

Anti-vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration

Phase II Study Results

The Eyetech Study Group

Purpose: There is evidence to suggest that anti-vascular endothelial growth factor (anti-VEGF) therapy may be useful in treating ocular neovascularization. A phase IA single intravitreal injection study of anti-VEGF therapy for patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) revealed a good safety profile. We performed a phase II multiple injection study of anti-VEGF therapy with and without photodynamic therapy for patients with subfoveal CNV secondary to AMD to determine the safety profile of multiple injection therapy.

Design: A phase II multiple-dose safety study.

Participants/Methods: Twenty-one patients were treated with intravitreal injection with and without photodynamic therapy.

Main Outcome Measures: Clinical evidence of toxicity and complications.

Results: No drug-related serious adverse events were revealed. Ophthalmic evaluation revealed that 87.5% of patients who received the anti-VEGF aptamer alone showed stabilized or improved vision 3 months after treatment and that 25% of eyes demonstrated a 3 line or greater improvement in vision on the Early Treatment of Diabetic Retinopathy Study chart during this period. A 60% 3 line gain at 3 months was noted in patients who received both the anti-VEGF aptamer and photodynamic therapy.

Conclusions: Anti-VEGF therapy is a promising treatment for various forms of ocular neovascularization, including AMD. Multiple intravitreal injections of the anti-VEGF aptamer were well tolerated in this phase II study. Further clinical trials are necessary to demonstrate the efficacy and long-term safety of anti-VEGF therapy for AMD. *Ophthalmology* 2003;110:979–986 © 2003 by the American Academy of Ophthalmology.

Choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) is a leading cause of blindness in the elderly.^{1,2} Thermal laser photocoagulation and photodynamic therapy (PDT) have been shown to be beneficial for subgroups of such patients.^{3–6} However, only a fraction of eyes meet the eligibility criteria for such therapeutic interventions, and those treated have a high recurrence rates.

Recent preclinical studies have suggested that pharmacologic intervention or antiangiogenesis therapy may be useful to treat various forms of ocular neovascularization, such as CNV. Much of this work has focused on blocking

vascular endothelial growth factor (VEGF),^{7–12} which has demonstrated potential importance in the pathogenesis of both diabetic retinopathy and CNV secondary to AMD. Studies have shown regression or prevention of neovascularization in multiple vascular beds (iris,¹³ retina,^{14–16} choroid,¹⁷ and cornea¹⁸) in several animal models (primate,¹³ mouse,¹⁵ and rat¹⁴) using various types of anti-VEGF agents (including aptamers¹⁴ and antibody fragments.¹⁷

In addition to a potential antiangiogenic effect, anti-VEGF therapy may be useful as an antipermeability agent.⁹ VEGF was initially termed “vascular permeability factor” because of its potent ability to induce leakage from blood vessels. Recent laboratory work suggests that anti-VEGF therapy may inhibit diabetes-induced blood–retinal barrier breakdown in animals.¹⁹

Anti-VEGF therapy may, therefore, represent a two-pronged attack on CNV by means of its antiangiogenic and antipermeability properties.

We have previously reported on a phase IA safety study of a single intravitreal injection of the anti-VEGF aptamer

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in patients with subfoveal CNV secondary to AMD.¹⁴ In this study 80% of eyes showed stabilized or improved vision, and 26.7% of eyes that completed a 3-month regimen had a 3 line improvement of vision on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. No local or systemic clinically significant related adverse events were reported.

We report the results of a phase II safety study using multiple intravitreal injections of the anti-VEGF aptamer (pegylatedoligonucleotide that binds VEGF) in patients with subfoveal CNV secondary to AMD with or without PDT.

Patients and Methods

Study Design

A multicenter, open-label, repeat-dose phase II study of 3 mg/eye of EYE001 (pegaptanib sodium; anti-VEGF aptamer) was performed in patients with subfoveal CNV secondary to AMD with a visual acuity worse than 20/100 in the study eye and better or equal to 20/400 in the fellow eye. If three or more patients experienced dose-limiting toxicity (DLT), the dose was reduced to 2 mg and then 1 mg, if necessary. The intended number of patients to be treated was 20; 10 patients with the anti-VEGF aptamer alone and 10 patients with both anti-VEGF therapy and PDT. Eleven sites in the United States were selected for the studies.

Definition of DLT(s)

Ophthalmic DLT

Photographic Evaluation

- Accelerated formation of cataract.

