

Intravitreal Bevacizumab in the Surgical Treatment of Proliferative Diabetic Retinopathy

Given at the time of surgery, the anti-VEGF agent reduces intraoperative and postoperative bleeding.

BY ROBERT L. AVERY, MD

Intravitreal bevacizumab (Avastin, Genentech) can be a useful surgical adjunct in the treatment of patients with proliferative diabetic retinopathy (PDR). This paper summarizes our experience with use of bevacizumab as an adjunct to surgery in diabetic patients, which is an off-label use of this drug.

TREATMENT OF PDR

In 2005, after our initial encouraging experience with intravitreal bevacizumab for age-related macular degeneration, I began to use it in patients with rubeosis. The first patient I treated presented with bilateral neovascularization, rubeosis in the right eye, and partial vitreous hemorrhage in the left eye.¹ I applied panretinal photocoagulation (PRP) for the left eye, and on the same day I injected bevacizumab into the right eye. Within 1 week, the neovascularization of the iris, nerve head, and posterior pole stopped leaking in the right eye, and the areas of nonperfusion looked smaller.

Presenting this case at the American Academy of Ophthalmology meeting in 2005,² I proposed a number of potential

roles for intravitreal bevacizumab in patients with PDR. These include treatment of rubeosis, persistent neovascularization despite PRP, vitreous hemorrhage precluding PRP, PDR associated with diabetic macular edema, and as an injection before vitrectomy to reduce bleed-

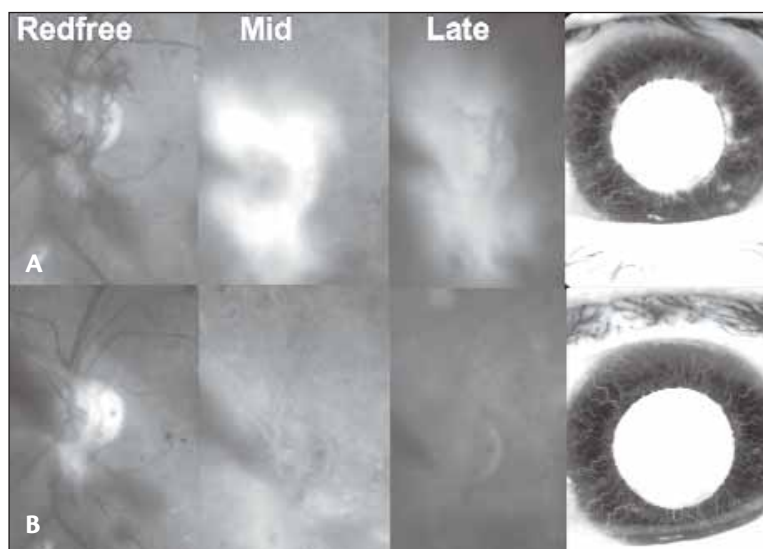


Figure 1. Red-free, midphase, and late-phase fluorescein angiograms and iris angiograms at (A) baseline and (B) 1 week after intravitreal injection of 1.25 mg of bevacizumab.

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NEW STUDY ADDS TO POSITIVE EVIDENCE FOR INTRAVITREAL BEVACIZUMAB BEFORE VITRECTOMY FOR PDR

A study recently published in the online edition of *Graefes Archives of Clinical and Experimental Ophthalmology*¹ showed benefit and tolerability to intravitreal injections of bevacizumab (Avastin, Genentech) prior to pars plana vitrectomy (PPV) for complications associated with severe proliferative diabetic retinopathy (PDR).

In the study of 22 patients, 11 patients who were diagnosed with severe PDR received intravitreal injections of 1.25 mg bevacizumab 5 to 7 days before surgery, while the other 11 patients underwent PPV alone. The main outcome of the study was feasibility of surgery and the secondary outcome was visual and anatomic outcome 6 months postoperative. Prior to surgery, the complexity of the PDR was recorded and surgery time and events were recorded intraoperatively.

Adjunctive Agent Improves Surgery Time and Procedure

The investigators calculated the complexity scores at ~5.5 for both groups. The surgical time recorded for the intravitreal bevacizumab group, however, was 57 minutes, compared with 83 minutes for the PPV alone group. Additionally, there were fewer tool exchanges in the bevacizumab + PPV group vs the PPV alone group (27 vs 53), as well as less bleeding during surgery in the bevacizumab + PPV group (5 vs 15) and only two endodiathermy procedures required in the first group vs nine for the PPV alone group.

