Effect of Serial Intrasilicone Oil Bevacizumab Injections in Eyes With Recurrent Proliferative Vitreoretinopathy Retinal Detachment

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• PURPOSE: To investigate the effect of serial intrasilicone oil bevacizumab injections (1.25 mg/0.05 mL) on visual acuity (VA) and anatomic outcomes in eyes undergoing proliferative vitreoretinopathy (PVR)-related retinal detachment (RD) repair.

• DESIGN: Prospective, nonrandomized, historical-control pilot study.

• METHODS: SETTING: Tertiary care center. STUDY POPULATION: Nondiabetic eyes undergoing pars plana vitrectomy (PPV) and silicone oil tamponade with or without scleral buckling procedure (SBP) for recurrent RD due to PVR. INTERVENTION: Intrasilicone oil injection of 1.25 mg bevacizumab was performed intraoperatively and at postoperative months 1, 2, and 3. OUTCOMES: Retinal reattachment rate, final VA, and rate of epiretinal membrane (ERM) formation at month 6.

• RESULTS: Twenty eyes of 20 patients were enrolled and compared to a historical control group composed of 35 age- and sex-matched controls. In the study group, logMAR VA improved from mean 1.78 ± 0.43 (Snellen 20/1205) to 1.43 ± 0.70 (Snellen 20/538, $P = .04$), retinal reattachment was achieved in 14 of 20 eyes (70%), and ERM formation was observed in 7 of 20 eyes (35%) at 6 months. In the control group, logMAR VA improved from mean 1.50 ± 0.74 (Snellen 20/632) to 1.43 ± 0.58 (Snellen 20/538, $P = .64$), retinal reattachment was achieved in 25 of 35 eyes (71%), and ERM formation was observed in 7 of 35 eyes (20%) at 6 months. No significant difference in final VA ($P = .96$), retinal reattachment rate ($P = .75$), or ERM formation ($P = .33$) was observed between groups. No intrasilicone oil injection–related adverse events occurred.

• CONCLUSIONS: Serial intrasilicone oil injections of bevacizumab did not improve retinal reattachment rate, improve final VA, or reduce ERM formation in patients undergoing PVR-related RD surgery. (Am J Ophthalmol 2015;■:■–■. © 2015 by Elsevier Inc. All rights reserved.)

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PROLIFERATIVE VITREORETINOPATHY (PVR) REMAINS the most significant obstacle to successful retinal detachment (RD) repair, accounting for up to 75% of all primary surgical failures.[1] Characterized by the proliferation of cells on the preretinal or subretinal surface, PVR ultimately leads to contraction, foreshortening, and ultimately recurrent detachment of the retina. Several PVR risk factors have been identified, including pre-existing uveitis, large retinal tears, multiple retinal breaks, detachments involving greater than 2 quadrants of the retina, vitreous hemorrhage, and choroidal detachment.[1,2]

Currently, there are no medical interventions that definitively lower the risk of PVR development. Multiple studies have identified growth factors and cytokines that may play an important role in PVR development, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and epidermal growth factor (EGF), among others.[3–5] However, pharmacologic agents targeting such factors have found little success as possible therapeutics for PVR.[6] Corticosteroids,[7–10] low-molecular-weight heparin with or without 5-fluorouracil,[11–18] isotretinoin,[19,20] daunorubicin,[21–24] and VIT100 ribozyme[25,26] have all been studied without proven efficacy in PVR, underscoring the difficulty in preventing this complex disease process.[6]

VEGF has received attention as a potential therapeutic target.[3,4,27,28] Prior reports found that VEGF levels were 2- to 3-fold higher in the subretinal fluid of eyes with PVR-related RDs compared to eyes having an uncomplicated RD without PVR.[27] In addition, others have found VEGF concentrations to be similar in PVR-related membranes (1417 pg/mg protein) and proliferative diabetic retinopathy–related membranes (1242 pg/mg protein), with the latter being a known VEGF-mediated disease.[28] More recent work found that competitive inhibition of PDGF by VEGF allows for indirect activation of PDGF receptors that is critical to the progression of experimental PVR.[4,29] Based on such findings, Ghasemi Falavarjani and associates evaluated the effect of a single intravitreal injection of bevacizumab at the time of PVR-related RD surgery and found no change in visual acuity (VA) or reattachment rate with this intervention when compared to age-matched controls.[30]

Since that report, no subsequent study has evaluated the use of anti-VEGF therapy on outcomes of PVR-related RD.

