PROGRESSIVE RETINAL DETACHMENT IN INFANTS WITH RETINOPATHY OF PREMATURITY TREATED WITH INTRAVITREAL BEVACIZUMAB OR RANIBIZUMAB

YOSHIHIRO YONEKAWA, MD,*† WEI-CHI WU, MD, PhD,‡ CRISTINA E. NITULESCU, MD,§
R.V. PAUL CHAN, MD,¶ ARISTOMENIS THANOS, MD,**†† BENJAMIN J. THOMAS, MD,‡‡
BOZHO TODORICH, MD, PhD,**†† KIMBERLY A. DRENSER, MD, PhD,**††
MICHAEL T. TRESE, MD,*†† ANTONIO CAPONE, Jr., MD**††

Purpose: Fibrovascular contraction and tractional retinal detachment (TRD) are recognized complications associated with the use of anti–vascular endothelial growth factor agents in vasoproliferative vitreoretinopathies. The authors characterize TRDs that developed after intravitreal bevacizumab or ranibizumab therapy for vascularly active retinopathy of prematurity.

Methods: This is an international, multicenter, interventional, retrospective, case series. Thirty-five eyes from 23 infants were included. Inclusion required anti–vascular endothelial growth factor treatment of Type 1 retinopathy of prematurity with progression to TRD.

Results: Mean gestational age was 26 ± 2 weeks, and mean birth weight was 873 ± 341 g. Mean postmenstrual age on the day of injection was 35 ± 2 weeks. Retinal detachment was noted a mean of 70 days (median, 34; range, 4–335) after injection. Eleven percent detached within 1 week, 23% within 2 weeks, and 49% within 4 weeks. The highest stage of retinopathy of prematurity noted was 4A in 29%, 4B in 37%, and 5 in 34% of eyes. Time to RD negatively correlated with postmenstrual age at the time of injection ($Rho = -0.54$; $P < 0.01$). Three TRD configurations were observed: 1) conventional peripheral elevated ridge or volcano-shaped Stage 5 detachment, 2) midperipheral detachment with tight circumferential vectors, and 3) very posterior detachment with prepapillary contraction. Full or partial reattachment was achieved with surgical intervention in 86% of eyes.

Conclusion: Progressive atypical TRD may occur after anti–vascular endothelial growth factor injections for retinopathy of prematurity. The configuration of the detachment varies with the extent of primary retinal vascularization present at the time of treatment.

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The vasoproliferation of advanced retinopathy of prematurity (ROP) develops in response to ischemia of the avascular peripheral immature retina. Vascular endothelial growth factor (VEGF) is a key cytokine that modulates this process. Anti-VEGF agents such as bevacizumab (Avastin; Genentech, South San Francisco, CA) and ranibizumab (Lucentis; Genentech) have become widely used in the management of acute ROP.

Despite the popularity of anti-VEGF therapy for acute ROP, important questions remain regarding rates and timing of recurrence, rate and impact of persistent avascular retina posttreatment, the consequences of systemic exposure of anti-VEGF agents, and local effects on the dynamic and complex cytokine milieu of the developing eye. Numerous cytokines are altered in ROP,[1] and adult studies have shown that anti-VEGF treatment causes a shift in the cytokine signalplex.[2] Upregulation or unopposed activity of cicatrizing cytokines such as transforming growth factor beta (TGF-β) have been shown and may predispose to progressive tractional retinal detachment (TRD).

Such a phenomenon occurs in proliferative diabetic retinopathy[3] and has been reported in ROP as well,

mostly as case reports.[4–9] Herein, we characterize a relatively large series of infants with ROP referred for management of progressive TRD after treatment with bevacizumab or ranibizumab to better understand this rare phenomenon. Of note, these are not consecutive infants treated with anti-VEGF; rather, this is a series only of infants who developed subsequent progressive TRD after anti-VEGF therapy.

Methods

This study is a retrospective, international, multicenter, interventional case series. Institutional review board approval was obtained from each institution, and the study complied with the Health Insurance Portability and Accountability Act of 1996 and the tenets of the Declaration of Helsinki. Informed consent was obtained from legal guardians before surgical intervention in the infants who underwent surgery.