The visual acuity findings postoperatively were based on the baseline best-corrected visual acuity (BCVA) measurements, which were not statistically different from group 1 to group 2 (group 1: 1.87 logMAR; group 2: 2.04 logMAR; $P=.70$). Although the mean postoperative vision difference between group 1 and group 2 was significant (group 1: 0.88 logMAR; group 2: 2.01 logMAR; $P=0.01$), the vision change from pre- to postoperative BCVA in both groups was not significant (group 1: $P=0.15$; group 2: $P=0.96$).

The anatomical outcomes were that all patients in the group that received bevacizumab plus PPV had reattachment, while nine of 11 patients in the PPV alone group had reattachment.

The researchers concluded that bevacizumab before vitrectomy helped to ease the surgical process by clearing neovascularization.

1. Rizzo S, Genovesi-Ebert F, DiBartolo E, Vento A, Miniaci S, Williams G. Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR). *Graefes Arch Clin Exp Ophthalmol*. 2008;Feb 20 [Epub ahead of print].

ing when fibrovascular tissue is cut.

We have published our short-term results using intravitreal bevacizumab in the treatment of PDR in a series of 45 eyes of 32 patients at California Retina Consultants and Retinal Consultants of Sacramento.³ No significant ocular or systemic adverse events were seen in that retrospective review with short-term follow-up. All 44 patients who had fluorescein angiography demonstrated partial or complete reduction of leakage within 1 week, and some as early as 1 day after injection. Complete resolution of neovascularization of the disc was seen angiographically in 19 of 26 eyes (73%) (Figures 1 and 2). Doses of bevacizumab from 1.25 mg to as little as 6.25 μ g were seen to result in reduction of retinal leakage (Figure 3), although the effect with 1/200 of the usual dose was less prominent than at higher doses. In two cases, a subtle effect was seen in the fellow uninjected eye, which suggests that systemic circulating levels reached a therapeutic level after intravitreal injection. This argues for the potential use of lower doses for PDR.

We concluded that intravitreal bevacizumab was well

tolerated in the short term and that it was associated with rapid regression of retinal and iris neovascularization due to PDR, although leakage tends to recur, usually within a few months.

USE AS SURGICAL ADJUNCT

We recently reviewed our results with intravitreal administration of bevacizumab before surgery for PDR.⁴

Administration as a surgical adjunct may be one of the most promising applications of bevacizumab in patients with PDR. Among the rationales for use of bevacizumab injection before surgery for PDR is that it may reduce bleeding intra- and postoperatively (Figure 4). Reduction in bleeding may in turn facilitate membrane dissection. In addition, bevacizumab may reduce edema and rubeosis and therefore the chance of hyphema obscuring visibility during surgery. Other beneficial effects may include a reduction of overall surgical time, as well as requiring less elevation of intraocular pressure to control intraoperative bleeding. The resulting improvement in ocular perfusion during surgery may be particularly important in this pop-

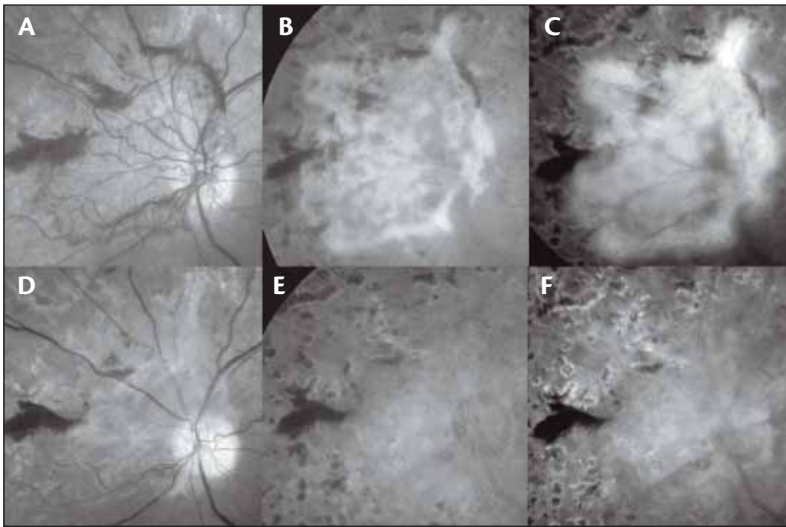


Figure 2. Red-free (A), midphase (B), and late-phase (C) angiograms at baseline and red-free (D), midphase (E), and late-phase (F) angiograms 3 weeks after intravitreal injection of 1.25 mg of bevacizumab.

ulation of patients who frequently have severely impaired vascular perfusion.