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Given the absence of a proven medical therapy for PVR and prior studies establishing VEGF as a potential therapeutic target, further clinical evaluation is warranted. Herein, we report outcomes of a prospective, nonrandomized, historical-control pilot study evaluating the effect of serial intrasilicone oil bevacizumab injections on outcomes of PVR-related RD repair.

METHODS

INSTITUTIONAL REVIEW BOARD APPROVAL FROM WILLS EYE Hospital was obtained for this prospective, nonrandomized, historical-control pilot study evaluating the effect of serial intrasilicone oil injections of bevacizumab on PVR-related RD outcomes. The study was performed at the Retina Service of Wills Eye Hospital and the offices of Mid Atlantic Retina from August 1, 2013 through August 1, 2014. All participants gave informed consent for RD repair surgery, completion of study protocol as detailed below, and collection of demographic and historical data prior to enrollment. The study was conducted in accordance with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov under the identifier NCT01860586.

Nondiabetic patients with recurrent RD who had grade C PVR (as defined by the modified Retina Society classification system[31]) and were scheduled for pars plana vitrectomy (PPV) with 1000 centistoke silicone oil tamponade were eligible for enrollment. Exclusion criteria included intravitreal anti-VEGF therapy in the preceding 3 months, history of glaucoma, history of uveitis, and history of diabetic or nondiabetic proliferative retinopathy.

Baseline data including age, sex, study eye, date of onset of symptoms, past medical and ocular history, details of prior RD repair surgeries, VA, slit-lamp examination findings, tonometry results, and dilated fundus examination findings (including macular detachment status and presence of PVR) were recorded. All patients underwent 23 gauge, transconjunctival microincision PPV using the Constellation Vitrectomy System (Alcon Laboratories, Fort Worth, Texas, USA). A core vitrectomy was performed followed by removal of the peripheral cortical gel over 360 degrees with scleral depression. Dissection of PVR membranes and, if necessary, retinectomy or retinotomy were performed per surgeon discretion. Instillation of perfluorocarbon liquid, fluid-air exchange, endolaser photocoagulation, and subsequent 1000 centistoke silicone oil instillation were used in all cases. Concurrent scleral buckling procedure (SBP) was performed at the discretion of the operating surgeon. All sclerotomy sites were sutured to ensure wound closure.

The following study protocol was then followed. Patients received an intrasilicone oil injection of bevacizumab (1.25 mg/0.05 mL) at the end of surgery and again at postoperative months 1, 2, and 3. If silicone oil was removed at postoperative month 3, the last intraocular bevacizumab injection was given at the end of the silicone oil removal surgery. Follow-up examinations were completed at postoperative day 1 and day 7, and then at months 1–6. At each postoperative visit, Snellen VA testing, tonometry, slit-lamp examination, and dilated fundus examination of the study eye was performed. Spectral-domain optical coherence tomography (OCT) at postoperative months 1, 3, and 6 was completed to evaluate epiretinal membrane (ERM) formation. If recurrent RD occurred during the study period, the study protocol was discontinued.

Twenty eyes of 20 patients were enrolled in the intervention group. Outcomes were compared with an age-matched, historical control group composed of 35 eyes of 35 patients with the identical inclusion and exclusion criteria as the prospective cohort. The primary outcome was retinal reattachment rate at postoperative month 6. Secondary outcomes included change in VA from baseline and development of ERM at postoperative month 6. Best available Snellen visual acuities (present correction with pinhole) were converted to logMAR equivalents for statistical analyses, with counting fingers (CF) and hand motions (HM) vision corresponding to 1.98 and 2.28, respectively.[32] Statistical analysis of VA outcomes was performed using a Student *t* test (GraphPad Software Inc, La Jolla, California, USA). Statistical analysis of retinal reattachment rate and ERM formation was performed using Fisher exact test (GraphPad Software Inc). A P value $< .05$ was considered statistically significant.