Clinical Examination

- Clinically significant inflammation, which is severe (obscuring visualization of the retinal vasculature) and vision threatening.
- Other ocular abnormalities not usually seen in patients with AMD, such as retinal, arterial, or venous occlusion, acute retinal detachment, and diffuse retinal hemorrhage.
- Visual acuity: doubling or worsening of the visual angle (loss of ≥ 15 letters); transition to no light perception for patients whose beginning visual acuity score is less than 15 letters, unless the loss of vision is due to a vitreous hemorrhage related to the injection procedure between days 2 and 7, days 30 and 35, or days 58 and 63.
- Tonometry: increase from baseline of intraocular pressure by ≥ 25 mmHg on two separate examinations at least 1 day apart or a sustained pressure of 30 mmHg for more than a week despite pharmacologic intervention.

Fluorescein Angiogram. Significant retinal or choroidal vascular abnormalities not seen at baseline, such as:

- Choroidal nonperfusion (affecting one or more quadrants)
- Delay in arteriovenous transit times (> 15 seconds)
- Retinal arterial or venous occlusion (any deviation from baseline)
- Diffuse retinal permeability alteration affecting retinal circulation in the absence of intraocular inflammation

Systemic DLT. These include grade III (severe) or IV (life-threatening) toxicities or any significant severe toxicity deemed related to study drug by the investigator.

Inclusion Criteria

The ophthalmic criteria included best-corrected visual acuity in the study eye worse than 20/100 on the ETDRS chart, best-corrected visual acuity in the fellow eye equal to or better than 20/400, subfoveal CNV with active CNV (either classic and/or occult) of less than 12 total disc areas in size secondary to AMD, clear ocular media and adequate pupillary dilatation to permit good quality stereoscopic fundus photography, and intraocular pressure of 21 mmHg or less. The cohort scheduled to receive PDT with Visudyne before their first dose of EYE001 had to have equal to or more than a 50% classic component (predominantly classic lesion).

General criteria included patients of either gender, aged ≥ 50 years; performance status ≤ 2 according to the Eastern Cooperative Oncology Group/World Health Organization scale, normal electrocardiogram or clinically nonsignificant changes; women must be using an effective contraceptive, be postmenopausal for at least 12 months before study entry, or surgically sterile; if not, a serum pregnancy test must be performed within 48 hours before treatment and the result made available before treatment initiation; adequate hematologic function; adequate renal function; adequate liver function; written informed consent; and ability to return for all study visits.

Exclusion Criteria

Patients were not eligible for the study if any of the following criteria were present in the study eye or systemically: patients who had received any prior PDT (for the cohort scheduled to receive EYE001 alone); significant media opacities, including cataract, which might interfere with visual acuity, assessment of toxicity, or fundus photography; presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis; patients in whom additional laser treatment for CNV might be indicated or considered; any intraocular surgery within 3 months of study entry; previous vitrectomy; previous or concomitant therapy with another investigational agent to treat AMD except multivitamins and trace minerals; previous radiation to the fellow eye with photons or protons; known allergies to the fluorescein dye used in angiography or to the components of pegaptanib sodium formulation; any of the following underlying systemic diseases: uncontrolled diabetes mellitus or presence of diabetic retinopathy, cardiac disease: myocardial infarction within 12 months before study entry, and/or coronary disease associated with clinical symptoms, and/or indications of ischemia noted on electrocardiogram, impaired renal or hepatic function, stroke, active infection, active bleeding disorders, any major surgical procedure within 1 month of study entry, active peptic ulcer disease with bleeding; concomitant systemic therapy with corticosteroids (e.g., oral prednisone) or other antiangiogenic drugs; previous radiation to the head and neck; any treatment with an investigational agent in the past 60 days for any condition; any diagnosis of cancer in the past 5 years, with the exception of basal or squamous cell carcinoma.

Study Medication

Drug Supply

Pegaptanib sodium drug substance is a pegylated anti-VEGF aptamer. It is formulated in phosphate-buffered saline at pH 5 to 7. Sodium hydroxide or hydrochloric acid may be added for pH adjustment.