There are theoretical systemic risks in the use of intravitreal bevacizumab in diabetic patients who are at elevated risk for thromboembolic events. Its use may also theoretically interfere with wound healing, although this was not observed in this series.

Administration of bevacizumab may also theoretically cause a rebound upregulation of vascular endothelial growth factor (VEGF) receptors when it is removed or diffuses from the eye. Also, there is an observed risk for advancement of traction retinal detachments in certain high-risk patients.

We identified 103 eyes of 86 consecutive patients who received intravitreal bevacizumab before undergoing pars plana vitrectomy for PDR. Thirteen eyes were excluded because they had been treated with intravitreal bevacizumab more than 2 months before surgery. We were initially using bevacizumab in eyes with vitreous hemorrhage in hopes of speeding clearance of the hemorrhage and allowing laser treatment, with the aim of avoiding vitrectomy. In some of these eyes, however, vitrectomy was eventually required because of persistent or recurrent hemorrhage. These eyes had good results, but they were excluded from this analysis because we were unsure if the bevacizumab was still having an effect on the vessels several months after injection.

RESULTS OF ANALYSIS

We analyzed results in the remaining 90 eyes of 74 patients. Mean age was 59 years (range, 20–77), and

mean duration of diabetes at the time of surgery was 15 years. Mean length of follow-up was 8 months. Preoperative diagnoses included vitreous hemorrhage in 72 eyes, traction retinal detachment in 38 eyes, and neovascular glaucoma in 10 eyes. Mean number of bevacizumab injections per eye was 1.33 (range, 1–3). The mean length of time between injection and surgery was 11.9 days (range, 1–61). Preoperatively, mean visual acuity was 2/200 (range, light perception–20/50). Postoperatively, mean visual acuity improved to 20/400 (range, light perception–20/25).

No systemic complications that were felt to be attributed to the bevacizumab were noted. Three patients developed postoperative retinal detachments that were repaired. One patient

with neovascular glaucoma developed an epiretinal membrane that was subsequently removed. In 36 of 90 eyes (40%), some level of postoperative vitreous hemorrhage developed, and in four patients this necessitated repeat vitrectomy. Two patients developed contraction of neovascular membranes, which progressed to retinal detachment 1 month after the injection.

It may be that postoperative vitreous hemorrhage is related to the surgical removal of the vitreous, which acts as a reservoir for bevacizumab. Theoretically, there could

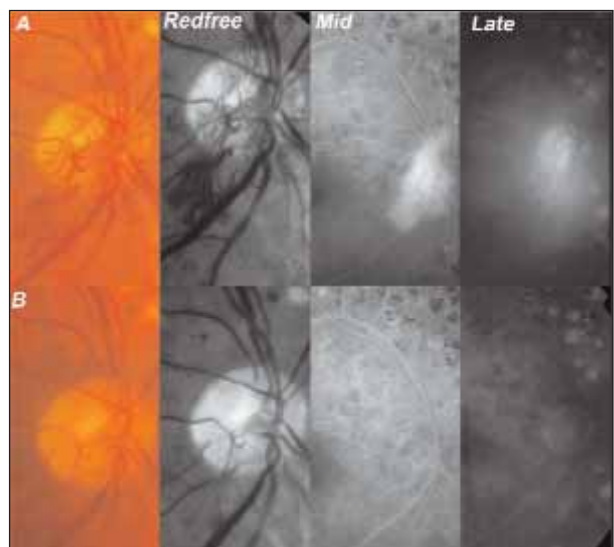


Figure 3. Color, red-free, midphase, and late-phase fluorescein angiograms at (A) baseline and (B) 1 week after intravitreal injection of 125 µg of bevacizumab.