We included infants with acute ROP treated with bevacizumab or ranibizumab between 2009 and 2015 who subsequently developed TRD. Patients were identified through billing searches and surgical logs. Excluded were those with preexisting Stage 4A, 4B, or 5 RDs who received anti-VEGF injections as a preoperative adjunct to planned vitrectomy.

Data collection included demographics, ROP staging, anti-VEGF medication and dose, timing of injections, surgery performed, and postoperative course. Visual acuities were converted to logarithm of minimum angle of resolution units, and Spearman's rank correlation, Fisher's exact, and the Mann–Whitney U tests were used in Stata version 9.0 for statistical analyses (StataCorp, LP, College Station, TX). Statistical tests were 2 tailed, and significance was defined as $P < 0.05$.

Results

Thirty-five eyes from 23 infants were included. Mean gestational age was 26 ± 2 weeks, and mean birth weight was 873 ± 341 g. Fourteen (61%) of the infants were male. Sixteen infants (70%) were white, 5 (22%) East Asian, 1 (4%) South Asian, and 1 (4%) was Latino. The majority were born at outside institutions (19 [83%]) and referred in for surgical intervention. Twenty-five eyes (71%) received anti-VEGF therapy alone, 7 (20%) had undergone previous laser photocoagulation, and 3 (9%) were also treated with laser at the time of anti-VEGF injection. Of the 25 treatment-naïve eyes, 15 (60%) underwent subsequent laser treatment.

Mean postmenstrual age (PMA) on the day of injection was 35 ± 2 weeks. Bevacizumab 0.625 mg was used in 29 (83%) eyes, and ranibizumab 0.25 mg in 6 (17%) eyes. Twenty-nine (83%) eyes were classified as having Zone I (83%), and six eyes were classified as having Zone II (17%). Physician-reported aggressive posterior ROP was present in 21 (60%) eyes. Anti-VEGF agents were injected bilaterally in all but 1 patient (96%). Thirty-one (89%) eyes received one injection, and 4 (11%) received two injections. Of the 35 eyes, 71% (25/35) received laser at some point in their course of treatment.

Progression to RD was noted as a mean of 70 days (median, 34; range, 4–335) after anti-VEGF injection. Four (11%) detached within 1 week, 8 (23%) within 2 weeks, and 17 (49%) within 4 weeks. The highest stage of ROP attained was 4A in 10 eyes (29%), 4B in 13 eyes (37%), and 5 in 12 (34%) eyes. Bilateral RD occurred in 11 (48%) patients. In bilateral cases, TRD was noted in both eyes on the same visit in all but one patient (91%). Time to detachment correlated negatively with PMA at the time of anti-VEGF injection ($Rho = -0.54$; $P < 0.01$), and trended toward a negative correlation with gestational age ($Rho = -0.30$; $P = 0.08$), but not with birth weight ($Rho = -0.21$; $P = 0.24$).

We observed three progressive TRD patterns: "Conventional" ROP detachments that are elevated peripheral ridges or volcano shaped (Figure 1), and two