Table 1A. Adverse Events Reported After Administration of Anti-VEGF Aptamer Alone or in Combination with Photodynamic Therapy

Adverse Event	Anti-VEGF Aptamer N (%) 10 Patients	Anti-VEGF Aptamer and Photodynamic Therapy N (%) 11 Patients
Ptosis	0	5 (45.4)
Lid edema/erythema	1 (10)	2 (18.2)
Conjunctival injection	1 (10)	0
Chemosis	0	1 (9.1)
Subconjunctival hemorrhage	1 (10)	1 (9.1)
Dry eye	1 (10)	0
Corneal abrasion	0	3 (27.3)
Anterior chamber inflammation	1+cells 3 (30) Trace cells Trace cells	Trace cells 4 (36.4) 1+KP; Trace cells Trace cells Trace cells
IOP increase	1 (10)	0
Pupillary abnormalities	0	0
Rubeosis	0	1 (9.1)
Cataract	0	0
Vitreous haze	1 (10)	2 (18.2)
Vitreous prolapse	0	1 (9.1)
Vitreous floaters	4 (40)	0
Asteroid hyalosis	1 (10)	0
Intraocular air	1 (10)	0
Peripapillary hemorrhage	0	1 (9.1)
Pigment epithelial detachment	0	1 (9.1)
Abnormal vision	1 (10)	0
Photopsia	1 (10)	0
Foreign body sensation	1 (10)	2 (18.2)
Eye pain	1 (10)	3 (27.3)
Blepharospasm	0	1 (9.1)
Ocular irritation	2 (20)	1 (9.1)
Ocular tenderness	0	1 (9.1)
Ocular pruritus	1 (10)	0
Tearing	1 (10)	0
Headache	1 (10)	0
Rhinorrhea	0	1 (9.1)
Fatigue	1 (10)	2 (18.2)
Weakness	1 (10)	0
Joint pain	0	1 (9.1)
Upper respiratory infection	0	1 (9.1)
Bladder infection	0	1 (9.1)

IOP = intraocular pressure.

Pegaptanib sodium was formulated at 3 mg/100 μ l and packaged in a sterile 1 ml, USP Type I graduated glass syringe fitted with a sterile 27-gauge needle. The drug product is preservative-free and intended for single use by intravitreal injection only.

The active ingredient is pegaptanib sodium drug substance (pegylated), anti-VEGF aptamer, at a concentration of 30 mg/ml. The excipients are sodium chloride, USP; sodium phosphate monobasic, monohydrate, USP; sodium phosphate dibasic, heptahydrate, USP; sodium hydroxide, USP; hydrochloric acid, USP; and water for injection, USP.

Dose and Administration

Preparation. The drug product is a ready-to-use sterile solution provided in a single-use glass syringe. The syringe was removed from refrigerated storage at least 30 minutes (but not longer than 4 hours) before use to allow the solution to reach room temperature. Administration of the syringe contents involved attaching the threaded plastic plunger rod to the rubber stopper inside the barrel of the syringe. The rubber end cap was then removed to allow administration of the product.

Treatment Regimen and Duration. Pegaptanib sodium was administered as 100 μ l intravitreal injections containing 3 mg/injection on three occasions at 28-day intervals. If three or more patients experienced DLT, the protocol called for dose reductions. The intravitreal injection was administered using a 27-gauge needle after application of topical anesthesia and povidone iodine or topical antibiotic. The entry site of the needle was to be 3.5 to 4.0 mm posterior to the limbus in phakic patients and 3.0 to 3.5 mm in aphakic or pseudophakic patients. Intraocular pressure was checked and monitored until less than 30 mmHg. Antibiotic ointment was placed twice daily for the following 2 days.

PDT Administration

PDT with Visudyne was given with pegaptanib sodium only in cases with predominantly classic (>50%) CNV. The standard requirements and procedures for PDT administration were used.⁶ PDT was required to be given 5 to 10 days before administration of the anti-VEGF aptamer.

Table 1B. Adverse events Reported After Administration of the Anti-VEGF Aptamer Alone

Adverse Event Relationship	Anti-VEGF Aptamer N = 10 Patients
Probably	
Vitreous floaters	4
Anterior chamber inflammation	3
Ocular irritation	2
Vitreous haze	1
Increased intraocular pressure	1
Intraocular air	1
Subconjunctival hemorrhage	1
Conjunctival injection	1
Eye Pain	1
Lid edema/erythema	1
Dry eye	1
Possibly	
Asteroid hyalosis	1
Abnormal vision	1
Fatigue	1
Unrelated	
Headache	1
Weakness	1

Study Conduct

Patient Enrollment. Before recruitment of patients into the study, written institutional review board approval of the protocol for each participating center and written informed consent from each patient were obtained. Case report form screening pages were completed by study site personnel. Patients who met the eligibility criteria and had provided written informed consent were enrolled in the study.

Visual Acuity Measurements. Best-corrected visual acuity measurements using retroilluminated Bailey-Lovie (ETDRS charts) were performed before each injection of pegaptanib sodium.

Blood Sampling. Blood samples were drawn before and 1 week after each injection for routine hematologic and biochemical analyses and at additional time points to monitor the circulating levels of pegaptanib sodium.

