Angiofibrotic Response to Vascular Endothelial Growth Factor Inhibition in Diabetic Retinal Detachment

Report No. 1

Elliott H. Sohn, MD; Shikun He, MD; Leo A. Kim, MD, PhD; Hani Salehi-Had, MD; Michael Javaheri, MD; Christine Spee, BA; Laurie Dustin, MS; David R. Hinton, MD; Dean Elliott, MD

**Objectives:** To assess the effect of bevacizumab injection on connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) in the ocular fluids of patients with diabetic traction retinal detachment, and to determine whether intraoperative and postoperative complications are decreased in eyes given adjunctive preoperative bevacizumab injection.

**Methods:** Twenty eyes of 19 patients were randomized to receive intravitreal bevacizumab or sham injection 3 to 7 days before vitrectomy for severe proliferative diabetic retinopathy. We collected aqueous samples before injection and at the time of vitrectomy and extracted undiluted vitreous samples.

**Results:** Five eyes had decreased vascularization of membranes from preinjection to the time of vitrectomy (all in the bevacizumab treatment arm). Median visual acuities were 20/400 in control eyes at baseline and postoperative month 3 (POM3) and 8/200 in the bevacizumab-treated group at baseline and 20/100 at POM3 (P = .30 between control and bevacizumab-treated groups at POM3). All retinas were attached at POM3. Vitreous levels of VEGF were significantly lower in the bevacizumab group than in the control group (P = .03). Vitreous levels of CTGF were slightly lower in the bevacizumab group compared with the control group, but this difference was not statistically significant (P = .38). Levels of CTGF in the aqueous were strongly correlated with CTGF levels in the vitreous of controls (Spearman correlation coefficient, 0.95 [P < .001]).

**Conclusions:** Intravitreal bevacizumab injection reduces vitreous levels of VEGF and produces a clinically observable alteration in diabetic fibrovascular membranes. Ocular fluid levels of CTGF are not significantly affected within the week after VEGF inhibition. Retinal reattachment rates and visual acuity are not significantly altered by preoperative intravitreal bevacizumab injection at POM3.

**Trial Registration:** clinicaltrials.gov Identifier: NCT01270542

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**DIABETIC RETINOPATHY is the leading cause of blindness for working-age adults in the Western world. Retinal detachment can occur in the advanced, proliferative form of diabetic retinopathy (PDR) when epiretinal fibrovascular proliferative membranes (FVPs) contract, resulting in traction retinal detachment (TRD).1 Traction retinal detachment requires surgical intervention when the macula is involved or threatened, when a combined rhegmatogenous component (TRD/RRD) is evident, or when neovascular glaucoma occurs secondary to TRD and ischemia. Retinal neovascularization is driven in large part by vascular endothelial growth factor (VEGF),2 and VEGF has been identified in aqueous,3 vitreous,4 epiretinal membranes,5 and whole retinas6 of eyes with diabetic retinopathy. Intraocular fibrogenic processes are characterized by inflammation, growth factor production, cellular proliferation and migration, and accumulation and contraction of the extracellular matrix.7 However, the precise mechanism of fibrovascular membrane formation causing TRD in PDR is unknown. Recently, connective tissue growth factor (CTGF) has been identified as a mediator of intraocular fibrosis in proliferative vitreoretinopathy8-11 and PDR.9,12,13**

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In PDR, new vessels become fibrotic over time, and this evolution appears accelerated in some eyes after panretinal pho-
tocoagulation. Similarly, intravitreal injection of bevacizumab has been observed to cause regression of neovascularization and accelerated fibrosis, leading to TRD in some patients with PDR. It has been proposed that this angioblastic "switch" may be mediated by a shift in the balance between VEGF-mediated angiogenesis and profibrotic CTGF.

To better understand the crucial relationship between CTGF and VEGF, we sought to examine angioblastic growth factors before and after VEGF inhibition in a randomized, double-masked, controlled translational study of patients with TRD due to PDR. How soon and to what degree ocular CTGF levels change after VEGF inhibition remain unknown. Based on previous studies examining VEGF and CTGF levels in eyes with PDR, we expected vitreous CTGF levels to be higher in eyes treated with bevacizumab compared with untreated eyes. However, because we placed the stringent requirement to operate within 7 days of bevacizumab injection (to prevent TRD progression), it was plausible that CTGF levels would be unchanged in this early postinjection period.

