Primary Intravitreal Bevacizumab for Diffuse Diabetic Macular Edema

The Pan-American Collaborative Retina Study Group at 24 Months

J. Fernando Arevalo, MD, FACS,[1] Juan G. Sanchez, MD,[2] Lihteh Wu, MD,[3] Mauricio Maia, MD,[4] Arturo A. Alezzandrini, MD,[5] Miguel Brito, MD,[6] Sergio Bonafonte, MD,[7] Silvio Lujan, MD,[8] Manuel Diaz-Llopis, MD,[9] Natalia Restrepo, MD,[2] Francisco J. Rodríguez, MD,[10] Patricia Udaondo-Mirete, MD,[9] for the Pan-American Collaborative Retina Study Group (PACORES)

Purpose: To report the 24-month anatomic and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) response after primary intravitreal bevacizumab (Avastin; Genentech, Inc., San Francisco, CA; 1.25 or 2.5 mg) in patients with diffuse diabetic macular edema (DDME). In addition, a comparison of the 2 different doses of intravitreal bevacizumab (IVB) used is presented.

Design: Retrospective, multicenter, interventional, comparative case series.

Participants: The clinical records of 115 consecutive patients (139 eyes) with DDME at 11 centers from 8 countries were reviewed.

Methods: Patients were treated with at least 1 intravitreal injection of 1.25 or 2.5 mg of bevacizumab. All patients were followed up for 24 months. Patients underwent ETDRS BCVA testing, ophthalmoscopic examination, optical coherence tomography (OCT), and fluorescein angiography (FA) at the baseline, 1-, 3-, 6-, 12-, and 24-month visits.

Main Outcome Measures: Changes in BCVA and OCT results.

Results: The mean age of the patients was 59.4±11.1 years. The mean number of IVB injections per eye was 5.8 (range, 1–15 injections). In the 1.25-mg group at 1 month, BCVA improved from 20/150 (0.88 logarithm of the minimum angle of resolution [logMAR] units) to 20/107, 0.76 logMAR units ($P<0.0001$). The mean BCVA at 24 months was 20/75 (0.57 logMAR units; $P<0.0001$). Similar BCVA changes were observed in the 2.5-mg group: at 1 month, BCVA improved from 20/168 (0.92 logMAR units) to 20/118 (0.78 logMAR units; $P = 0.02$). The mean BCVA at 24 months was 20/114 (0.76 logMAR units; $P<0.0001$). In the 1.25-mg group, the mean central macular thickness (CMT) decreased from 466.5±145.2 μm at baseline to 332.2±129.6 μm at 1 month and 286.6±81.5 μm at 24 months ($P<0.0001$). Similar results were obtained in the 2.5-mg group.

Conclusions: Primary IVB at doses of 1.25 to 2.5 mg seem to provide stability or improvement in BCVA, OCT, and FA in DDME at 24 months. The results show no evident difference between IVB at doses of 1.25 or 2.5 mg.

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Group members of PACORES listed in Appendix 1 (available at http://aaojournal.org).

Diabetic retinopathy remains the major threat to sight in the working-age population in the developed world. Furthermore, it is increasing as a major cause of blindness in other parts of the world, especially developing countries.[1] Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision and is now the most common cause of moderate vision loss in persons with diabetes.[2] Macular edema within 1 disc diameter of the fovea is present in 9% of the diabetic population.[3] Although visual loss secondary to proliferative changes is more common in patients with type 1 diabetes, visual loss in patients with type 2 diabetes more commonly is the result of macular edema.[4] Diabetic macular edema can occur at any stage of diabetic retinopathy and is caused by excessive vascular permeability resulting in the leakage of fluid and plasma constituents, such as lipoproteins, and a secondary thickening and distortion of the central retina, together with stretching of neurons and an initial reversible loss of vision. Because in the course of time these disturbed neurons can die off, permanent sight reduction also can result.[2]

There is good evidence that focal laser treatment preserves vision in eyes with DME. The Early Treatment Diabetic Retinopathy Study (ETDRS)[5] randomized 1490 eyes with DME to receive focal laser treatment or observa-

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tion. At 3 years, treatment significantly reduced moderate visual loss as compared with observation,[5] with the greatest benefits in eyes with clinically significant DME.[6] Although the ETDRS[5] demonstrated that immediate focal photocoagulation reduced moderate visual loss by 50% (from 24% to 12%, 3 years after initiation of treatment), 12% of treated eyes still lost 15 ETDRS letters or more at the 3-year follow-up. Approximately 40% of treated eyes that had retinal thickening involving the center of the macula at baseline still had thickening involving the center at 12 months, as did 25% of treated eyes at 36 months. Furthermore, only 3% of laser-treated eyes experienced a gain of 3 lines of vision or more. This suggests that a distinct subgroup of eyes exists with DME resistant to conventional laser photocoagulation. In addition, some reports have indicated that diffuse diabetic macular edema (DDME) is refractory to macular photocoagulation.[6–8] Lee and Olk[9] demonstrated that with modified grid laser macular photocoagulation, visual acuity was stabilized in 60.9%, decreased in 24.6%, and increased in only 14.5% of eyes with DDME. The low frequency of improvement, gain of significant vision (≥3 lines), or both, after focal laser photocoagulation for DME has prompted interest in alternative or adjunct treatments, such as intravitreal triamcinolone acetonide,[10–14] pars plana vitrectomy,[15] and antibodies directed against vascular endothelial growth factor (VEGF).[16–19]

Vascular endothelial growth factor has been shown to be an endothelial cell-specific mitogen and an angiogenic inducer in a variety of in vitro and in vivo models.[20] Vascular endothelial growth factor, also known as vascular permeability factor, has been demonstrated to increase retinal vessel permeability by increasing the phosphorylation of tight junction proteins. Also, hypoxia has been shown to be a major inducer of VEGF gene transcription.[20] All variants of VEGF (particularly VEGF-A) have been implicated in the occurrence of increased vascular permeability by affecting endothelial tight-junction proteins in ocular vascular diseases such as DME.[21] It has been shown that VEGF-A levels are considerably higher in DME patients with extensive leakage in the macular region than in patients with minimal leakage.[22,23] Recent work has found elevated levels of VEGF in the ocular fluids of patients with proliferative diabetic retinopathy (PDR).[24–26] These studies also found that the growth of new vessels from the retina or optic nerve occurred as a result of VEGF release into the vitreous cavity as a response to ischemia.[24–26] Furthermore, injection of VEGF into normal primate eyes induces the same pathologic processes seen in diabetic retinopathy, including microaneurysm formation and increased vascular permeability.[27,28]