From the *Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts; †Pediatric Retina Surgery Service, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; ‡Department of Ophthalmology, Chang Gung Memorial Hospital and Chang Gung University, College of Medicine, Taoyuan, Taiwan; §Department of Ophthalmology, National Institute for Mother and Child Health Alessandrescu-Rusescu, Bucharest, Romania; ¶Retina Service, Department of Ophthalmology, Illinois Eye and Ear Infirmary, University of Illinois College of Medicine, Chicago, Illinois; **Associated Retinal Consultants, Royal Oak, Michigan; ††Department of Ophthalmology, Oakland University William Beaumont School of Medicine, Rochester, Michigan; and ‡‡Florida Retina Institute, Jacksonville, Florida.
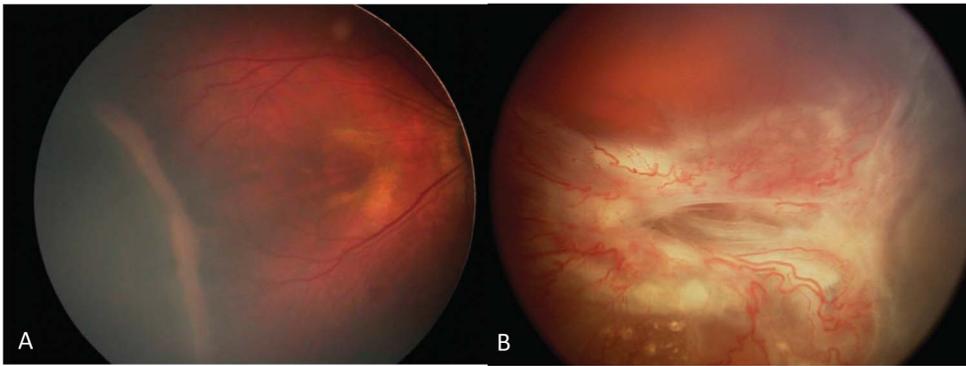
Fig. 1. Conventional RDs in ROP. These photographs are also of infants who progressed to RD after anti-VEGF treatment, but they have conventional configurations. In **A**, there is an elevated peripheral ridge with a focal RD. In **B**, this is the classic volcano-shaped Stage 5 RD in ROP where it peaks anteriorly.

configurations that were unique to anti–VEGF-treated eyes: "circumferential," (Figure 2) and "prepapillary" (Figure 3). Conventional volcano-shaped RDs were noted in 12 (34%) eyes. In 12 (34%) eyes, the TRD was characterized by tight circumferential vectors that were relatively peripheral. These infants were more premature (24 vs. 27 weeks; $P = 0.02$) and had lower birth weights (669 vs. 1,034 g; $P < 0.01$). In 10 (29%) eyes, the TRD was very posterior and caused by pre-papillary contraction. This phenomenon was bilateral in all infants. One eye had a chronic RD that was mostly effusive in nature.

Twenty-nine (83%) eyes underwent surgery, and 25 (86%) attained full or partial retinal reattachment. Mean PMA at surgery was 46 ± 10 weeks (range, 35–81). Six of the 8 (66%) peripheral/circumferential TRDs, 4 of the 6 (67%) prepapillary TRDs, and 15 of the 15 (100%) conventional RDs were reattached. Six of the 6 (100%) eyes exposed to ranibizumab and 19 of the 29 (66%) exposed to bevacizumab were reattached. There was a trend toward a correlation between highest stage and visual outcomes ($Rho = 0.56$; $P = 0.07$). All six eyes that did not undergo surgery progressed to Stage 5 ROP ($P < 0.01$). Final visual acuities, available for 11 eyes, ranged from 20/33 – light perception. Mean follow-up after surgery was 97 ± 115 weeks.

Discussion

Laser photocoagulation has been the gold standard of treatment for Type 1 ROP for many years, and the indications, timing of treatment, expected response, and even the complications and how to treat the complications have all been well characterized. In the past few years, there has been an increasing body of literature on the use of intravitreal anti-VEGF agents, particularly for posterior ROP. Vascular endothelial growth factor–driven fibrovascular proliferation is certainly implicated in ROP pathogenesis, and the ability of anti-VEGF agents to cause regression of neovascular tissue is well known.

However, in contrast to age-related macular degeneration, diabetic macular edema, and retinal vein occlusions, anti-VEGF use in ROP has not been systematically studied. There are many unanswered questions, as noted earlier. Anti-VEGF medications are not Food and Drug Administration approved for ROP and are currently used off-label. In this study, we examined a series of cases who failed anti-VEGF treatment, and progressed to RD, to better understand this rare but unfavorable phenomenon.

