

INTRAVITREAL BEVACIZUMAB (AVASTIN) TREATMENT OF PROLIFERATIVE DIABETIC RETINOPATHY COMPLICATED BY VITREOUS HEMORRHAGE

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Purpose: To report the short-term anatomic and visual acuity response after intravitreal injection of bevacizumab (Avastin, Genentech) in patients with proliferative diabetic retinopathy complicated by vitreous hemorrhage.

Methods: Two patients with vitreous hemorrhage due to proliferative diabetic retinopathy were treated with at least one intravitreal injection of bevacizumab 1.25 mg in 0.05 mL. The patients underwent Snellen visual acuity testing, ophthalmoscopic examination, and fluorescein angiography at baseline and follow-up visits.

Results: Both patients had proliferative diabetic retinopathy with vitreous hemorrhage extensive enough to preclude panretinal photocoagulation. Following intravitreal injection of bevacizumab both patients experienced improvement in visual acuity starting within the first week. At 1 month of follow-up one patient had 2 lines of improvement in visual acuity and the other 5 lines. Each patient had regression of retinal neovascularization at 1 month of follow-up. Repeat injection was given to one patient at the 1-month follow-up because of slight leakage from neovascularization on the nerve, and to the other patient at 3 months because the retinal neovascularization showed early signs of reperfusion. The vitreous hemorrhage in each patient showed partial resolution at 1 week and nearly complete regression at 1 month. No adverse events were observed in either patient.

Conclusions: Initial treatment results of patients with vitreous hemorrhage and proliferative diabetic retinopathy did not reveal any short-term safety concerns. Intravitreal bevacizumab resulted in marked regression of neovascularization and rapid resolution of vitreous hemorrhage. The favorable short-term results suggest further study is needed in a larger group of patients.

RETINA 26:275–278, 2006

In developing countries the incidence of diabetes is growing at an alarming rate.¹ In industrialized countries proliferative retinopathy due to diabetes is the leading cause of blindness. Proliferative diabetic reti-

nopathy (PDR), the growth of new vessels from the retina or optic nerve, is thought to occur in response to ischemia driven release of vascular endothelial growth factor (VEGF) into the vitreous cavity.^{2–4} The ischemia occurs because diabetes causes microvascular occlusion in the eye resulting in local hypoperfusion. The ischemic retina secretes VEGF, which leads to a number of related events in the eye. VEGF causes vascular leakage,^{5,6} and increased levels of VEGF are

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The authors have no proprietary interests in this study.

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related to macular edema.⁷ Increased VEGF levels also can contribute to,²⁻⁴ although may not be solely responsible for,^{8,9} the formation of new vessels arising from the plane of the retina, which by definition is PDR. VEGF also has a curious property of causing microvascular occlusion, telangiectasis, and microaneurysm formation, all hallmarks of diabetic retinopathy itself.^{9,10} The microvascular occlusion can lead to increasing ischemia in a self-reinforcing cycle. Accompanying the proliferating vessels is fibroglial tissue, which with the vitreous, may contract and lead to hemorrhage because of traction on the proliferating vessels. Laser photocoagulation currently is the principal therapy for sight-threatening PDR, unless the patient already has extensive vitreous hemorrhage, which would preclude the possibility of laser photocoagulation.¹¹ Thus one of the principal complications of diabetic retinopathy inhibits its own treatment. Vitreous hemorrhage complicating PDR currently is managed one of two ways: observation hoping the blood will resorb enough to allow laser photocoagulation or surgical intervention to remove the blood and fibrovascular tissue and at the same time perform laser photocoagulation. However, a third option may be the inhibition of VEGF. A recombinant humanized monoclonal antibody directed against VEGF is available (bevacizumab, Avastin, Genentech) for cancer therapy.¹² Intravitreal bevacizumab in humans has been previously described for the treatment of central retinal vein occlusion and age-related macular degeneration in single case reports.^{13,14} We offered intravitreal bevacizumab to two patients with the hopes of interrupting the downward spiral of PDR complicated by vitreous hemorrhage.

Methods

The patients were evaluated with a comprehensive ophthalmologic examination that included best-corrected visual acuity, biomicroscopic examination of the fundus, and fluorescein angiography. After informed consent was obtained an intravitreal injection of bevacizumab 1.25 mcg/0.05 cc was given. All injections were performed in the usual sterile fashion¹⁵ and prophylactic topical antibiotics were given for 2 days postinjection. The patients were examined at 1 week and 1 month after injection.

Results

Both patients had vitreous hemorrhage that precluded additional panretinal photocoagulation, which was attempted in both patients. Each patient was considered a possible vitrectomy candidate because of the nonclearing vitreous hemorrhage complicating the

PDR causing loss of visual acuity. Neither patient had any observable adverse effect from the injection; specifically, no patient had any intraocular inflammation, retinal tears, detachments, or any systemic problem.