Human VEGF-A is found in at least 9 isoforms. Currently used anti-VEGF drugs are pegaptanib sodium (Macugen; OSI Eyetech Pharmaceuticals, Melville, NY), ranibizumab (Lucentis; Genentech, Inc., San Francisco, CA), and bevacizumab (Avastin; Genentech, Inc.). Bevacizumab is a complete full-length humanized antibody that binds to all subtypes of VEGF and is used successfully in tumor therapy as a systemic drug.[29] Studies have demonstrated the usefulness of intravitreal bevacizumab (IVB) with promising effects in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability, fibrovascular proliferation in retinal neovascularization secondary to PDR, rubeosis iridis, retinopathy of prematurity, choroidal neovascularization secondary to age-related macular degeneration and in the treatment of DME.[30–43] The amount of human retinal penetration for a complete full-length anti-VEGF antibody is not known at present. However, full-thickness retinal penetration of IVB was observed in an animal model.[44,45] Additionally, IVB does not seem to be toxic to the albino rabbit retina at a concentration of up to 2.5 mg.[46] The use of anti-VEGF drugs is becoming increasingly prevalent; however, some unresolved issues such as the ideal regimen or dose, duration of treatment, potential of combination treatments, and safety concerns with long-term VEGF inhibition deserve further investigations.

The purpose of this retrospective study was to report the 24-month anatomic and ETDRS best-corrected visual acuity (BCVA) response after primary IVB (1.25 or 2.5 mg) in patients with DDME. This report comprises a series of 139 eyes, including 38 eyes with DDME from a previously reported series[43] with longer follow-up. In addition, a comparison of the 2 different doses of IVB used was carried out.

Patients and Methods

A multicenter, retrospective study was conducted of eyes with DDME treated with off-label IVB between September 2005 and July 2006 at 11 institutions in Venezuela, Colombia, Costa Rica, Brazil, Argentina, Spain, Peru, and Mexico. The clinical records were reviewed of 115 consecutive patients (139 eyes) with DDME treated with at least 1 intravitreal injection of 1.25 or 2.5 mg bevacizumab. All patients were followed up for 24 months. Whether a dose of either 1.25 or 2.5 mg was to be used to treat a patient was determined at the discretion of the treating physician. If a patient received one of the doses at baseline, the same dose was delivered throughout the study. Approval was obtained from each participating center's institutional ethics committee, and informed consent was obtained for this study. In addition, this study

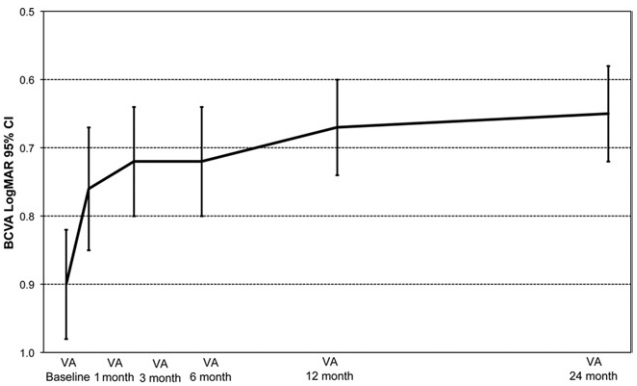

Figure 1. Graph showing changes in best-corrected visual acuity (BCVA) after intravitreal bevacizumab. The BCVA improved at 1 month from 0.90 to 0.76 logarithm of the minimum angle of resolution (logMAR) units, a difference that was statistically significant ($P<0.001$). This level of BCVA was maintained throughout 3, 6, 12, and 24 months of follow-up. CI = confidence interval.

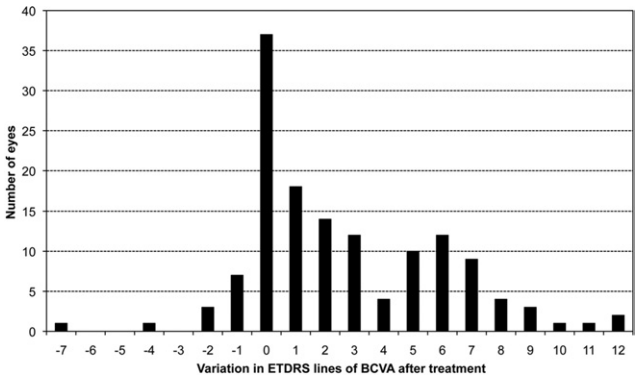

Figure 2. Bar graph showing the number of patients losing, maintaining, or gaining Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) from baseline to the 24-month follow-up.

has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients.

The definition of DDME required evidence of diffuse retinal thickening, hard exudates (without a circinate ring pattern) involving the center of the macula (clinically significant DME as defined by the ETDRS on slit-lamp biomicroscopic examination), or both, and diffuse fluorescein leakage involving the center of the macula on fluorescein angiography (FA) with less than 33% of leakage associated with microaneurysms.[47] In addition, a significant reduction in the reflectivity (cysts) of the outer retinal layers, subretinal fluid collection by optical coherence tomography (OCT; Stratus OCT; Carl Zeiss, Dublin, CA), or both, should be present.[48] Exclusion criteria included patients (eyes) with DDME previously treated with laser photocoagulation or intravitreal triamcinolone, macular ischemia, intraocular inflammation, uncontrolled intraocular pressure, cataract surgery within the past 6 months or a prior history of vitreoretinal surgery, and the presence of an epiretinal membrane or vitreomacular traction syndrome. Although not a formal exclusion criterion, patients with a history of uncontrolled hypertension and recent thromboembolic events usually were not injected with bevacizumab, but this decision was left at the discretion of the treating physician.

Each patient underwent BCVA measurement with ETDRS charts and ophthalmic examination, including slit-lamp biomicroscopy. Baseline central retinal characteristics were analyzed by OCT using 6 diagonal slow 6-mm radial line scans, with software version 4.0, through a dilated pupil performed by a retina specialist. The retinal thickness of the 1-mm central retina was obtained using the macular thickness map for the calculations. The scans were reviewed and manual caliper-assisted measurements were used in case of delineation errors.

A 0.18-ml aliquot of commercially available bevacizumab was prepared for each patient and placed in a tuberculin syringe using aseptic techniques. After the eye had been prepared in a standard fashion using 5% povidone–iodine, an eyelid speculum was used to stabilize the eyelids, and the injection of 1.25 mg (0.05 ml) or 2.5 mg (0.1 ml) bevacizumab was performed 3.5 to 4 mm posterior to the limbus through the inferotemporal pars plana with a 30-gauge needle under topical anesthesia or subconjunctival lidocaine. After the injection, retinal artery perfusion was checked with the indirect ophthalmoscope (no anterior chamber paracentesis was necessary), and patients were instructed to administer topical antibiotics for 7 days.