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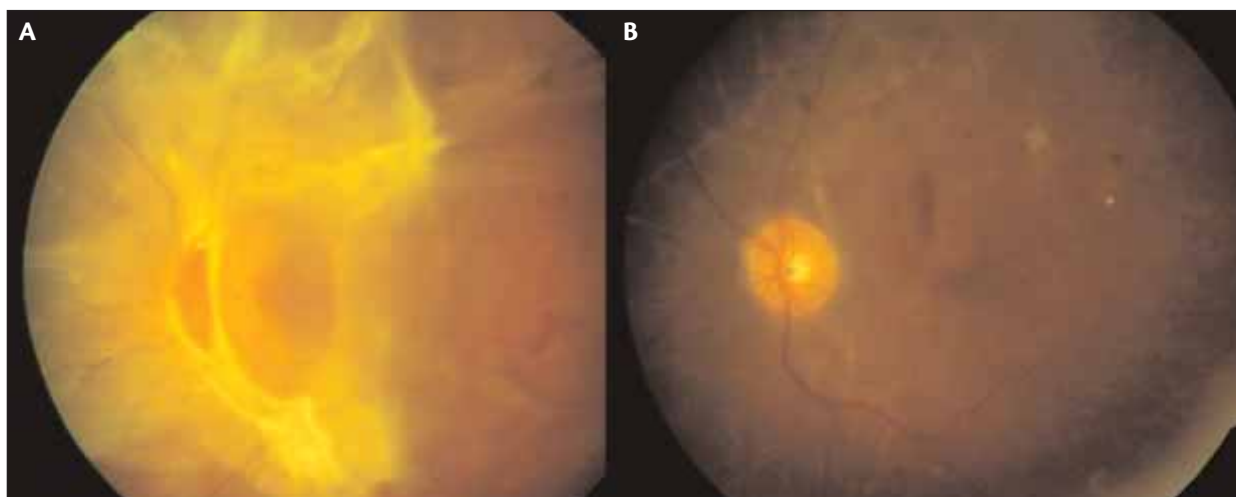


Figure 4. Fundus appearance 1 week after intravitreal injection of 1.25 mg bevacizumab and just before vitrectomy (A), postoperative appearance 2 months after surgery (B).

be a rebound effect related to upregulation of VEGF receptors. Therefore, we now frequently inject intravitreal bevacizumab at the conclusion of the operation. Alternatively, preoperative bevacizumab may mask the activity of neovascularization, which could be overlooked intraoperatively if the surgeon had been unable to observe it preoperatively due to vitreous hemorrhage (Figure 2).

Although intraoperative bevacizumab may lower the risk of early recurrent vitreous hemorrhage, late recurrent hemorrhages still occur. Surgeons should consider performing extensive intraoperative laser to the ora serrata in these eyes to reduce ischemia and production of VEGF.

In two patients, contraction of neovascularization developed after injection of bevacizumab but before surgery, and this progressed to traction retinal detachment. These patients had very severe fibrovascular proliferations in a ring configuration with pre-existing partial traction retinal detachment before the bevacizumab injection. This phenomenon has recently been reported.⁵ In that report, combining our cases and those from several other centers, 11 eyes experienced detachment out of 211 injected patients at a mean of 13 days after injection (range, 3–31). Poorly controlled diabetes mellitus was a risk factor for detachment.

CONCLUSIONS

Intravitreal injection of bevacizumab produces a rapid anatomic effect in eyes with PDR, but neovascularization tends to recur after a few months. Still, it is a useful adjunct in the surgical treatment of PDR.

Potential advantages of preoperative intravitreal bevacizumab include reduction of intraoperative and

postoperative bleeding, facilitation of membrane dissection, reduction of macular edema, reduction of iris neovascularization and hyphema, and reduction of operating time.

Intravitreal bevacizumab is well-tolerated in the short term, although caution is warranted because patients with PDR have a higher risk for systemic thromboembolic events. The drug has been observed to induce contraction of fibrovascular tissue and progression of traction retinal detachment. In high-risk patients, it is advisable to inject bevacizumab less than 1 week before vitrectomy and after the patient has been cleared for surgery. Intraoperative administration of additional bevacizumab may reduce the early recurrence of vitreous hemorrhage.

Prospective trials will be needed to properly assess the safety and efficacy of the use of bevacizumab as a surgical adjunct in the treatment of PDR. ■

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