Table 1C. Adverse Events Reported After Administration of the Anti-VEGF Aptamer and Photodynamic Therapy

Adverse Event Relationship	Anti-VEGF Aptamer and Photodynamic Therapy N = 11 Patients
Probably	
Prosis	5
Anterior chamber inflammation	4
Corneal abrasion	3
Eye pain	3
Foreign body sensation	2
Chemosis	1
Subconjunctival hemorrhage	1
Vitreous prolapse	1
Possibly	
Fatigue	2
Unrelated	
Pigment epithelial detachment	1
Joint pain	1
Upper respiratory infection	1
Bladder infection	1

Follow-Up Schedule

Patients were clinically evaluated by the ophthalmologist 2 and 8 days after each injection and again 1 month later just before the next injection. ETDRS visual acuities, Kodachrome photography, and fluorescein angiography were performed monthly for the first 4 months.

End Points

Local ocular and systemic safety were the primary end points of the studies. In addition, the percentage of patients with stabilized (0 line change or better) or improved vision at 3 months, the percentage of patients with a 3 line or greater improvement at 3 months, and the need for PDT re-treatment at 3 months as determined by the investigator were other end points studied.

Results

No serious drug-related adverse events were noted for the 21 patients treated in this study. Three patients experienced serious unrelated adverse events. One patient, an 86-year-old woman with a long-standing history of peripheral vascular disease, as well as borderline hypertension and type II diabetes mellitus, experienced two myocardial infarctions, the second of which was fatal. The first event occurred 11 days after the first intraocular injection of anti-VEGF aptamer. The second event occurred 16 days after the third and last injection. The acute myocardial infarctions took place approximately 2 months apart. A second patient, a 76-year-old man with a 10-month history of depression, attempted suicide with ingestion of acetaminophen 11 days after the third and last dose of anti-VEGF aptamer. The patient's mental condition improved. Treatment of the patient has remained unchanged, and the patient is presently followed in the study. A third patient, a 74-year-old man with a medical history significant for a 14-month history of supraventricular tachycardia and a 1-month history of sick sinus syndrome, experienced palpitations requiring hospitalization 2 days after the first dose of anti-VEGF aptamer. The patient was cardioverted successfully and discharged from the hospital on the following day. Twelve days after discharge, the patient again experienced palpitations and was diagnosed with atrial fibrillation and supraventricular tachycardia. Cardioversion was attempted pharmacologically without success. The patient was then electrically cardioverted, which restored normal sinus rhythm. A dual-chamber pacemaker was placed, and the patient was maintained on propafenone and digoxin. Treatment of the patient has remained unchanged, and the patient is presently followed in the study. The Pharmacokinetic (PK) data revealed that these patients did not have elevated drug levels, because the levels were at the mean level of values for all the patients. Thus, there was no clear correlation between these serious adverse events and the circulating levels of pegaptanib sodium. Levels ranged from 4.0 (1 hour after dosing) to 278 ng/ml (24 hours after dosing) in all patients, whereas at the time close to the preceding events the levels in the patients experiencing these events ranged from 10.0 to 80.0 ng/ml.

Tables 1A, 1B, and 1C show the non serious events reported in the study. In patients treated with the anti-VEGF aptamer alone, ocular adverse events probably associated with the administration of the anti-VEGF aptamer included vitreous floaters, mild anterior chamber inflammation, ocular irritation, increased intraocular pressure, intraocular air, vitreous haze, subconjunctival hemorrhage, eye pain, lid edema/erythema, dry eye, and conjunctival injection. Events possibly related to administration of anti-VEGF

Table 2. Visual Data of Patients with Subfoveal Choroidal Neovascularization Treated with the Anti-VEGF Aptamer Alone

Patient No.	Baseline	Day 8	Day 29	Day 57	Day 85	± No of Lines at Day 85
03-001	20/50	20/40	20/40	20/32	20/32	+2
04-001	20/125	20/64	20/80	20/80	20/80	+2
06-001	20/160	20/125	20/100	20/125	Out	—
07-001	20/100	20/100	20/64	20/80	20/80	+1
07-002	20/320	20/80	20/64	20/64	20/50	+8
08-001	20/125	20/125	20/100	20/100	20/160	−1
09-001	20/500	20/200	20/400	20/320 (Day 36)	Out	—
10-001	20/500	20/640	20/500	20/400	20/500	0
10-002	20/200	20/125	20/160	20/160	20/160	+1
10-003	20/400	20/160	20/160	20/160	20/126	+5
Change in Vision at 3 Months						
				Stabilized or Improved	≥ 3 Line Improvement	
Pegaptanib sodium treated—(N = 8), which represents all eyes that completed the protocol				87.5%	25.0%	