Patients were examined at 1 and 2 weeks and 1 month after the first injection, and monthly thereafter. One, 3, 6, 12, and 24 months after the initial injection, the ophthalmic examination included OCT and FA. However, OCT was performed earlier (weeks 1 and 2) in some patients according to the investigator's decision and preference. In addition, FA was performed at the discretion of the examiner and not at every postinjection evaluation, rather, usually every 6 weeks.

Patients received reinjections whenever there was a recurrence of DDME. Recurrence was defined as a decrease of BCVA associated with an increase of intraretinal fluid because of macular edema on OCT ($\geq$50 μm in central macular thickness [CMT]), FA, or both, after complete or partial resolution in previous follow-up visits.

All data were collected in a Microsoft Excel 2003 spreadsheet (Microsoft Corporation, Unterschleissheim, Germany) and were analyzed using SPSS software version 13.0 for Windows (SPSS, Inc., Chicago, IL). For statistical analysis, the Friedman test was performed and $P<0.05$ was considered significant. Interval data were analyzed at the 1-, 3-, 6-, 12-, and 24-month follow-up time points. Patients' ETDRS BCVAs were transferred from their records and were converted to a logarithm of the minimum angle of resolution (logMAR) scale for analysis. Repeated measures of the analysis of variance were used to compare mean values to analyze mean retinal thickness and logMAR visual acuity (VA) statistically. An increase or decrease in BCVA was considered to have occurred if there was a change of 2 or more ETDRS lines. Main outcome measures included changes in BCVA and CMT measured by OCT.

Results

The clinical records of 115 consecutive patients (139 eyes) with DDME were reviewed. All patients had a minimum follow-up of 24 months. Seventy-six (66.1%) patients were Hispanic, 37

Table 1. Best-Corrected Visual Acuity Analysis by Subgroup (139 eyes)

	First Month, No. Eyes (%)		Third Month No. Eyes (%)		Sixth Month, No. Eyes (%)		Twelfth Month, No. Eyes (%)		Twenty-fourth Month, No. Eyes (%)	
	1.25 mg	*2.5 mg*	*1.25 mg*	*2.5 mg*	*1.25 mg*	*2.5 mg*	*1.25 mg*	*2.5 mg*	*1.25 mg*	*2.5 mg*
Decreased 2 or more ETDRS lines of BCVA	6 (8.1)	5 (6.8)	5 (6.8)	4 (6.2)	9 (12.2)	11 (16.9)	3 (4.0)	8 (12.3)	2 (2.7%)	3 (4.6)
Remained stable	29 (39.2)	40 (54.1)	31 (41.9)	36 (55.4)	19 (25.7)	32 (49.2)	21 (28.4)	31 (47.7)	25 (33.8)	37 (56.9)
Improved 2 or more ETDRS lines of BCVA	39 (52.7)	20 (27.0)	38 (51.3)	25 (38.4)	46 (62.1)	22 (33.8)	50 (67.6)	26 (40.0)	47 (63.5)	25 (38.5)

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

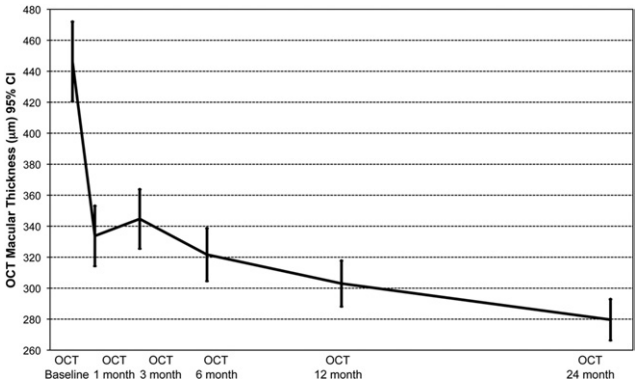

Figure 3. Graph showing the changes in macular thickness with optical coherence tomography (OCT) during follow-up after intravitreal bevacizumab. The foveal thickness improved after 1 month, mean 1-mm central macular thickness (CMT) measurement decreased from 446.4±154.4 μm to 333.75±117 μm ($P<0.001$), and this overall improvement continued throughout the 24-month follow-up. At 3-, 6-, 12-, and 24-month follow-up, CMT measurements were 344.7±115.3 μm, 321.7±102.7 μm, 303±89.1 μm, and 279.7±80 μm, respectively, which were significantly lower than baseline ($P<0.001$). CI = confidence interval.

(32.2%) were white, and 2 (1.7%) were black. The patients had a mean age of 59.4±11.1 years, and 51.3% were male (59 men, 56 women). In the current study, patients had a glycosylated hemoglobin mean of 9.1±1.86%. Regarding the severity of diabetic retinopathy (DR), 17 (12.2%) eyes had mild DR, 25 (18%) eyes had moderate DR, 39 (28.1%) eyes had severe DR, and 58 (41.7%) eyes had PDR. All these 58 cases with PDR had undergone prior scatter panretinal photocoagulation at least 6 months before undergoing IVB. All eyes had DDME diagnosed by biomicroscopic slit-lamp examination, FA, and OCT at baseline.

Within 1 month after the initial bevacizumab injection, improvements in BCVA and CMT measurements were observed, and these significant changes continued throughout the 24-month follow-up. At 1 month, BCVA improved from 0.90 to 0.76 logMAR units, a difference that was statistically significant ($P = 0.0001$). This improvement in BCVA was maintained throughout the 3-, 6-, 12-, and 24-month follow-up (Fig 1). In addition, the mean BCVA at 24 months was 20/100 (0.70 logMAR units; $P<0.001$), a statistically significant difference from baseline BCVA. Twenty-four–month BCVA analysis by subgroups demonstrated that 62 (44.6%) eyes remained stable, 72 (51.8%) eyes