The aims of this first report are to (1) describe study design and summarize patient baseline characteristics; (2) provide early clinical results; (3) determine the levels of 2 key angioblastic growth factors, CTGF and VEGF, in eyes with severe TRD with and without VEGF inhibition; and (4) examine the correlation of aqueous to vitreous levels of these growth factors.

**METHODS**

This prospective, randomized, double-masked, interventional study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board at Doheny Eye Institute, University of Southern California and Los Angeles County hospitals. In the 2 treatment arms of the study, half the enrolled eyes were randomized to receive intravitreal bevacizumab injection (1.25 mg) and the other half received sham injection (control eyes). Periodic data monitoring and safety assessments were maintained on a regular basis by a clinical trials quality assurance coordinator.

**ENROLLMENT**

Patients with TRD or combined TRD/RRD secondary to PDR who were given anesthesia clearance for pars plana vitrectomy (PPV) at the Doheny Eye Institute, University of Southern California and Los Angeles County hospitals, qualified for enrollment. Indications for PPV included TRD involving the macula, TRD/RRD, and nonclearing or recurrent vitreous hemorrhage precluding complete panretinal photocoagulation with TRD not necessarily involving the macula. Exclusion criteria consisted of a history of PPV; dense vitreous hemorrhage preventing preoperative grading of fibrovascular membranes; an inability to return for PPV within 3 to 7 days after randomization; a history of stroke, thromboembolic event, or heat attack within 6 months; being younger than 18 years; and pregnancy. On the day of enrollment (baseline), informed written consent was obtained and the baseline preoperative evaluation, randomization, and intervention (detailed in the "Intervention" subsection) were performed.

**CLINICAL ASSESSMENT**

Preoperative (ie, before randomization) and intraoperative assessments for all patients were performed by a single surgeon (E.H.S.). We obtained a complete medical and ophthalmic history. The most recent hemoglobin A1c level was recorded. Best-corrected distance visual acuity (VA) testing was performed by trained ophthalmic personnel using a Snellen chart, pinhole, and refraction. Detailed ophthalmic examination was performed.

Before randomization and at the time of the vitrectomy, the retinal detachment was classified as TRD or TRD/RRD and graded according to the extent of hyaloideal attachment as mild (local vitreoretinal attachment), moderate (broad vitreoretinal attachment), or severe (complete vitreous attachment). Epiretinal FVPs causing the TRD were also graded as predominantly neovascular, mixed neovascular and fibrotic, and predominantly fibrotic. At baseline, on the day of the vitrectomy, and at postoperative month 3 (POM3), fundus photography and spectral-domain optical coherence tomography (3D OCT-1000; Topcon Medical Systems, Inc) were performed. If clinically significant macular edema was evident on slitlamp biomicroscopy, fluorescein angiography was also performed.

**INTERVENTION**

All patients were given a subconjunctival injection of lidocaine hydrochloride, 2%. For eyes randomized to receive intravitreal injection, 1.25 mg bevacizumab in 0.05 ml was administered. Eyes randomized to the control group had a syringe without a needle placed to simulate intravitreal injection. All patients received oculofloxacin eyedrops for 4 days. The patients and surgeon were masked to the patients’ randomization group. At the baseline evaluation, the appropriate intervention was performed by the injecting physician (different than the surgeon).

**SURGICAL PROCEDURES**

Vitrectomy was performed on all patients 3 to 7 days after baseline. Particular attention was given to changes in vascularity and extent of the FVP (using the same preoperative grading system described in the “Clinical Assessment” subsection). Retinohyaloidal attachments and any areas of increased subretinal fluid (ie, worsening of retinal detachment) were compared with baseline. These findings were detailed in a comprehensive intraoperative record. All patients underwent 20-gauge PPV using a combination of delamination and segmentation techniques. In some cases where the FVP extended anterior to the equator, scleral buckling and/or pars plana lensectomy was performed. Extensive panretinal photocoagulation was applied in all cases.