aptamer included asteroid hyalosis, abnormal vision, and fatigue. Events termed unrelated to administration of anti-VEGF aptamer included headache and weakness. In patients treated with the anti-VEGF aptamer and PDT, adverse events probably associated with this combination of therapy included ptosis, mild anterior chamber inflammation, corneal abrasion, eye pain, foreign body sensation, chemosis, subconjunctival hemorrhage, and vitreous prolapse. Events possibly related to combination therapy included fatigue. Events unrelated to combination therapy included pigment epithelial detachment, joint pain, upper respiratory infection, and bladder infection. The increase in ptosis and corneal abrasion seen in the setting of combination therapy may be related to the use of a contact lens in association with PDT. Of note, all instances of anterior chamber inflammation or vitreous haze were mild and transient (less than 24 hours) in nature.

Two patients elected to terminate their participation in the study prematurely. One patient believed that her vision was not improving and did not want further injections. The other patient

had emotional depression and transportation problems. Both patients withdrew from the study before the third and last injection of the aptamer. Visual acuity in both patients remained stable throughout their participation in the study. One patient, previously described, died before the final visit.

No dose decrease was required for any patients in the study. Review of color photographs and fluorescein angiograms of these patients revealed no signs of retinal vascular or choroidal toxicity.

Tables 2 and 3 and Figures 1 to 3 summarize the visual data for these patients and illustrate several potential clinical and/or angiographic responses.

Of those patients (N = 8) who completed the 3-month treatment regimen of the anti-VEGF aptamer alone, 87.5% had stabilized (<0 lines increase) or improved vision, and 25.0% had a 3 line improvement of vision on the ETDRS chart at 3 months (Table 2 and Fig 3).

Table 3. Visual Data of Patients with Subfoveal Choroidal Neovascularization Treated with the Anti-VEGF Aptamer Combined with Photodynamic Therapy

Patient No.	Baseline	Day 8	Day 29	Day 57	Day 85	Repeat Photodynamic Therapy	± No of Lines at Day 85
06-011	20/400	20/320	20/100	20/640	20/200	No	+3
06-012	20/250	20/160	20/125	20/125	20/80	No	+5
08-011	20/40	20/32	20/20	20/20	20/26	Yes	+2
10-011	20/160	20/160	20/160	20/160	Out	No	—
05-011	20/100	20/64	20/64	20/64	20/40	No	+4
12-011	20/160	20/100	20/250	20/200	20/200	No	−1
06-013	20/800	20/640	20/800	20/800	20/320	Yes	+4
02-011	20/500	20/200	20/160	20/80	20/126	Yes	+6
06-014	20/100	20/80	20/80	20/80	20/100	No	0
06-015	20/125	20/40	20/64	20/50	20/80	No	+2
02-012	20/500	20/500	20/125	20/320	20/250	Yes	+3
Change in Vision at 3 Months							
					Stabilized or Improved	≥ 3 Line Improvement	
Pegaptanib sodium Treated—(N = 10), which represents all eyes that completed the protocol					90%	60%	