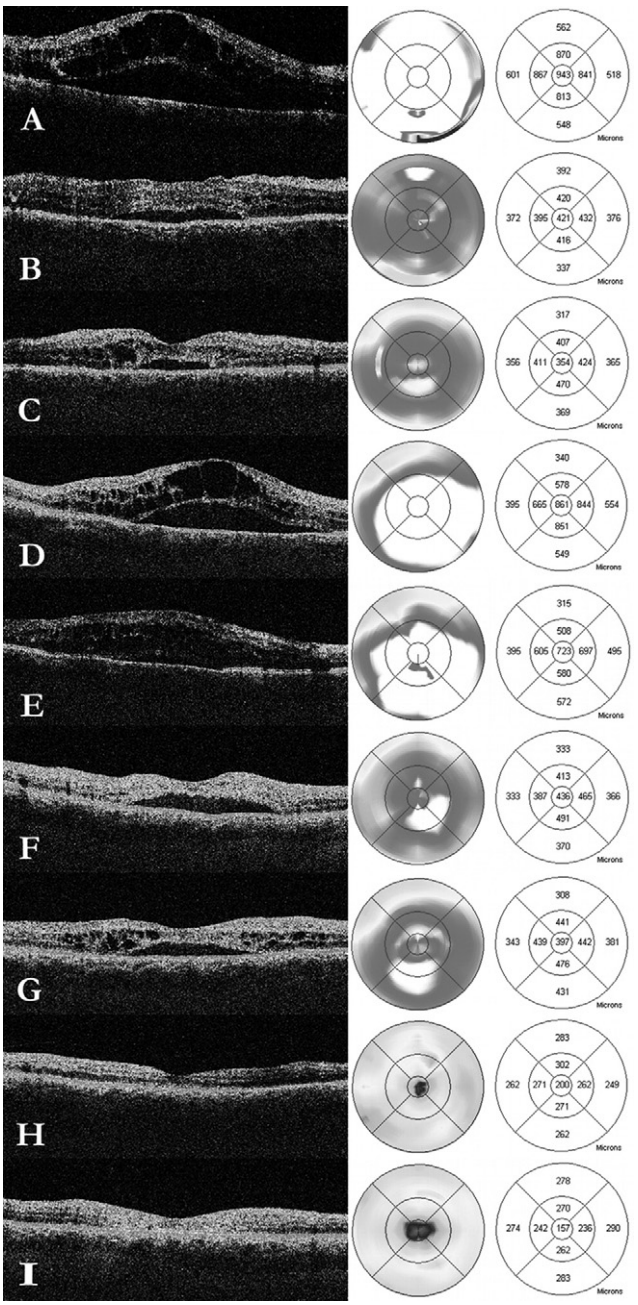

Figure 4. Sequential optical coherence tomography (OCT) of a 32-year-old diabetic man with a 3-month history of loss of vision to counting fingers (CF) in his right eye, in which diabetic macular edema (DME) had developed. **A**, Horizontal OCT scan obtained through the fovea revealing loss of the normal foveal contour, diffuse macular thickening, areas of low intraretinal reflectivity consistent with intraretinal cysts, and subretinal fluid (SRF). The retinal map analysis revealed a foveal thickness of 943 μm. The patient underwent an intravitreal injection of bevacizumab at a dose of 2.5 mg in this eye. **B**, Optical coherence tomography image revealing decrease of macular edema and SRF at 1 month after bevacizumab injection. The retinal map analysis indicates a central foveal thickness of 421 μm. Visual acuity (VA) improved to 10/200. **C**, Three months after the injection, OCT scan showing improvement in foveal thickness (354 μm) and almost complete resolution of the SRF. The VA improved to 20/200. **D**, Four months after the first injection, VA diminished to 20/400 and OCT scan demonstrated the reappearance of macular edema associated with an increase of intraretinal cysts and SRF. Central foveal thickness increased to 861 μm. He received a second injection of intravitreal bevacizumab at a dose of 2.5 mg at this point. **E–G**, Optical coherence tomography scans obtained at (**E**) 5, (**F**) 6, and (**G**) 9 months showing a progressive decrease in macular edema, intraretinal cysts, and SRF, which were confirmed with decrease of central foveal thickness (723 μm, 436 μm, and 397 μm, respectively). The VA also improved progressively (20/200, 20/160, and 20/125, respectively). **H**, Twelve months after the first injection, OCT scan showed resolution of DME, with complete reabsorption of SRF and restoration of foveal anatomy. Central foveal thickness decreased to 200 μm, and visual acuity was 20/80. **I**, Optical coherence tomography scan obtained at 24 months showing a marked resolution of DME, with complete reabsorption of SRF and restoration of foveal anatomic features. Central foveal thickness was 157 μm, and the visual acuity improved to 20/50.

improved 2 or more ETDRS lines of BCVA, and 5 (3.6%) eyes decreased 2 or more ETDRS lines of BCVA (Fig 2 and Table 1).

Optical coherence tomography results were available for all 139 eyes at the 1-, 3-, 6-, 12-, and 24-month follow-up examinations. At 1 month, the mean 1-mm CMT measurements decreased from 446.4±154.4 μm to 333.75±117 μm ($P<0.001$), and this overall improvement continued throughout the 24-month follow-up (Figs 3–5). At the 3-, 6-, 12-, and 24-month follow-up examinations, mean CMTs were 344.7±115.3 μm, 321.7±102.7 μm, 303±89.1 μm, and 279.7±80 μm, respectively, which were significantly different from baseline ($P<0.001$).

The response to treatment between patients with PDR and previous panretinal photocoagulation were compared with that of patients with nonproliferative diabetic retinopathy and DDME to see if there was any difference. However, when the repeated-measures analysis of variance was carried out to compare mean values to analyze statistically the mean retinal thickness and logMAR VA adjusting for the grade of diabetic retinopathy as a covariate, no statistical significance ($P = 0.511$ for BCVA and $P = 0.483$ for CMT) was found.

All eyes received an intravitreal injection at the initial visit; however, recurrences were retreated at the discretion of the treat-