We described two progressive TRD configurations unique to acute ROP treated with anti-VEGF agents: one relatively peripheral with a circumferential
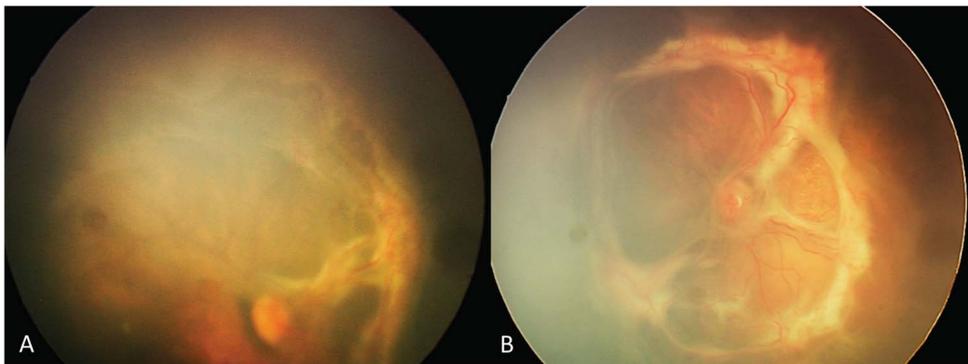

Fig. 2. Anti–VEGF-associated circumferential RD. An infant with ROP born at 24 weeks gestational age and 430 g birth weight received a half dose of intravitreal bevacizumab at 38 weeks PMA, for Zone I, Stage 3, with plus disease. Retinal detachment was noted 1 week later, and the patient was referred to our practice. Note the severe circumferential hyaloidal contraction in both eyes (**A**, right eye; **B**, left eye). He underwent successful lens-sparing vitrectomy in both eyes.

Fig. 3. Anti–VEGF-associated prepapillary RD. An infant with ROP born at 33 weeks gestational age and 1800 g birth weight received intravitreal bevacizumab at 39 weeks PMA, for Zone I, Stage 3, with plus disease (**A**, right eye; **B**, left eye). The patient was referred back for progressive disease and was noted to have contracted prepapillary fibrous proliferation with TRD bilaterally (**C**, right eye, **D**, left eye).
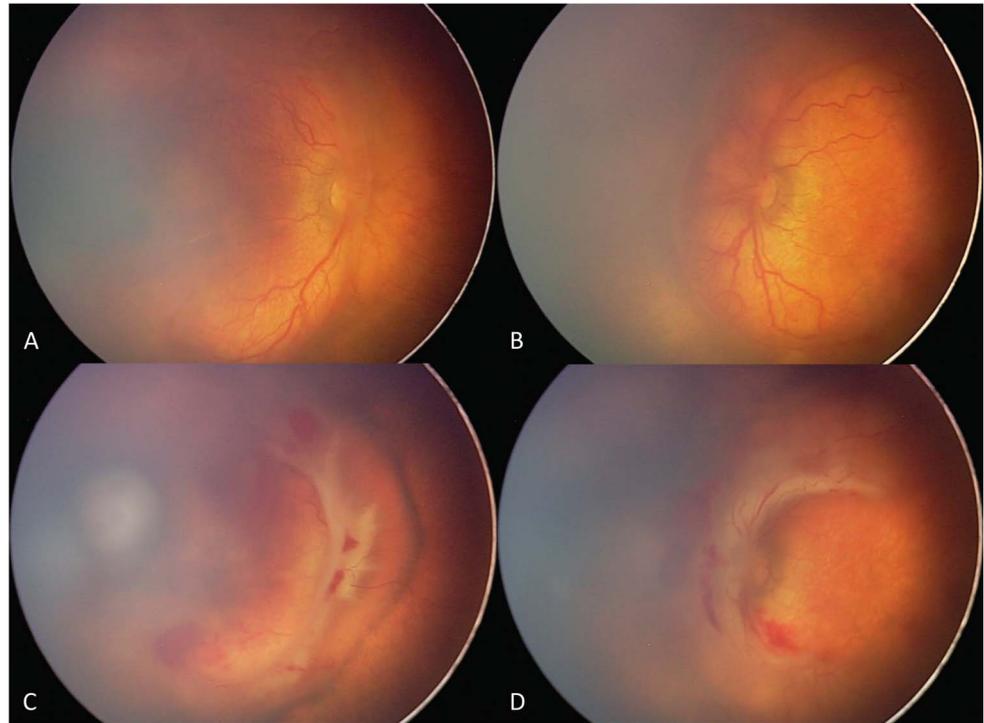
configuration ("circumferential"), and one very posterior with prepapillary contraction ("prepapillary"). For the circumferential configuration, we postulate that anti-VEGF agents induce fibrosis and contraction of flat neovascularization peripherally to create a tight and circular detachment. For the prepapillary configuration, the anti-VEGF agents likely cause the immature prepapillary vascular precursor cells to contract, resulting in pulling of the retina toward the disk. The former detachments were noted primarily in eyes vascularized more anteriorly before the development of acute ROP, the latter in eyes with more posterior disease.