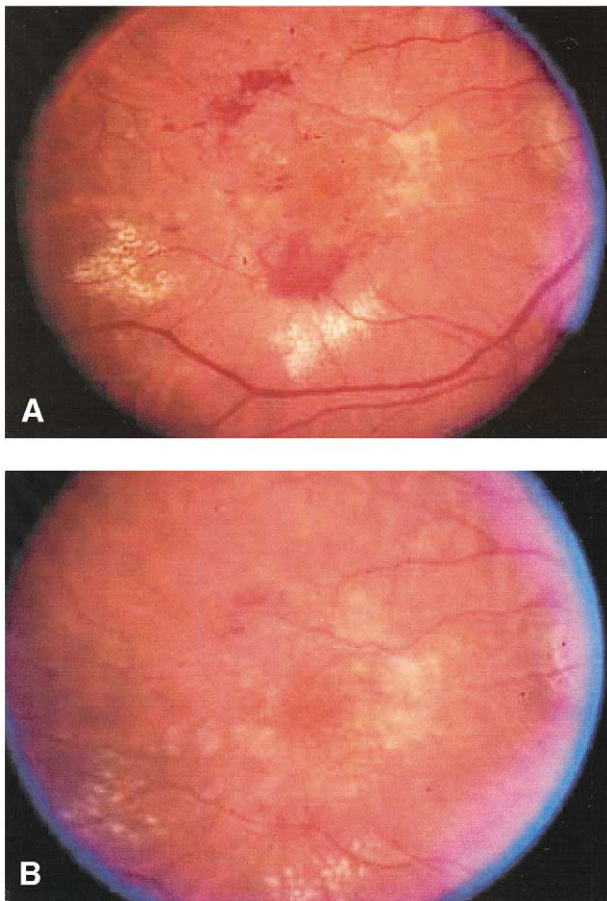


Figure 1. (Case report 1) This patient with subfoveal CNV (A) was treated with both photodynamic therapy (PDT) and three monthly injections of the anti-vascular endothelial growth factor aptamer. The patient's vision improved by 5 Early Treatment of Diabetic Retinopathy Study lines (20/250 to 20/80) with markedly decreased exudation clinically several months after initiating therapy (B). Repeat PDT was not performed at 3 months per the decision of the investigator.

Eleven patients were treated with both the anti-VEGF aptamer and PDT. In this group of patients (N = 10) who completed the 3-month treatment regimen, 90% had stabilized (<0 lines increase) or improved vision, and 60% showed a 3 line improvement of vision on the ETDRS chart at 3 months (Table 3 and Figs 1 and 2). These 3 line improvements included gains of +3, +5, +4, +4, +6, and +3 ETDRS lines of vision.

Of the remaining patients who did not show a 3 line gain, only one showed a loss of vision at 3 months, and this patient lost only 1 line of vision at this time point. No patient in this group lost more than 1 line of vision at 3 months.

Repeat PDT treatment at 3 months (whose need was solely determined by the investigator) was performed in 4 of 10 eyes (40%) that participated for the complete duration of the study.

Discussion

Angiogenesis, or abnormal blood vessel growth, has been implicated as an important cause of pathologic states in many areas of medicine, including ophthalmology, oncol-

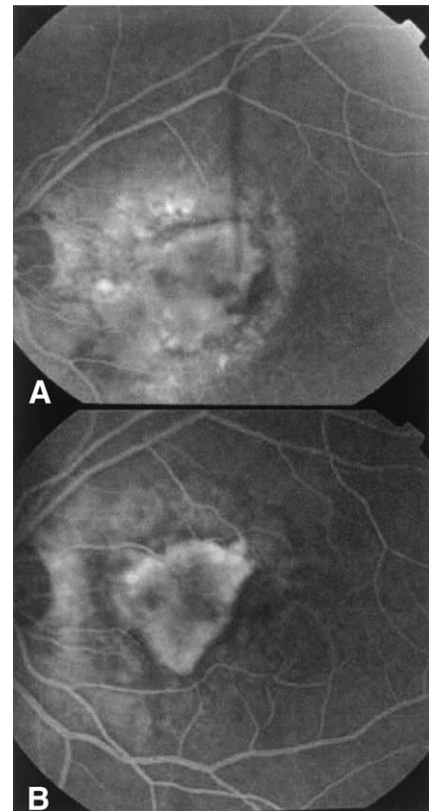


Figure 2. (Case Report 2) This patient was initially seen with subfoveal choroidal neovascularization and marked peripheral hyperpermeability (A), which was greatly decreased (B) after three monthly injections of the anti-vascular endothelial growth factor aptamer and one treatment with photodynamic therapy.

ogy, and rheumatology. VEGF appears to be critical in the development of ocular neovascularization^{13–18, 20–22} and, thus, anti-VEGF therapy may be promising as a new therapy for AMD and diabetic retinopathy.

Studies in humans have shown that high concentrations of VEGF are present in the vitreous in angiogenic retinal disorders but not in inactive or non neovascularization disease states.^{21,22} Excised human CNV after experimental submacular surgery have also shown elevated VEGF levels.²⁰

Animal studies have shown that injection of VEGF into the vitreous can cause a diabetic retinopathy-like state.²³ In addition, anti-VEGF has shown powerful inhibitory effects on both angiogenesis and permeability in various animal models of ocular neovascularization. For example, in the mouse model of retinopathy of prematurity, the anti-VEGF aptamer (Eyetechn) showed 80% inhibition of retinal neovascularization compared with controls.¹⁴ In the monkey model of laser-induced CNV, the incidence of CNV (defined angiographically) was significantly lower in prevention eyes (eyes treated with a recombinant anti-VEGF antibody fragment from Genentech South San Francisco, CA) than in control eyes ($P < 0.001$).¹⁷ Subsequent treatments in this model were associated with less leakage in eyes with established CNV.