Case 1

A 68-year-old patient with PDR had incomplete panretinal photocoagulation in both eyes. She developed a rhegmatogenous detachment in the right eye complicated by proliferative vitreoretinopathy and a visual acuity of counting fingers. She underwent multiple vitrectomy procedures and had reattachment of her retina, but her visual acuity in the right eye was 20/400. She could not have completion of her panretinal photocoagulation in the left eye because of vitreous hemorrhage of several years duration, although she had extensive retinal neovascularization. There was a localized tractional retinal detachment detected by contact b-scan ultrasonography superior to the optic nerve head that did not involve the macula. She declined vitrectomy surgery. She had a visual acuity of 20/60 in that eye. She was offered intravitreal bevacizumab as a possible means to treat the retinal neovascularization. She consented to the injection and was given 1.25 mg of bevacizumab without incident. One week later her visual acuity was 20/40 in the left eye. She showed marked regression of the retinal neovascularization and remarkable clearing of the vitreous hemorrhage (Figure 1). The patient reported that she was very happy because she could read a newspaper for the first time in 2 years. Repeat examination with fluorescein angiography was performed monthly after the injection. Her visual acuity remained stable at 20/40. At 2 months after injection the patient had no signs of recurrent growth of the retinal neovascularization (Figure 1). Three months after injection the patient started to show subtle signs of reperfusion of the retinal neovascularization. She was given a repeat injection of 1.25 mg of bevacizumab. She was not interested in additional laser photocoagulation. The tractional retinal detachment did not change in size.

Case 2

A 38-year-old man with insulin-dependent diabetes mellitus had PDR in the right eye and PDR with a nonclearing vitreous hemorrhage in the left (Figure 2). He could have panretinal laser photocoagulation in the right eye, which was completed. He had a tractional retinal detachment in the left eye superior to the superotemporal arcade with retinal neovascular vessels approaching the caliper of his arcade vessels. The tractional detachment did not involve the macula. He had extensive vitreous hemorrhage in the left eye that

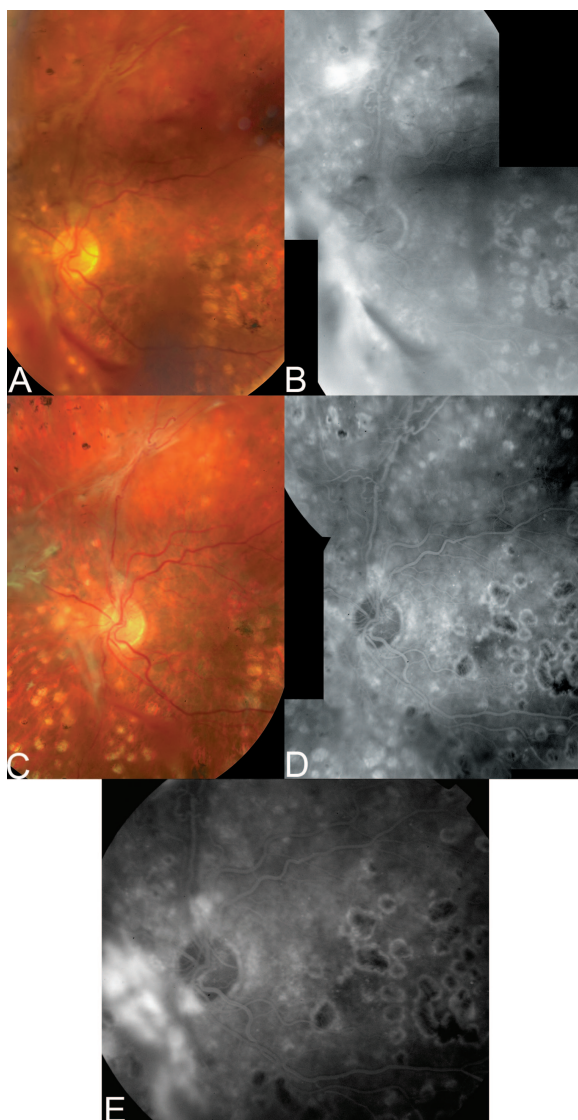


Fig. 1. This 68-year-old patient with proliferative diabetic retinopathy and vitreous hemorrhage could not have any additional panretinal photocoagulation because of the presence of widespread vitreous hemorrhage (A). Her visual acuity was 20/60. B, The fluorescein angiogram showed extensive retinal neovascularization but no evidence of macular edema. Observation of the posterior pole is partially obscured by the vitreous hemorrhage. C, Two months after one injection of bevacizumab there was nearly complete resorption of the vitreous hemorrhage and (D) no apparent retinal neovascularization. E, Three months after injection the patient showed signs of reperfusion of the retinal neovascularization. She was reinjected with 1.25 mg of bevacizumab.

precluded laser photocoagulation. The patient was offered intravitreal bevacizumab with the hopes of decreasing the size of the neovascularization in the left eye. His visual acuity was 20/70—when he was given an injection of 1.25 mg of bevacizumab. One week later his visual acuity improved to 20/50 and he was seen to have had a reduction in his vitreous hemor-