Both progressive TRD configurations are amenable to surgical repair, but the approach differs somewhat from that traditionally used in the management of ROP-related RD. The contracted proliferation is much tighter to the retinal surface, and segmentation along the seams of contracture requires extra care. We recently reported on a technique to use a combination of either 23- or 25-gauge cannula-based instrumentation, with the insertion of a 27-gauge vitreous cutter to enter tighter planes, which may be useful in select cases.[10]

We also found that infants who were injected at a relatively older PMA progressed to Stage 4/5 faster. Older patients are more likely to have fibrotic components to the neovascularization, which are more likely to contract with anti-VEGF treatment.

Theoretically, earlier anti-VEGF treatment would be less likely to lead to TRD. Proof of this theory is beyond the scope of this study, and infants injected at younger PMAs still detached albeit after a longer latency period. Regardless, there was a wide range of timing of progression to TRD posttreatment, as has been noted by others.[4–9] Longer follow-up is indicated after anti-VEGF treatment even in eyes with concurrent laser photocoagulation.

Studies in adults have demonstrated that the profibrotic cytokine TGF-β may increase with anti-VEGF treatment.[3,11,12] In addition for preterm infants, there is an endogenous rise in systemic TGF-β as they approach term.[13] In the eye, vitreal TGF-β has been shown to be elevated in advanced ROP as well.[13] Such upregulation of TGF-β from multiple sources seems to drive the progression to TRD that peaks in the incidence close to term.[14] Anti-VEGF agents may exacerbate this profibrotic state in some eyes, especially if treatment is delayed until near or after 40 weeks PMA.

Furthermore regarding the interplay between VEGF and TGF-β, studies have shown that VEGF plays an important role in normal vascular development,[15,16] and that the choriocapillaris, choroidal plexus, and other vessels throughout the body may lose fenestrations if VEGF is suppressed.[17] Of interest, this effect seems to be more pronounced with concurrent TGF-β suppression.[18] Therefore, TGF-β suppression alone

may not be the simplistic solution to prevent poor outcomes in eyes treated with anti-VEGF agents.

Intravitreal anti-VEGF injections result in a very acute and precipitous suppression of VEGF within (and outside) the eye for infants. Instead, a treatment that can lower VEGF more gradually may provide less risk for fibrovascular and hyaloidal contraction. Laser accomplishes this, and works well and predictably, but is not invariably effective. Both anti-VEGF and laser treatments have revolutionized the way we treat ROP, but a more sophisticated way of modulating the cytokine milieu in these eyes may further improve outcomes for infants with advanced ROP.

Although this is the largest of anti-VEGF failures in infants with ROP, full assessment of the risk factors predisposing to RD awaits prospective study. Routine photoscreening may also allow us to identify specific clinical findings which predispose a given eye to anti-VEGF failure, such as degrees of preexisting fibrosis. We also cannot comment on the incidence of progressive RD. We do not routinely use anti-VEGF to treat ROP, and almost all the cases in the study were referred from other institutions for surgical intervention, many internationally. The denominator of the total numbers of infants treated with anti-VEGF injections is therefore unknown. Finally, we excluded eyes that received anti-VEGF injections for vascularly active Stage 4/5, either for attempted monotherapy or a surgical adjunct. Theoretically, these eyes have higher risk for progressive TRD because of the preexisting fibrosis that can contract.

In summary, we report that progression to RD can be seen after anti-VEGF treatment of infants with ROP. They can progress in atypical circumferential or prepapillary configurations. Further studies are warranted to determine the incidence and risk factors for failure of anti-VEGF treatment.

Key words: anti-VEGF, bevacizumab, ranibizumab, retinal detachment, retinopathy of prematurity.

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