Recently, preclinical work has shown that VEGF may be

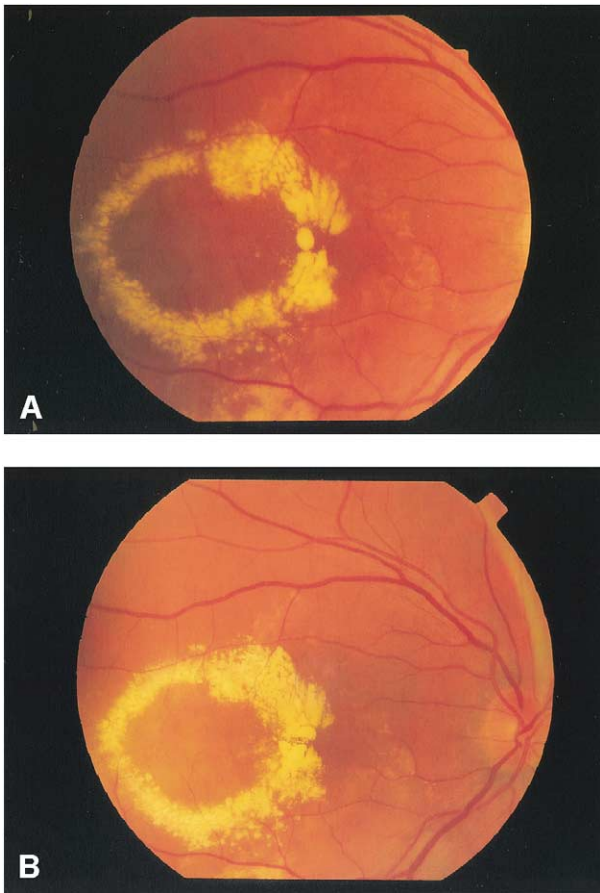


Figure 3. (Case Report 3) This patient had subretinal fluid in the macular region secondary to choroidal neovascularization and age-related macular degeneration (A). The baseline visual acuity was 20/320. After three injections of the anti-vascular endothelial growth factor aptamer, the subretinal fluid was reabsorbed, and the vision increased by 8 Early Treatment of Diabetic Retinopathy Study lines to 20/50 (B).

important in causing vessel leakage in diabetic retinopathy and that the diabetes-induced blood–retinal barrier breakdown can be dose-dependently inhibited with anti-VEGF therapy (in this experiment using VEGF TrapA₄₀—a highly specific VEGF-neutralizing soluble Flt/Fc construct from Regeneron Tarrytown, NY).¹⁹ These studies highlight the potential antiangiogenic and/or antipermeability properties of anti-VEGF therapy.

The results of this phase II multiple intravitreal injection clinical study of anti-VEGF therapy expand the excellent safety profile reported by our phase IA single-injection study. Specifically, the phase II study shows the intraocular and systemic safety of three consecutive anti-VEGF aptamer intravitreal injections given monthly. No serious drug-related adverse events were noted. The adverse events encountered seemed to be unrelated or minor events in some cases, probably because of the intravitreal injection or PDT therapy itself. The two cardiac events described seemed to be unrelated to drug, and indeed Pharmacokinetic data showed that the drug levels were not elevated and were at the mean of the values of all the patients. However, other causal possibilities include the perioperative stress of intra-

vitreal injection and problems with inhibition of systemic vascularization. Only longer term and larger studies, which are presently underway, will definitively answer this question. Further study is necessary and underway to determine the long-term safety profile of the anti-VEGF aptamer.

No definitive conclusions regarding efficacy can be deduced from this study because of the lack of controls, small sample size, and limited follow-up period. Nevertheless, the 3 line gain observed in 25% of the aptamer-only treated group at 3 months compares favorably with data from other series, such as the results of the trial of PDT, in which only 2.2% of treated eyes experienced a 3 line gain in visual acuity at 3 months,⁶ and the radiation study, in which the sham radiation control group showed no more than a 3% improvement at this same time period.²³

The 25% 3 line gain at 3 months is consistent with the 26.7% improvement rate noted in the phase IA study of the aptamer. It may be that the antipermeability effects of the drug caused resorption of subretinal fluid and thus improved vision in these cases. Interestingly, a recent study using an anti-VEGF antibody fragment from Genentech, South San Francisco, CA, also showed a 26% 3 line gain rate in a phase I clinical trial.¹⁷ This antibody fragment similarly blocks extracellular VEGF like the anti-VEGF aptamer.