RESULTS

BASELINE FEATURES INCLUDING PATIENT AGE, SEX, PREOPERATIVE VA, lens status, macular status, history of PPV, history of SBP, and PVR grade were statistically similar between the intervention and control group (Table 1). In the intervention group (n = 20 patients), mean age at the time of study enrollment was 59 ± 8 years. Seven patients (35%) were female. The study surgery occurred at a mean of 37 ± 17 days after prior RD surgery. Patients in the intervention group underwent a mean of 1.1 (median 1, range 1–2) prior RD repair surgeries prior to study enrollment. Four eyes (20%) underwent combined PPV and SBP, 10 eyes (50%) had prior SBP, and the remaining 6 eyes (30%) had no SBP. A macula-off RD was present in 18 eyes (90%) and 10 eyes (50%) were phakic at the time of surgery.

In the control group (n = 35 patients), mean age at the time of PVR-related RD surgery was 65 ± 12 years and 15 patients (43%) were female. The study surgery occurred at a mean of 50 ± 18 days after the prior RD surgery. Patients in the control group underwent a total of 1 prior RD repair

TABLE 1. Effect of Serial Intrasilicone Oil Bevacizumab Injections in Eyes With Recurrent Proliferative Vitreoretinopathy Retinal Detachment: Patient Demographic Features

Feature	Bevacizumab Group (N = 20 Eyes)	Control Group (N = 35 eyes)	*P* Value
Mean age (y)	59 ± 8	65 ± 12	.09[b]
Sex			
Female	7	15	.78[a]
Male	13	20	
Lens status			
Phakic	10	10	.15[a]
Pseudophakic	10	24	
Prior surgical history			
Pars plana vitrectomy	20	35	>.99[a]
Scleral buckle	10	19	.79[a]
Macular status			
On	2	4	>.99[a]
Off	18	31	
Presence of proliferative vitreoretinopathy grade C	20	35	>.99[a]
Presenting logMAR visual acuity	1.78 ± 0.43	1.49 ± 0.74	.11[b]

LogMAR = logarithm of the minimal angle of resolution.
[a]Fisher exact test (2-tailed).
[b]Student paired *t* test.

TABLE 2. Effect of Serial Intrasilicone Oil Bevacizumab Injections in Eyes With Recurrent Proliferative Vitreoretinopathy Retinal Detachment: Study Outcomes at 6 Months

Outcome	Bevacziumab Group (N = 20 Eyes)	Control Group (N = 35 Eyes)	*P* Value
Final logMAR visual acuity	1.43 ± 0.70	1.42 ± 0.58	.96[b]
Recurrent detachment	6 (30%)	10 (29%)	.75[a]
Epiretinal membrane	7 (35%)	7 (20%)	.33[a]
Silicone oil removal completed during study period	2 (10%)	8 (23%)	.30[a]

LogMAR = logarithm of the minimal angle of resolution.
[a]Fisher exact test (2-tailed).
[b]Student paired *t* test.

surgery. Nine eyes (26%) underwent combined PPV and SBP, 19 eyes (54%) had prior SBP, and the remaining 7 eyes (20%) had no SBP. A macula-off RD was present in 31 eyes (89%) and 10 eyes (29%) were phakic at the time of recurrent RD surgery.

Primary outcomes are summarized in Table 2. In regard to visual acuity, logMAR VA improved significantly from a mean of 1.78 ± 0.43 preoperatively to 1.43 ± 0.70 at 6 months ($P = .04$) in the intervention group. In the control group, logMAR visual acuity improved from a mean of 1.49 ± 0.74 preoperatively to 1.42 ± 0.58 at 6 months ($P = .64$). No statistically significant difference existed between groups in regard to preoperative vision ($P = .11$) and macula status at time of study enrollment ($P > .99$).

Overall, mean logMAR VA in macula-on detachments (n = 6 eyes) worsened from 0.94 ± 0.70 preoperatively to 1.35 ± 0.78 at 6 months ($P = .39$). In macula-off detachments (n = 49 eyes), mean VA improved from 1.56 ± 0.55 preoperatively to 1.44 ± 0.61 at 6 months ($P = .13$). Comparing macula-on detachments in the intervention (n = 2) and control (n = 4) groups, no statistical difference was present in regard to preoperative (1.52 ± 0.67 vs 0.60 ± 0.50, $P = .12$) and final (0.62 ± 0.11 vs 1.5 ± 0.74, $P = .18$) logMAR VA. The observed change in visual acuity was not statistically significant in the intervention ($P = .16$) or control ($P = .13$) groups. Two of 4 macula-on detachments in the control group re-detached under silicone oil in the follow-up period, while neither of the 2 macula-on detachments in the intervention group re-detached. Similarly, comparing the macula-off detachments in the intervention (n = 18) and control (n = 31) groups, no statistical difference was present in regard to preoperative (1.80 ± 0.43 vs 1.61 ± 0.69, $P = .28$) and final (1.64 ± 0.48 vs 1.43 ± 0.57, $P = .20$) visual acuity. The observed change in visual acuity was not statistically significant in the intervention ($P = .11$) or control ($P = .20$) groups.