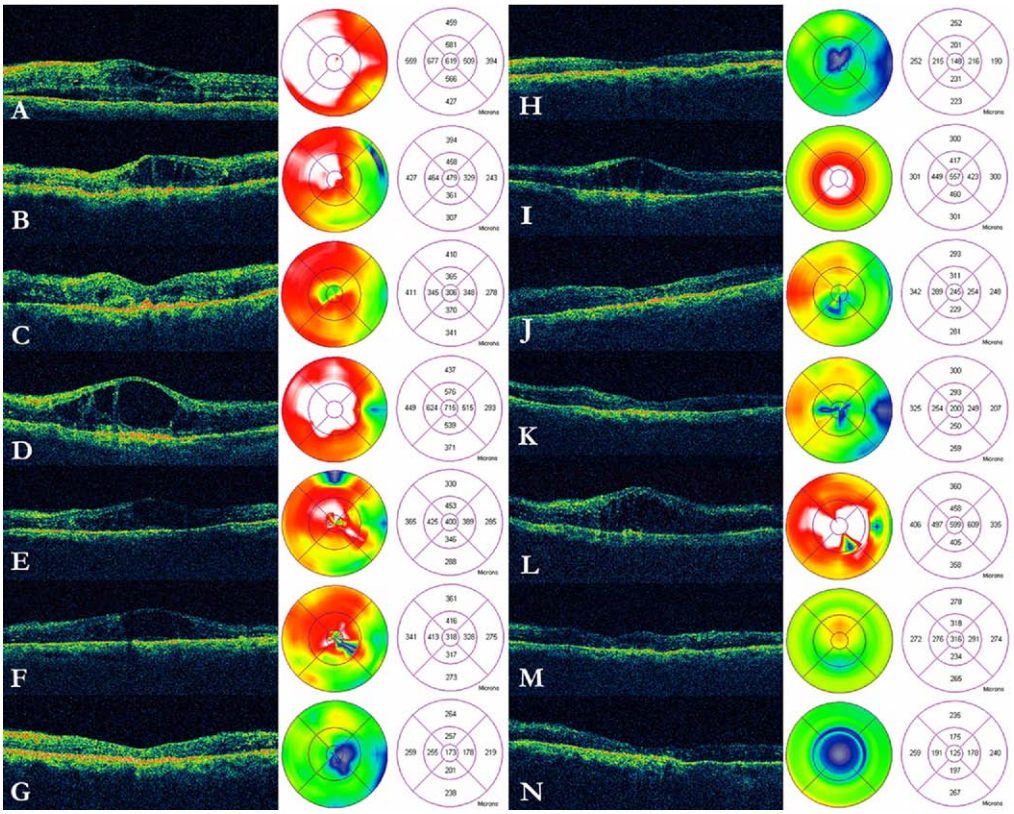

Figure 5. Sequential optical coherence tomography (OCT) imaging of a 69-year-old diabetic woman with a 6-month history of loss of vision to counting fingers (CF) in her left eye, in which diabetic macular edema (DME) had developed. **A**, Horizontal OCT scan obtained through the fovea revealing loss of the normal foveal contour, diffuse macular thickening, areas of low intraretinal reflectivity consistent with intraretinal cysts, and subretinal fluid (SRF). The retinal map analysis revealed a foveal thickness of 619 μm. The patient underwent an intravitreal injection of bevacizumab at a dose of 2.5 mg in this eye. **B**, Optical coherence tomography image revealing partial resolution of intraretinal macular edema and complete reabsorption of SRF at 1 month after bevacizumab injection. The retinal map analysis indicates a central foveal thickness of 479 μm. Visual acuity (VA) improved to 20/400. **C**, Three months after the injection, OCT scan showing improvement in foveal thickness (306 μm). The VA improved to 20/200. **D**, Four months after the first injection, VA diminished to CF, and OCT scan showed the reappearance of macular edema associated to increase of intraretinal cysts. Central foveal thickness increased to 715 μm. She received a second injection of intravitreal bevacizumab at a dose of 2.5 mg at this point. **E–G**, At month 6, she received a third injection of intravitreal bevacizumab at dose of 2.5 mg. The OCT scans at (**E**) 5, (**F**) 6, and (**G**) 9 months showed a progressive resolution in macular edema and intraretinal cysts, which were confirmed with decrease of central foveal thickness (400 μm, 318 μm, and 173 μm, respectively). Her VA also improves progressively (20/200, 20/200, and 20/125, respectively). **H**, Twelve months after the first injection, the OCT scan showed resolution of DME, with complete reabsorption of SRF and restoration of foveal anatomic features. Foveal thickness decreased to 148 μm, and visual acuity was 20/125. **I**, Sixteen months after the first injection, VA diminished to 20/400, and the OCT scan showed a reappearance of macular edema associated to increase of intraretinal cysts. Central foveal thickness increased to 557 μm. She received a fourth injection of intravitreal bevacizumab at dose of 2.5 mg. **J**, Optical coherence tomography scan obtained at 17 months showing a resolution in macular edema and intraretinal cysts. Central foveal thickness decreased to 245 μm and VA was 20/160. **K**, Eighteen months after the first injection (2 months after the previous injection), OCT scan showing improvement in foveal thickness (200 μm). The VA improved to 20/125. **L**, Nineteen months after the first injection, her visual acuity diminished to 20/400. Optical coherence tomography scan showing the reappearance of macular edema. The retinal map analysis indicates a central foveal thickness of 599 μm. She received a fifth injection of intravitreal bevacizumab at a dose of 2.5 mg at this point. **M**, Optical coherence tomography scan obtained at 20 months showing resolution in macular edema and intraretinal cysts. Central foveal thickness decreased to 316 μm. The VA improved to 20/200. **N**, Twenty-four months after the first injection, OCT showing a marked resolution in macular edema and restoration of foveal anatomic features. Central foveal thickness was 125 μm, and VA improved to 20/160.

Table 2. Analysis of the Frequency of Injections by Subgroups 1.25 mg (74 Eyes) and 2.5 mg (65 Eyes)

Injections Required by Eye during 24 Months	1.25 mg		2.5 mg		Both Groups	
	Frequency	*Percentage*	*Frequency*	*Percentage*	*Frequency*	*Percentage*
No reinjection	7	9.5	0	0	7	5
2 Injections	17	23	6	9.2	23	16.5
3 Injections	3	4.1	7	10.8	10	7.2
4 Injections	9	12.2	14	21.5	23	16.5
5 Injections	20	27.1	6	9.2	26	18.7
6 Injections	5	6.7	8	12.3	13	9.3
7 Injections	4	5.4	5	7.7	9	6.4
8 Injections	6	8.1	5	7.7	11	7.9
9 Injections	1	1.3	7	10.8	8	5.7
10 Injections	0	0	1	1.5	1	0.7
11 Injections	2	2.7	2	3.1	4	2.8
12 Injections	0	0	1	1.5	1	0.7
14 Injections	0	0	1	1.5	1	0.7
15 Injections	0	0	1	1.5	1	0.7

ing physician. There were a total of 807 IVB injections performed. The mean number of IVB injections per eye was 5.8 (range, 1–15 injections) at a mean interval of 12.2±10.4 weeks (Tables 2 and 3). Seventy-four (53.2%) cases were treated with an intravitreal injection of 1.25 mg bevacizumab and 65 (46.8%) cases were treated with a 2.5-mg dose of IVB.

Adverse events included transient high blood pressure in 1 (0.9%) patient, cerebrovascular accident in 1 (0.9%) patient, heart attack in 1 (0.9%) patient, transient increased intraocular pressure in 7 (5%) eyes, cataract in 5 (3.6%) eyes, and tractional retinal detachment in 1 (0.7%) eye.