**INTRAOPERATIVE BLEEDING**

The amount of bleeding was recorded in the intraoperative record using the following grading system: none, 1 (minor bleeding stopping spontaneously or with transient bottle elevation), or 2 (moderate to severe bleeding requiring endodiathermy or with formation of broad sheets of clots).

**OCULAR SAMPLES FOR LABORATORY ANALYSIS**

Immediately before intraocular injection of bevacizumab (or sham injection) and on the day of the vitrectomy, aqueous was sampled. Undiluted vitreous samples were also obtained for each patient at the start of the procedure. Samples were promptly centrifuged at 10,000 rpm at 4°C, and the supernatants were frozen at −80°C until assayed. Fibrovascular membranes dis-
sected during each vitrectomy were placed in iced balanced salt solution and stored for analysis.

**ENZYME-LINKED IMMUNOSORBENT ASSAY**

Concentrations of VEGF were assayed using enzyme-linked immunosorbent assay (ELISA) (Quantikine; R&D Systems) according to the manufacturer’s instructions. Levels of CTGF were obtained using the precoated human CTGF ELISA kit (Super X; Antigenix American, Inc.). For each assay, standard curves were performed to determine the appropriate dilution factor (1:5 for CTGF and 1:10 for VEGF).

**STATISTICS**

To study the difference between median VEGF levels in the aqueous and vitreous for the bevacizumab and control groups, we calculated Wilcoxon rank sum test P values (because the distributions were not normal); for mean CTGF levels, we calculated the independent samples t test. Spearman correlation coefficient (SCC) analysis was performed to correlate levels of CTGF and VEGF to each other and to compare the aqueous and vitreous concentrations of these growth factors.

The analysis of VA only included subjects who had 3 months of follow-up. Visual acuity was converted to logMAR units. For counting fingers, the best-corrected VA was considered equivalent to 1/200 (logMAR VA, 2.3). For hand motions, light perception, and no light perception, logMAR VA of 3.3, 4.3, and 5.3, respectively, was assigned. We used the Wilcoxon rank sum test to compare median VA at individual points between bevacizumab-treated eyes and controls. The frequency of VA change was determined with the Fisher exact test.

**RESULTS**

**CLINICAL DATA**

Twenty eyes of 19 patients at Los Angeles County Hospital were enrolled in the study. The demographics and clinical information are listed in Table 1. The median patient age was 52 years, and 12 patients were men. All eyes had undergone previous panretinal photocoagulation. Ten eyes received intravitreous bevacizumab injection and 10 received sham injection (controls). Five eyes had moderate TRD, 8 had severe TRD, and 7 had combined TRD/RRD. Four of the 5 eyes with moderate TRD were randomized to the control group. Preoperative best-corrected VA ranged from 20/70 to hand motions in the bevacizumab group and 20/400 in the control arm (Table 2). Median VA at POM3 was 20/100 in the bevacizumab arm and 20/400 in the control arm (P = .15). All retinas were attached at POM3, thus the POM3 data were not available on these patients (Table 2).

**LABORATORY DATA**

Median VEGF levels in the vitreous were significantly higher in the control group (397 [range, 0-1073] pg/mL) compared with the bevacizumab-treated group (un-detectable with conditions applied [range, 0-559 pg/mL]; P = .03) (Table 2). Median aqueous VEGF levels measured at baseline (13 [range 0-1652] pg/mL in the bevacizumab group; 0 [range, 0-868] pg/mL in the control group) and at the time of PPV were low in both groups and not statistically different between groups. Aqueous

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**Table 1. Demographics and Clinical Information of Enrolled Patients**

