proximity to the ora serrata for 360°.¹⁸ This often requires scleral indentation with or without FFA under general anesthesia as babies grow older and become more difficult to examine. However, we identified that 82% of eyes were not fully vascularized at 3 months. In addition, 39% were not vascularized into zone III on angiographic evidence at a mean follow-up of 24 months. This poses a dilemma on the frequency and length of follow-up as the peripheral retina becomes progressively more difficult to visualize. At our institution if vascularization has not reached zone III, we follow children every 2 weeks until vascularization has arrested in close proximity to ora serrata, then monthly. Beyond 6 months post-treatment, we perform FFA under general anesthesia if still not vascularized into zone III to assess for peripheral extraretinal neovascularization. If the eyes are not showing signs of active disease, then we follow-up on a

3 monthly basis without scleral indentation. Parents are taught to check for obvious signs of retinal detachment through monocular testing on a weekly basis and report immediately, if poor vision is noted in between clinic visits.

Bevacizumab is also used as an adjunct to laser or surgery in the treatment of ROP.^{3,5,19} Law *et al*¹⁹ reported on 13 eyes of 7 infants who received initial treatment with IVB to improve visualization of retina. Definitive treatment was then performed within 72 h with either laser or surgery. In all eyes marked regression of anterior segment vascularization and improvement of pupillary dilatation was noted in the first 48 h post injection. Our study also confirms early and rapid improvement of plus disease (73% in 3 days and 100% in 8 days). However, unlike Law *et al*, we did not need to further treat any patients and did not experience recurrence or unfavorable structural outcomes. There may be differences in our patients' cohort to explain this as none of our treated eyes had initial disease that prevented viewing of the fundus. Whether this represents earlier disease recognition or differences in patient characteristics is unclear. We demonstrate that although involution can be seen as early as 3 days, it took >3 weeks to observe involution in two infants. Therefore in this patient group, early retreatment may not be indicated for all cases and regression may still occur as long as disease worsening is not observed following IVB.

Our study is retrospective in nature and therefore has the limitations associated with this research method. However, we present detailed clinical information at relevant time points to describe an involution pattern following IVB injection. The relatively small number of eyes and lack of unfavorable structural outcomes does not allow us to predict which regression pattern carries a poor prognosis. By the conclusion of study period, our experience suggests that in this cohort of infants, recurrence requiring retreatment and development of unfavorable structural outcome are not common once involution occurs in the pattern described within the first 3 months post treatment.

In conclusion, involution of type 1 ROP following treatment with IVB occurred in all eyes by 1 month of treatment. Despite recurrence of stage 1 or 2 ROP within the first 3 months all regressed and no eye required retreatment or had unfavorable structural outcome at prolonged follow-up of up to 5 years.

Our cohort is the first to describe regression patterns following IVB with details on structural results. There remains a need for long-term multicenter prospective studies to fully assess favorable and unfavorable regression patterns that can predict outcome, to define standardized guidelines for follow-up, and to develop clear indications for retreatment.

Summary

What was known before

- Off label use of bevacizumab has been shown to be an effective treatment for type 1 ROP in zone I.
- Late recurrence and risk of development of retinal detachment require frequent follow-up for an extended time-period post treatment.

What this study adds

- This study describes regression patterns of type 1 retinopathy of prematurity following monotherapy with 0.625 mg of intravitreal bevacizumab injection and relationship to structural outcome.
- Plus disease resolved by 8 days and stage 3 by week four in all eyes. Despite recurrence of ROP (stage 1 or 2) within the first 3 months, no patient required retreatment or developed unfavorable structural outcome with up to 5.0 years of follow-up.
- At 3 months post-treatment 82% of eyes were not fully vascularized, whereas 39% were not vascularized into zone III as seen on fluorescein angiography with scleral indentation performed at a mean of 24 months post treatment.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Design and conduct of the study (MI, KM, NNT); collection, management, analysis, and interpretation of data (MI, KM, NNT); and preparation, review, or approval of manuscript (MI, KM, NNT).

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Involution patterns of retinopathy of prematurity after treatment with intravitreal bevacizumab: implications for follow-up

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1. You are evaluating a newborn delivered at gestational age 32 weeks who was just diagnosed with stage III plus retinopathy of prematurity (ROP). According to the current study by Isaac and colleagues, treatment with intravitreal bevacizumab promoted which of the following patterns in plus disease among infants?
- A No regression at day 3; 39% regression at day 8
B 5% regression at day 3; 51% regression at day 8
C 73% regression at day 3; 100% regression at day 4
D 100% regression at days 3 and 8
2. Which of the following statements *best* characterizes the degree of regression of ROP during the short term in the current study?
- A Less than 10% of eyes regressed to no ROP
B More than 70% of eyes regressed to no ROP
C Most eyes regressed to stage I ROP
D Most eyes regressed to stage II ROP
3. Which of the following statements regarding retinal vascularization after treatment with intravitreal bevacizumab for ROP in the current study is *most* accurate?
- A At 3 months after treatment, most eyes had vascularized to zone II
B Nearly one-quarter of eyes with zone 1 ROP had vascularized to zone III at 3 months
C Rates of vascularization to zone III were stagnant between 3 months and final follow-up
D All eyes had fully vascularized by the final follow-up point
4. The patient undergoes treatment of ROP with intravitreal bevacizumab. What can you tell her parents regarding long-term outcomes of intravitreal bevacizumab in the current study?
- A All recurrences of stage I or II retinopathy had regressed
B An estimated 20% of eyes required repeated treatment
C Nearly 60% of eyes required repeated treatment
D The rate of unfavorable structural outcomes was 14%
- Activity evaluation**

1. The activity supported the learning objectives.
Strongly disagree Strongly agree
1 2 3 4 5

2. The material was organized clearly for learning to occur.
Strongly disagree Strongly agree
1 2 3 4 5

3. The content learned from this activity will impact my practice.
Strongly disagree Strongly agree
1 2 3 4 5

4. The activity was presented objectively and free of commercial bias.
Strongly disagree Strongly agree
1 2 3 4 5

Activity evaluation

1. The activity supported the learning objectives.				
Strongly disagree			Strongly agree	
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly disagree			Strongly agree	
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly disagree			Strongly agree	
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly disagree			Strongly agree	
1	2	3	4	5