The 87.5% rate of stabilization or improvement in vision observed at 3 months in this study also compares favorably with the 50.5% rate for the treated patients in the PDT trial,⁶ the 44% rate in the PDT controls,⁶ and 48% rate in the radiation study control group.²⁴

The 60% 3 line gain at 3 months in the patients who received both the anti-VEGF aptamer and PDT was also very encouraging. In the phase III PDT trial only 2.2% of patients showed such visual improvement.⁶ Although the entry criteria differed, both of these study groups included eyes with classic subfoveal CNV. A corollary to the improvement in vision observed in these eyes is supported by the finding that the investigators choose to re-treat with PDT at 3 months in only 40% of aptamer-treated cases compared with the 93% retreatment rate reported in the PDT trial.⁶ This suggests a possible investigator-observed improvement in angiographic leakage.

This study confirms the short-term safety of repeated intravitreal injections of the anti-VEGF aptamer in patients with subfoveal CNV. Future studies must address the long-term safety of such therapy. No conclusions concerning efficacy can be made from the data in this small, uncontrolled limited phase II safety study. Only a prospective randomized controlled clinical trial can determine whether anti-VEGF therapy is beneficial and safe for patients with CNV. Phase II/III trials are presently underway to evaluate this potential treatment in more than a 1000 patients in more than 100 centers worldwide.

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Financial Disclosure

Drs Adamis, Blumenkranz, Goldberg, Gragoudas, Guyer, Miller, O'Shaughnessy, Patel, Schwartz, Singerman, and Yannuzzi all have a financial interest and/or a managerial position in Eyetech Pharmaceuticals, Inc.

References

- Ghahfouri IM, Allan D, Foulds WS. Common causes of blindness and visual handicap in the west of Scotland. *Br J Ophthalmol* 1983;67:209-13.
- Hyman L. Epidemiology of eye disease in the elderly. *Eye* 1987;1:330-41.
- Krypton laser photocoagulation for neovascular lesions of age-related macular degeneration. Results of a randomized trial. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1990;108:816-24.
- Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group [published erratum appears in *Arch Ophthalmol* 1992;110:761]. *Arch Ophthalmol* 1991;109:1109-14.
- Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1991;109:1220-31.
- Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP Report 1. Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group [published erratum appears in *Arch Ophthalmol* 2000;118:488]. *Arch Ophthalmol* 1999;117:1329-45.
- Ferrara N, Houck K, Jakeman L, Leung DW. Molecular and biological properties of the vascular endothelial growth factor family of proteins. *Endocr Rev* 1992;13:18-32.
- Leung DW, Cachianes G, Kuang WJ, et al. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science* 1989;246:1306-9.
- Senger DR, Galli SJ, Dvorak AM, et al. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 1983;219:983-5.
- Ferrara N, Carver-Moore K, Chen H, et al. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature* 1996;380:439-42.
- Carmeliet P, Ferreira V, Breier G, et al. Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. *Nature* 1996;380:435-9.
- Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* 1993;362:841-4.
- Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. *Arch Ophthalmol* 1996;114:66-71.
- Preclinical and Phase IA clinical evaluation of an anti-VEGF pegylated aptamer (EYE001) for the treatment of exudative age-related macular degeneration. The Eyetech Study Group. *Retina* 2002;22:143-52.
- Smith LE, Wesolowski E, McLellan A, et al. Oxygen-induced retinopathy in the mouse. *Invest Ophthalmol Vis Sci* 1994;35:101-11.
- Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. *Proc Natl Acad Sci USA* 1995;92:10457-61.
- Krzystolik MG, Afshari MA, Adamis AP, Gaudreault J, Gragoudas ES, Michaud NA, Li W, Connolly E, O'Neill CA, Miller JW. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. *Arch Ophthalmol*. 2002 Mar; 120(3): 338-46.
- Amano S, Rohan R, Kuroki M, et al. Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization. *Invest Ophthalmol Vis Sci* 1998; 39:18-22.
- Qaum T, Xu Q, Jousen AM, et al. VEGF-initiated blood-retinal barrier breakdown in early diabetes. *Invest Ophthalmol Vis Sci* 2001;42:2408-13.
- Lopez PF, Sippy BD, Lambert HM, et al. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1996;37:855-68.
- Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 1994; 118:445-50.
- Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med* 1994;331: 1480-7.
- Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreal injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. *Ophthalmology* 1996;103:1820-8.
- A prospective, randomized, double-masked trial on radiation therapy for neovascular age-related macular degeneration (RAD Study). The Radiation Therapy for Age-related Macular Degeneration (RAD) Study Group. *Ophthalmology* 1999;106: 12:2239-47.