<table>
<thead>
<tr>
<th>Case No./Sex/ Age, y</th>
<th>Eye</th>
<th>Preoperative TRD Severity</th>
<th>Interval, Injection to Vitrectomy, d</th>
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<tr>
<td>1/F/64/C</td>
<td>OS</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>2/M/42/B</td>
<td>OS</td>
<td>Severe</td>
<td>3</td>
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<tr>
<td>3/M/47/B</td>
<td>OS</td>
<td>TRD/RRD</td>
<td>5</td>
</tr>
<tr>
<td>4/M/31/C</td>
<td>OD</td>
<td>Moderate</td>
<td>4</td>
</tr>
<tr>
<td>5/M/62/C</td>
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<td>Severe</td>
<td>6</td>
</tr>
<tr>
<td>6/M/45/B</td>
<td>OD</td>
<td>Severe</td>
<td>6</td>
</tr>
<tr>
<td>7/F/57/C</td>
<td>OD</td>
<td>TRD/RRD</td>
<td>4</td>
</tr>
<tr>
<td>8/F/46/B</td>
<td>OD</td>
<td>TRD/RRD</td>
<td>4</td>
</tr>
<tr>
<td>9/M/62/B</td>
<td>OD</td>
<td>TRD/RRD</td>
<td>4</td>
</tr>
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<td>OD</td>
<td>Moderate</td>
<td>4</td>
</tr>
<tr>
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</tr>
<tr>
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<td>TRD/RRD</td>
<td>4</td>
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<td>Severe</td>
<td>6</td>
</tr>
<tr>
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<td>TRD/RRD</td>
<td>3</td>
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<td>Severe/SR bands</td>
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<td>OD</td>
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<tr>
<td>19/F/54/C&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>20/F/51/B</td>
<td>OD</td>
<td>Moderate</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: B, bevacizumab; C, control; OD, right eye; OS, left eye; RRD, rhegmatogenous retinal detachment; SR, subretinal; TRD, traction retinal detachment.

<sup>a</sup>Case 19 is the left eye of case 11.

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Levels of VEGF did not correlate with those in the vitreous ($P = .19$).

Levels of CTGF were detectable in the aqueous but were not significantly different between the 2 arms at the time of vitrectomy. However, in the bevacizumab group, median aqueous levels of CTGF were slightly higher at the time of PPV (1211 [range, 0-3020] pg/mL) compared with preinjection (956 [range, 0-1890] pg/mL). Median levels of CTGF in the vitreous were 1235 (range, 0-2089) pg/mL in the control arm and 980 (range, 0-1927) pg/mL in the bevacizumab arm ($P = .38$) (Table 2). Median ratios of CTGF to VEGF vitreous levels were 39 in the bevacizumab group and 2.5 in the control group ($P = .09$, Wilcoxon rank sum test).

With all 20 eyes combined, aqueous levels of CTGF were significantly correlated with vitreous levels ($R=0.95; P<.001$) (Figure 1). The SCC increased to 0.95, singling out the control group (n=10), but was not significant in the bevacizumab group alone (10 patients; SCC, 0.52 [$P = .13$]), suggesting that VEGF inhibition has an effect on CTGF. In addition, we found a statistically significant correlation between vitreous CTGF and VEGF levels that was observed in the bevacizumab group (SCC, 0.75 [$P = .01$]) and not in the control group (SCC, −0.31 [$P = .38$]).

### REPORT OF A CASE

Case 12 was an African American man aged 38 years with type 1 diabetes mellitus for 21 years who had undergone previous TRD repair of the left eye at an outside hos-
pital. Visual acuity was 1/200 in the right eye and light perception in the left eye. The right eye had early cataract and a macula-off traction retinal detachment with rhegmatogenous component and mixed neovascular-fibrotic epiretinal proliferative membranes. He was randomized to the bevacizumab group. At vitrectomy, decreased vascularization of the FVP was noted (Figure 2B). The preinjection aqueous VEGF level was 124 pg/mL; at vitrectomy, 34 pg/mL. The undiluted vitreous VEGF level was undetectable. The preinjection aqueous CTGF level was 452 pg/mL; at vitrectomy, 858 pg/mL. The vitreous CTGF level was 993 pg/mL. Vitrectomy, scleral buckle, and 14% perfluoropropane tamponade were performed. Three months after vitrectomy, the patient’s VA was 20/40−2 and the retina was attached (Figure 2C).