Analysis of Visual Acuity and Central Macular Thickness by Doses of 1.25 and 2.5 mg

No statistically significant differences in changes of BCVA between doses of 1.25 and 2.5 mg of IVB were observed (Table 4 and Fig 6). In the 1.25-mg group at 1 month, BCVA improved from 20/150 (0.88 logMAR units) to 20/107 (0.73 logMAR units), a difference that was statistically significant ($P<0.0001$). This improvement was maintained throughout the 3-, 6-, 12-, and 24-month follow-up. The mean BCVA at 24 months was 20/75 (0.57 logMAR units; $P<0.0001$), a statistically significant difference from baseline BCVA (Fig 6). Similar BCVA changes were observed in the 2.5-mg group: at 1 month, BCVA improved from 20/168 (0.92 logMAR units) to 20/118 (0.78 logMAR units), a difference that was statistically significant ($P = 0.02$). This improvement in BCVA was maintained throughout the 3-, 6-, 12-, and 24-month follow-up. The mean BCVA at 24 months was 20/114 (0.76 logMAR units; $P<0.0001$), a statistically significant difference from baseline BCVA (Fig 6). In addition, in the 1.25-mg group, at 1 month there was an average gain of 3.1±2.1 lines of BCVA, at 3 months there was an average gain of 3.2±2.5 lines of BCVA, at 6 months there was an average gain of 2.4±1.8 lines of BCVA, at 12 months there was an average of 3.8±2.6 lines of BCVA, and at 24 months there was an average gain of 2.4±1.6 lines of BCVA ($P<0.001$). In the 2.5-mg group, at 1 month eyes gained 4.2±3.3 lines of BCVA, 1.8±1.3 lines of BCVA at 3 months, 3.0±2.1 lines of BCVA at 6 months, 2.6±2.3 lines of BCVA at 12 months, and 2.4±2.2 lines of BCVA at 24 months ($P<0.01$).

No statistically significant differences in macular thickness with OCT were observed between doses of 1.25 and 2.5 mg of IVB (Fig 7). In the 1.25-mg group, the mean CMT decreased from 466.5±145.2 μm at baseline to 332.2±129.6 μm at 1 month, 358.8±111.8 μm at 3 months, 317.6±87.7 μm at 6 months, 299.1±79.4 μm at 12 months, and 286.6±81.5 μm at 24 months ($P<0.0001$). In the 2.5-mg group, the mean CMT decreased from 423.4±163.5 μm at baseline to 335.5±102.8 μm at 1 month, 328.7±118.8 μm at 3 months, 326.3±118.7 μm at 6 months, 307.5±99.9 μm at 12 months, and 271.8±78.8 μm at 24 months ($P<0.0001$).

Table 3. Interval between Reinjections (132 Eyes)

Reinjections Required by Eye during 24 Months	No. of Eyes	Mean±Standard Deviation (Wks)	Range (Wks)	Percentage*
2 Injections	132	10.9±11.5	1–52	94.9
3 Injections	109	13.3±4.8	4–75	78.4
4 Injections	99	15.2±13.7	4–83	71.2
5 Injections	76	16.1±10.9	3–83	54.7
6 Injections	50	18.4±12.3	4–86	36
7 Injections	37	13.3±5.1	4–24	26.6
8 Injections	28	18.4±12.3	4–86	20
9 Injections or more	16	15.7±4.8	4–40	11.5

*Total percentage is more than 100% because 132 eyes needed 2 or more injections.

Discussion

Diabetic macular edema is a manifestation of DR that produces loss of central vision. Although several treatment methods are under investigation, the only demonstrated means to reduce the risk of vision loss from DME are laser photocoagulation, as shown by the ETDRS[5]; intensive glycemic control, as reported by the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study; and blood pressure control, as demonstrated by the United Kingdom Prospective Diabetes Study.[49,50] Taking into account that most eyes with DDME treated with laser photocoagulation show no improvement in VA,[9] there has been an interest in other treatment methods such as pharmacologic therapy with oral protein kinase

Table 4. Best-Corrected Visual Acuity in Eyes Injected with Doses of 1.25 and 2.5 mg Intravitreal Bevacizumab at 24 Months of Follow-up

	1.25 mg		2.5 mg	
	Best-Corrected Visual Acuity	*Logarithm of the Minimum Angle of Resolution Units*	*Best-Corrected Visual Acuity*	*Logarithm of the Minimum Angle of Resolution Units*
Baseline	20/150	0.88	20/168	0.92
1 month	20/107	0.73	20/118	0.78
Third month	20/100	0.70	20/114	0.76
Sixth month	20/94	0.67	20/118	0.78
Twelfth month	20/80	0.60	20/114	0.76
Twenty-fourth month	20/75	0.57	20/114	0.76

C inhibitors and the use of intravitreal corticosteroids.[51,52] The use of antibodies targeted at VEGF is another treatment method that has generated considerable interest and is being investigated.[10–19]

Retinal hypoxia and various rheological disturbances play a role in DME. Several medical articles point to leukocyte dynamics as one of the causes of diabetic retinopathy.[53–54] Leukocytes have decreased deformability,[55] increased activation,[44] and increased adhesiveness to vascular endothelium in diabetes.[54] The levels of intercellular adhesion molecule 1 immunoreactivity were reported to be elevated in the retina of diabetic patients.[54] A previous study demonstrated that the vitreous levels of intercellular adhesion molecule 1 and VEGF were significantly higher in DME patients than in control patients.[23] Leukocyte entrapment, which is promoted by intercellular adhesion molecule 1 expression, is considered the critical early event in the pathogenesis of diabetic retinopathy. The trapped leukocytes cause transient or permanent microcirculatory disturbances and release cytotoxic products, such as cytokines, oxygen-free radicals, or proteolytic enzymes, and result in vascular endothelial cell damage and promote vascular permeability.[53,54] Long-term circulatory disturbance may lead to functional vascular obstruction, relative retinal ischemia, and release of cytokines such as VEGF. In 2 studies, Funatsu et al[22,23] reported that the levels of VEGF were elevated in the vitreous fluid of subjects with DME. Vascular endothelial growth factor causes conformational changes in the tight junctions of retinal endothelial cells[56,57] and plays a major role in increasing vascular permeability and in the progression of DME.[58]

This study reports on 139 consecutive eyes with DDME treated with intravitreal bevacizumab, which resulted in both anatomic and functional improvement. In most of the patients, the reduction of retinal thickness and improvement of BCVA were detected within the first 4 weeks after the injection. In addition, both doses (1.25 and 2.5 mg) were associated with improvement of BCVA and a greater reduction in CMT, and no differences in between were found. Ocular tolerance of the 2 different doses of IVB was dem-