A total of 6 eyes (30%) in the intervention group and 10 eyes (29%) in the control group were diagnosed with recurrent PVR-related retinal detachment during the 6-month study period ($P = .75$). Recurrent RD occurred a mean of 37 ± 17 days following surgery in the intervention group and a mean of 53 ± 43 days in the control group, respectively ($P = .12$). Seven eyes (35%) in the intervention group and 7 eyes (20%) in the control group developed an ERM as identified on clinical examination and/or OCT testing at 6 months ($P = .33$). A total of 10 eyes were deemed appropriate for silicone oil removal during the study period, including 2 eyes (10%) in the intervention group and 8 eyes (23%) in the control group ($P = .30$). No eye that underwent silicone oil removal during the study period re-detached during the 6 month follow-up interval.

At 6 months, no statistically significant difference in final visual acuity ($P = .96$), retinal reattachment rate ($P = .75$), ERM formation ($P = .33$), or rate of silicone oil removal ($P = .30$) was observed between the intervention and control group. There were no complications related to the intrasilicone oil injections.

DISCUSSION

IN THIS NONRANDOMIZED, HISTORICAL-CONTROL PILOT study, we prospectively evaluated the effect of serial

intrasilicone oil injections of bevacizumab on visual acuity and anatomic outcomes in 20 eyes undergoing PPV and silicone oil tamponade for recurrent, grade C PVR-related RD.

Ghasemi Falavarjani and associates previously evaluated the effect of intrasilicone oil injection of bevacizumab at the time of surgery in a pilot study of 19 eyes with grade C PVR.[33] At a mean follow-up of 7.3 months, the authors reported no significant difference in retinal reattachment rate or final VA between eyes treated with bevacizumab and matched controls. The treatment protocol in our study differs from the work of Ghasemi Falavarjani and associates in several ways. While both series were of patients with grade C PVR, all surgeries in our series were completed in eyes with recurrent RD, as opposed to primary RD in the work of Ghasemi Falavarjani and associates. Also, eyes in the intervention group of our study received 4 intrasilicone oil injections of bevacizumab, as opposed to 1 injection at the time of surgery in their study. In creating the protocol for our study, we chose 4 monthly injections based on the fact that most recurrent PVR-related RDs occur within 3 months of surgery, and we hypothesized that ongoing VEGF inhibition might be important to prevent recurrence of PVR. An additional outcome, ERM formation, was also included in our study. ERMs may be considered a milder form of PVR and occur in some eyes after development of retinal breaks or rhegmatogenous RDs. We conjectured that if anti-VEGF therapy prevented the proliferative response seen in PVR, it might also be capable of preventing ERM formation. However, despite these differences in protocol, longer-term VEGF inhibition as used in our study did not appear to improve the outcomes of PVR-related RD or rate of ERM formation when compared to our historical control group.

Recent work has helped to identify a molecular mechanism by which VEGF may promote PVR development.[29] Indirect activation of the PGDF-receptor alpha by factors other than PDGF has been implicated in the cellular cascade that promotes cellular viability within the vitreous, a key feature of PVR development.[3,5,29] The work of Pennock and associates demonstrates that VEGF competitively inhibits binding of PDGF to PDGF-receptor alpha in the PVR vitreous, thereby allowing the non-PDGF-mediated activation of the PDGF-receptor alpha to predominate and promote the PVR process.[29,34] This competitive inhibition has multiple consequences, including downstream inhibition of p53, an important regulator of cell cycle growth, and increased availability of PDGF receptors.[29] Moreover, this competitive inhibition of PDGF-mediated activation of PDGF-receptor alpha is VEGF-receptor independent,[35] helping to explain why neovascularization and vascular leakage, features commonly associated with VEGF-mediated angiogenic stimulation, may not be present in PVR. Blocking this inhibition of PDGF with anti-VEGF therapy has reduced rates of PVR development in rabbit models,[3,5,29] further supporting the hypothesis that VEGF blockade may be a suitable target for PVR prevention.