COMMENT

In this randomized, controlled, reverse-translational study of patients with TRD due to PDR, a clinically observable alteration in FVP was noted, and vitreous VEGF levels were suppressed after a single 1.25-mg intravitreal bevacizumab injection, given a median of 4 days before vitrectomy. Vitreous CTGF levels in the bevacizumab-treated group were lower but not significantly different between the groups at the time of vitrectomy; however, several pieces of evidence suggest that VEGF inhibition has an effect on CTGF level in these eyes. First, a correlation between VEGF and CTGF levels was statistically significant only in the bevacizumab group. Second, the aqueous CTGF level was highly correlated with vitreous CTGF levels only in the control group.

EFFECT OF VEGF INHIBITION ON ANGIOFIBROTIC GROWTH FACTORS

Suppression of vitreous VEGF levels after intravitreal bevacizumab injection has been demonstrated previously. Similarly, we found that vitreous levels of VEGF were significantly lower in those treated with bevacizumab compared with controls. Unlike previous reports, a significant change was not seen in the aqueous of the bevacizumab-treated group. Because most of these uninsured, predominantly Hispanic patients at Los Angeles County Hospital had severe, predominantly fibrotic TRDs with no obscuring vitreous hemorrhage, these study eyes may represent a unique situation in which VEGF levels have dissipated due to long-standing disease; thus, the concentration of VEGF is highest in the vitreous, closest to where it is produced. This theory could explain the relatively low levels of aqueous VEGF in the patients at baseline (ie, before injection) but relatively high levels in the vitreous at the time of vitrectomy.

Evidence suggests that CTGF plays an important profibrogenic role in the body and eye and is induced in wound healing. It is upregulated by—and promotes—the fibrotic response induced by transforming growth factor β. Dysregulation of CTGF expression has been implicated in abnormal fibroproliferative disease states of the kidney, heart, liver, and skin. Elevated levels of CTGF have been associated with proliferative vitreoretinopathy, choroidal neovascular membranes, and PDR.

The precise relationship between VEGF and CTGF is unclear, but VEGF has been demonstrated to increase expression of CTGF. On the other hand, CTGF can also bind VEGF and thereby downregulate VEGF-induced angiogenesis. Elevated CTGF levels in eyes with PDR may explain in part why eyes with predominantly dense fibrotic membranes do not tend to continue to develop epiretinal neovascularization.

The lack of a significant difference between vitreous CTGF levels in the control and bevacizumab groups could be explained by several reasons. First, the number of eyes...
studied may be too small to detect a significant difference. Second, considering that VEGF can upregulate CTGF, decreased VEGF expression may downregulate CTGF, especially in the early phases of VEGF suppression. Finally, vitreous samples may have been extracted too early to detect a significant alteration in CTGF expression. This study was designed to limit the potential for TRD progression observed by Arevalo and colleagues that occurred a mean of 13 days after intravitreal bevacizumab injection. Thus, all patients underwent PPV within 7 days. Because TRD progression is thought to occur by further contraction of fibrotic membranes, the downstream effects of contraction may take more than 7 days to occur.

CORRELATION OF AQUEOUS TO VITREOUS CONCENTRATIONS OF VEGF AND CTGF

Although several studies have analyzed vitreous levels of VEGF independently, to date no studies have correlated aqueous to vitreous measurements of VEGF (or CTGF) levels after bevacizumab injection in patients with PDR. Aqueous VEGF levels did not correlate well with vitreous VEGF levels, probably owing to the advanced stage of disease in the eyes studied in this trial. Low aqueous levels of VEGF were expected because most of these eyes did not have active neovascularization. The lack of correlation between aqueous and vitreous VEGF in severe PDR has not been previously demonstrated, and this merits further study.

On the other hand, aqueous CTGF is a good marker for vitreous CTGF in eyes not treated with VEGF inhibition. That this effect was not seen in the bevacizumab-treated group suggests that the reduction of VEGF levels has an effect on CTGF levels that was not borne out in the primary comparison of CTGF levels between the bevacizumab-treated and control groups. This effect may be better elucidated in subsequent analysis of membranes extracted from these eyes. Because VEGF inhibition appears to have some effect on CTGF, aqueous CTGF may not be substituted for vitreous CTGF in eyes treated within 7 days with bevacizumab. This finding may be useful in future studies when undiluted vitreous is not available but the patient can undergo the less invasive aqueous paracentesis in the clinic.