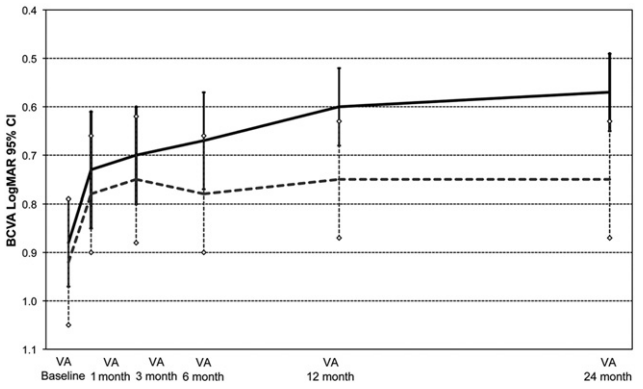

Figure 6. Graph showing changes in best-corrected visual acuity (BCVA) between doses of 1.25 and 2.5 mg of intravitreal bevacizumab. In the 1.25-mg group (solid line), BCVA at 1 month improved from 0.88 to 0.73 logarithm of the minimum angle of resolution (logMAR) units, a difference that was statistically significant ($P<0.0001$). This improvement was maintained throughout the 3-, 6-, 12-, and 24-month follow-up examinations. The mean BCVA at 24 months was 0.57 logMAR units ($P<0.0001$), a statistically significant difference from baseline BCVA. Similar BCVA changes were observed in the 2.5-mg group (doted line): at 1 month, BCVA improved from 0.92 to 0.78 logMAR units, a difference that was statistically significant ($P = 0.02$). This improvement in BCVA was maintained throughout the 3-, 6-, 12-, and 24-month follow-up examinations. The mean BCVA at 24 months was 0.76 logMAR units ($P<0.0001$), a statistically significant difference from baseline BCVA. CI = confidence interval; — = 1.25 mg; --- = 2.5 mg.

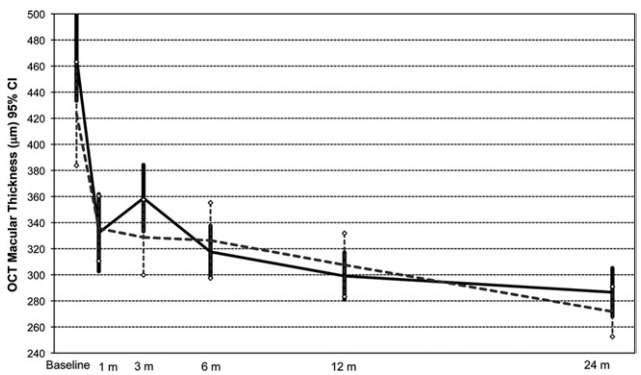

Figure 7. Graph showing changes in macular thickness with optical coherence tomography (OCT) during follow-up between doses of 1.25 and 2.5 mg intravitreal bevacizumab. In the 1.25-mg group (solid line), the mean central macular thickness (CMT) decreased from 466.5±145.2 μm at baseline to 332.2±129.6 μm at 1 month, 358.8±111.8 μm at 3 months, 317.6±87.7 μm at 6 months, 299.1±79.4 μm at 12 months, and 286.6±81.5 μm at 24 months ($P<0.0001$). In the 2.5-mg group (dotted line), the mean CMT decreased from 423.4±163.5 μm at baseline to 335.5±102.8 μm at 1 month, 328.7±118.8 μm at 3 months, 326.3±118.7 μm at 6 months, 307.5±99.9 μm at 12 months, and 271.8±78.8 μm at 24 months ($P<0.0001$). CI = confidence interval; — = 1.25 mg; --- = 2.5 mg.

onstrated, and no seriously adverse systemic events were noted during the study.

There are several studies in the literature on the intravitreal administration of antibodies against VEGF for DDME. Two studies previously reported IVB as a primary treatment for DME, including a previously reported series at 6 months[43] and a study by Soheilian et al[59] that reported 103 eyes with 12 weeks follow-up comparing IVB alone or combined with intravitreal triamcinolone versus macular focal or grid laser photocoagulation. They reported better results with IVB regarding visual outcome than with laser photocoagulation, although it was not associated with a significant decrease in CMT. No further beneficial effect of intravitreal triamcinolone could be demonstrated in their study.[59] Haritoglou et al[18] reported that intravitreal ranibizumab has the potential to maintain or improve BCVA and to reduce retinal thickness in patients with DDME not responding to previous treatments such as photocoagulation, intravitreal injection of triamcinolone, or vitrectomy. Their follow-up period was too short (6 weeks) to provide specific treatment recommendations. Kumar and Sinha[60] reported results of 20 eyes with DDME treated with IVB at a dose of 1.25 mg that had not responded to previous photocoagulation. Their follow-up period was 6 months. They concluded that IVB resulted in a significant decrease in macular thickness and improvement in VA at 3 months, but that the effect was somewhat blunted, although still statistically significant, at the end of 6 months. The results of the current study compare favorably with those of these reports and confirm their findings with longer follow-up and a larger number of patients.

The 2 doses of bevacizumab evaluated in this study were 1.25 mg, which is the one that has been used most commonly in clinical practice, and 2.5 mg, which also has been used, although less commonly. The results of this retrospective study demonstrated the efficacy of 1.25 or 2.5 mg of IVB as primary treatment of DDME, because 51.8% of eyes showed anatomic and functional improvement. In addition, the results suggest a reduced risk of VA loss in eyes with DDME treated with IVB (97.1% of eyes). The anatomic and visual benefit of intravitreal bevacizumab appears and reaches its maximum value during the first month and is maintained over 24 months. This study had an 80% power with an α of 5% to detect a 25% difference between the 1.25-mg and the 2.5-mg groups with respect to BCVA and CMT variations. No statistically significant differences in duration or anatomic or functional effectiveness were found between the 2 doses of bevacizumab evaluated.

These results indicate that IVB injections may have a beneficial effect on macular thickness and BCVA in DDME. Therefore, in the future, this new treatment method may replace or complement focal or grid laser photocoagulation. Furthermore, focal or grid laser photocoagulation may be used to consolidate the results obtained with 1 IVB injection and may decrease the need for reinjections. A recently published multicenter study, funded by the National Eye Institute and conducted through the Diabetic Retinopathy Clinical Research Network, studied 840 eyes of 693 subjects with DME involving the fovea and with VA of 20/40 to 20/320. This 2-year study demonstrated that focal or grid photocoagulation is more effective and has fewer side effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone for most patients with DME who have characteristics similar to the cohort in this clinical trial.[61] This study showed that at 2 years, focal or grid photocoagulation is more effective than expected. Schachat[62] recently pointed out 2 main reasons for these findings: longer-term follow-up than in previous intravitreal triamcinolone studies and the fact that in the ETDRS, subjects mainly had good vision at baseline. If the subject starts out with VA better than 20/40, it is harder to gain 5, 10, or 15 letters or 1 to 3 ETDRS lines than if the patient has worse vision at baseline. Therefore, we should all consider laser therapy for patients with DME while we await advances and better outcomes from new therapies still under investigation. Although the evidence currently supports focal or grid photocoagulation as the most effective treatment, the authors from the Diabetic Retinopathy Clinical Research Network study commented that combining laser therapy with corticosteroids may prove useful.[61] The same may be true for anti-VEGF therapies, and combination therapies should be considered.