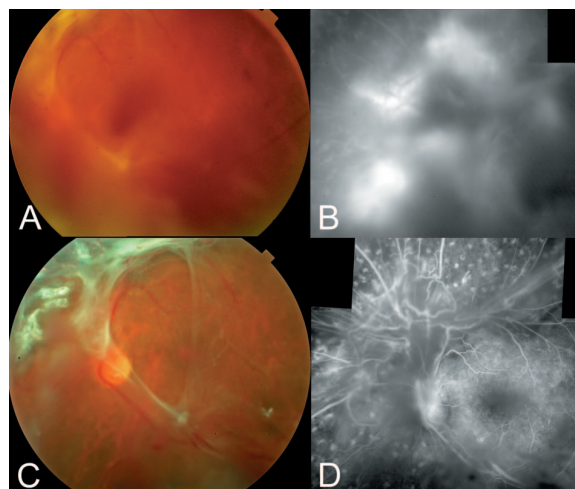


Fig. 2. A, This 38-year-old patient had proliferative diabetic retinopathy with extensive retinal neovascularization and vitreous hemorrhage. His visual acuity was 20/70—. B, The fluorescein angiogram showed large regions of retinal neovascularization. C, Five weeks after the first injection of bevacizumab and 1 week after the second, there was remarkable clearing of the vitreous hemorrhage. The fibrovascular proliferation was nearly white because the contained retinal neovascularization regressed. D, The fluorescein angiogram showed no apparent retinal neovascularization. The visual acuity was 20/25+.

rhage. One month after the first injection he had a visual acuity of 20/30— and a marked reduction of his vitreous hemorrhage. The fibrovascular proliferation was nearly white with very little in the way of observable retinal neovascularization. During fluorescein angiography he had some leakage from remnants of neovascularization near his nerve. He was given an additional 1.25 mg injection of intravitreal bevacizumab. When examined 1 week after the second injection his visual acuity was 20/25+. He had some devitalized blood in the most inferior portion of his vitreous cavity, but otherwise there was almost no remaining hemorrhage in the vitreous cavity. Fluorescein angiography showed remarkable regression of the neovascularization. Since the vitreous cavity was clear, the patient underwent laser panretinal photocoagulation in the left eye. By 1 month after the second injection almost all of the devitalized blood was gone from the vitreous cavity. The tractional retinal detachment did not change in size.

Discussion

Michelson proposed a “Factor X” as the cause of neovascularization nearly 60 years ago.¹⁶ Although retinal neovascularization actually may be due to more than one cytokine, VEGF is an important, if not the most important cytokine involved. We found that intravitreal injection of an antibody against VEGF, be-

vacizumab, caused regression of the retinal neovascularization in two patients with PDR, at least temporarily, in two patients. Each patient was a vitrectomy candidate in that each had vitreous hemorrhage with PDR and had decreased visual acuity. Both patients had regression of the retinal neovascularization within 1 month following the injection with no observable morbidity from the injection. The vitreous hemorrhage also cleared with unexpected rapidity. Both patients had a coincident improvement in visual acuity with the clearing of the vitreous hemorrhage. One of these patients had no observable macular edema before injection by ophthalmoscopy or by fluorescein angiography. The other patient had too much hemorrhage to detect macular edema before injection, but after the vitreous hemorrhage cleared there were no stigmata of macular edema such as intraretinal lipid. Therefore the improvement of visual acuity in these patients appeared to be from the clearance of the vitreous hemorrhage and not the improvement in macular edema.

The rapid clearing of the vitreous hemorrhage seen in these patients suggests a mechanism by which the rapid clearing may have occurred. Certainly some patients may have such a sudden large accumulation of blood in the vitreous cavity that the blood would not resorb within a reasonable period. Patients with massive vitreous hemorrhage secondary to bleeding retinal arterial macroaneurysms or breakthrough bleeding from choroidal neovascularization have a sudden appearance of blood in the vitreous cavity. The blood is initially red, but over time converts to a yellowish-brown color. On the other hand nonclearing vitreous hemorrhages seen in PDR are often red any time the patient is examined. This suggests that there may be bleeding at more than one occasion in patients with PDR. However, for the amount of blood visualized to appear to remain a stable over time, there must be simultaneous resorption of blood from the vitreous cavity if there actually is repeated bleeding. With injection of intravitreal bevacizumab and the regression of the neovascularization there may be a cessation of bleeding. This would stop the inflow of blood into the vitreous cavity while the concomitant resorption of hemorrhage would remain unabated. With the inflow of blood stopped while there is continued outflow, the vitreous hemorrhage would clear.

The short-term results of this study, which was nonrandomized, uncontrolled, and retrospective, preclude any estimation of the long-term efficacy or safety of intravitreal bevacizumab. However, the results were promising and show the need for further investigation.

Key words: bevacizumab, proliferative diabetic retinopathy, vascular endothelial growth factor, vitreous hemorrhage

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