A reason for the lack of treatment effect observed with bevacizumab in this study is speculative. While prior pharmacologic studies have suggested a similar half-life of bevacizumab in silicone oil–filled eyes compared to nonvitrectomized eyes,[33,36,37] the presence of oil may alter the distribution of bevacizumab within the vitreous cavity.[37] As a result, it is possible that monthly injections may have been insufficient to reach the desired effect of halting the regrowth of PVR membranes. Perhaps more frequent intrasilicone oil injections may be more efficacious. Alternatively, anti-VEGF therapy may be more effective in preventing PVR in eyes without silicone oil. To test this hypothesis, an argument could be made for use of alternate tamponade agents (eg, gas) or early silicone oil removal in combination with serial anti-VEGF injections.

Another possible reason for lack of effect was that we only included eyes with advanced stages of PVR, grade C or worse, in our trial. In the European Vitreo-Retinal Retinal Detachment Study (EVRS) Report No. 4, Adelman and associates identified grade C PVR as an independent risk factor for primary RD repair failure by multivariate analysis, indicative of eyes with a generally poor prognosis.[38] Perhaps, once the cascade of inflammatory events has reached a threshold, use of anti-VEGF antibodies is insufficient to halt the profibrotic process. Intervention at an early stage in the disease process may have resulted in a better effect, for example at the time of primary uncomplicated retinal detachment repair. However, such a study would require large numbers of subjects to prove the efficacy of anti-VEGF injections as a PVR prevention treatment, since the development of PVR after uncomplicated primary RD is relatively infrequent. Choosing high-risk primary RD patients who have earlier stages of PVR (grades A or B) or other risk factors for PVR development (eg, associated vitreous hemorrhage or uveitis, extensive retinal detachments, large retinal breaks, etc) may be a better strategy. Finally, it is possible that the PVR process may be too multifactorial and targeting a single molecular pathway is insufficient to prevent disease progression.

In this study, intrasilicone oil injection of bevacizumab was well tolerated and no injection-related complications were encountered. Compared to age- and sex-matched historical controls, no difference in final VA, retinal reattachment rate, or ERM formation was observed at 6 months. Of note, eyes in the intervention group did exhibit a statistically significant improvement in mean visual acuity ($P = .04$) that was not seen in the historical control group. While preoperative visual acuity was comparable between the intervention and control group ($P = .11$), preoperative values were worse in the intervention group (1.78 ± 0.43 vs 1.49 ± 0.74). It is possible that the intervention group therefore had more potential visual acuity to gain after RD repair. As best-corrected visual acuity was not available

for all patients and patient numbers were small, this difference in visual acuity improvement must be interpreted with caution.

This pilot study has several limitations, including small sample size, its nonrandomized nature, and use of historical controls. In addition, while all patients underwent 23 gauge PPV with 1000 centistoke silicone oil tamponade, the study surgery could not be completely standardized and multiple surgeons were involved in the study completion. Similarly, the decision whether or not to remove silicone oil was at the discretion of the individual surgeons. As a result, the majority of patients still had silicone oil at the 6 month endpoint. However, given that a comparable minority of patients in both the intervention and control groups had oil removal, the presence of silicone oil did not likely alter the outcomes to any significant extent. Also, owing to the heterogeneity of PVR-related detachments, exact matching of clinical cases among control and study groups was not possible. Lastly, as all patients had PVR grade C and were treated exclusively with bevacizumab, the role of alternative anti-VEGF agents or efficacy in patients with milder forms of PVR was not evaluated.

In conclusion, intrasilicone oil injections of bevacizumab did not improve retinal attachment rate, improve final VA, or reduce ERM formation in eyes undergoing surgery for recurrent grade C PVR-related RD at 6 months. While a larger randomized study might better define the role and limitations of anti-VEGF therapy for the management of PVR-related RD, our pilot study showed no clear benefit. Evaluation of anti-VEGF therapy on surgical outcomes in eyes with milder forms of PVR or no PVR, but deemed at high risk, may be worthy of future consideration.

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Biosketch

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