CLINICAL RESPONSE OF TRD IN PDR TO VEGF INHIBITION

Regression of neovascularization in PDR after intravitreal bevacizumab injection was first demonstrated in 2006. Since then, preoperative bevacizumab injection has been touted as an adjunctive therapy to decrease intraoperative bleeding, postoperative hemorrhage, and surgical times and to improve surgical outcomes. The efficacy of preoperative adjunctive bevacizumab injection has been debated recently, especially with regard to the incidence of postoperative vitreous hemorrhage. Many studies examining the effect of preoperative bevacizumab were retrospective; studies that were prospective and controlled included patients with vitreous hemorrhage that precluded grading of the fibrovascular tissue.

As expected among these patients with advanced disease, most eyes (15 of 20 [75%]) enrolled in this study had severe TRD or TRD/RRD. Extension of FVPs to the far periphery occurred in 6 eyes. Owing to randomization, more eyes with severe TRD or TRD/RRDs were enrolled in the bevacizumab group, which could be associated with a bias toward worse results. However, overall, no significant differences in anatomic or visual outcomes were found between the 2 groups at POM3.

Although most patients had predominantly fibrotic membranes, all 6 eyes judged preoperatively to have continued vascularization (ie, mixed neovascularization and fibrosis) were randomized to the bevacizumab group by chance. Under masked conditions, 5 (83%) had an alteration in the membrane to complete fibrosis noted intraoperatively. No eyes experienced an alteration in the retinohyaloidal interface or in progression of TRD within the 7-day window after intravitreal bevacizumab injection. Studies involving smaller doses of intravitreal bevacizumab (as low as 0.16 mg) have demonstrated similar clinical response and suppression of VEGF levels.

The clinical observation of transition from a predominantly neovascular to a fibrotic epiretinal membrane in PDR over time is well known. The growth factors responsible for this transition remain unclear. Although regression of neovascularization after bevacizumab injection occurs relatively rapidly (as early as 3 days in this study), the persistently elevated CTGF levels in the face of low VEGF levels demonstrated in this study may foster a profibrotic environment. This balance between CTGF and VEGF levels has been termed the angiofibrotic switch. Although we expected CTGF levels to be elevated after intravitreal bevacizumab injection, we found that they were unchanged or possibly lower in the 3 to 7 days after injection. Because CTGF has a heparin-binding domain and binds to the extracellular matrix in its native state, soluble CTGF that is freely circulating in ocular fluid may degrade. This event may help to explain the minimal change in CTGF fluid levels after VEGF inhibition. On the other hand, VEGF inhibition may decrease levels of CTGF, at least in the short term.

In a retrospective analysis, Van Geest et al found higher CTGF levels and fibrosis in eyes with PDR that had undergone previtreous intravitreal bevacizumab injection. Although a subset of their patients underwent vitrectomy within 1 week of injection, the levels of CTGF in these patients remained unclear. As illustrated in our case report, without careful comparison of neovascularization and fibrosis from preinjection to the time of PPV (which requires relatively clear media), one might mistake an increase in fibrosis when this change represents a regression of neovascularization in an area of preexisting fibrosis. Because our patients had CTGF levels measured within 1 week of bevacizumab injection, this angiofibrotic switch might begin with only decreased vascularization and VEGF levels within the first 7 days of injection.
Ongoing examination of the membranes extracted from eyes in our study should provide insight into the relationship between VEGF inhibition and CTGF levels. Additional reports will also detail anatomic and long-term outcomes of the patients in this study.

At this time, we recommend cautious use of intravitreal bevacizumab as a preoperative adjunct treatment for diabetic PPV that may be most useful in eyes with predominantly neovascular membranes. The finding that levels of CTGF are still relatively low in the 3 to 6 (maximum, 7) days after intravitreal bevacizumab injection provides some rationale to perform traction detachment surgery during this early postinjection period.

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Correspondence: Elliott H. Sohn, MD, Department of Ophthalmology, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, Iowa City, IA 52242 (Elliott.Sohn@gmail.com).

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REFERENCES