Limitations of this study include that it is nonrandomized, uncontrolled, and retrospective, that is, features that preclude any estimation of the long-term efficacy or safety of IVB. In addition, because no control group is present, the possibility that some of the improvement in macular edema may be associated with improvement in systemic health cannot be ruled out. It is not uncommon that additional attention is directed toward improving systemic health when patients become involved in a clinical trial or new treatment. Furthermore, there was no standardized adverse event form to collect the safety data. However, the results are very promising and suggest the need for further investigation. In addition, it can be safely assumed (with 95% confidence) that the true rate of ocular complications in this study was less than 4.3% and that the true rate of systemic complications was less than 2.6%.[56,63]

In summary, primary IVB at doses of 1.25 or 2.5 mg seem to provide stability and improvement in BCVA, OCT, and FA results in DDME at 24 months. No difference in outcomes between IVB at doses of 1.25 or 2.5 mg was identified. Therefore, doses lower than 2.5 mg should be preferred. Evaluation in a multicenter, randomized, controlled clinical trial comparing IVB and focal or grid photocoagulation is needed to evaluate the safety and efficacy of this treatment method.

References

1. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414:782–7.
2. Nguyen QD, Tatlipinar S, Shah SM, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. Am J Ophthalmol 2006;142:961–9.
3. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464–74.
4. Richter B, Kohner E. Medical interventions for diabetic retinopathy. In: Wormald R, Smeeth L, Henshaw K, eds.

Evidence-Based Ophthalmology. London: BMJ Books; 2004: 331–40.
5. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–806.
6. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 2. Ophthalmology 1987;94: 761–74.
7. Ferris FL III, Patz A. Macular edema: a complication of diabetic retinopathy. Surv Ophthalmol 1984;28(suppl):452–61.
8. Bresnick GH. Diabetic maculopathy: a critical review highlighting diffuse macular edema. Ophthalmology 1983;90: 1301–17.
9. Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema: long-term visual results. Ophthalmology 1991;98:1594–602.
10. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. Ophthalmology 2004;111:2044–9.
11. Massin P, Aurden F, Haouchine B, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. Ophthalmology 2004;111:218–25.
12. Gillies MC, Sutter FK, Simpson JM, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology 2006;113:1533–8.
13. Jonas JB, Kamppeter BA, Harder B, et al. Intravitreal triamcinolone acetonide for diabetic macular edema: a prospective, randomized study. J Ocul Pharmacol Ther 2006;22:200–7.
14. Audren F, Erginay A, Haouchine B, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. Acta Ophthalmol Scand 2006;84:624–30.
15. Pendergast SD, Hassan TS, Williams GA, et al. Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid. Am J Ophthalmol 2000;130: 178–86.
16. Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112:1747–57.
17. Chun DW, Heier JS, Topping TM, et al. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. Ophthalmology 2006;113:1706–12.
18. Haritoglou C, Kook D, Neubauer A, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina 2006;26:999–1005.
19. Starita C, Patel M, Katz B, Adamis AP. Vascular endothelial growth factor and the potential therapeutic use of pegaptanib (Macugen) in diabetic retinopathy. Dev Ophthalmol 2007;39: 122–48.
20. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581–611.
21. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. Semin Ophthalmol 1999;14:223–32.
22. Funatsu H, Yamashita H, Ikeda T, et al. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology 2003;110: 1690–6.
23. Funatsu H, Yamashita H, Sakata K, et al. Vitreous levels of vascular endothelial growth factor and intercellular adhesion molecule 1 are related to diabetic macular edema. Ophthalmology 2005;112:806–16.
24. 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.
25. 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.
26. Malecaze F, Clamens S, Simorre-Pinatel V, et al. Detection of vascular endothelial growth factor messenger RNA and vascular endothelial growth factor-like activity in proliferative diabetic retinopathy. Arch Ophthalmol 1994;112:1476–82.
27. Tolentino MJ, McLeod DS, Taomoto M, et al. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. Am J Ophthalmol 2002;133: 373–85.
28. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. Ophthalmology 1996;103:1820–8.
29. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004;3:391–400.
30. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. Retina 2006;26:275–8.
31. Michels S, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005;112:1035–47.
32. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006;113:363–72.
33. Iturralde D, Spaide RF, Meyerle CB, et al. Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study. Retina 2006;26: 279–84.
34. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006;113:1695–705.
35. Spandau UH, Ihloff AK, Jonas JB. Intravitreal bevacizumab treatment of macular oedema due to central retinal vein occlusion [letter]. Acta Ophthalmol Scand 2006;84:555–6.
36. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006;26:383–90.
37. Rich RM, Rosenfeld PJ, Puliafito CA, et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina 2006;26:495–511.
38. Ladewig MS, Ziemssen F, Jaissle G, et al. Intravitreal bevacizumab for neovascular age-related macular degeneration [in German]. Ophthalmologe 2006;103:463–70.
39. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. Am J Ophthalmol 2006;142:155–8.
40. Bakri SJ, Donaldson MJ, Link TP. Rapid regression of disc neovascularization in a patient with proliferative diabetic retinopathy following adjunctive intravitreal bevacizumab [letter]. Eye 2006;20:1474–5.

41. Mason JO III, Albert MA Jr, Mays A, Vail R. Regression of neovascular iris vessels by intravitreal injection of bevacizumab. Retina 2006;26:839–41.
42. Shah PK, Narendran V, Tawansy KA, et al. Intravitreal bevacizumab (Avastin) for post laser anterior segment ischemia in aggressive retinopathy of prematurity. Indian J Ophthalmol 2007;55:75–6.
43. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, et al, Pan-American Collaborative Retina Study Group. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. Ophthalmology 2007; 114:743–50.
44. Maturi RK, Bleau LA, Wilson DL. Electrophysiologic findings after intravitreal bevacizumab (Avastin) treatment. Retina 2006;26:270–4.
45. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). Retina 2006;26:262–9.
46. Manzano RP, Peyman GA, Khan P, Kivilcim M. Testing intravitreal toxicity of bevacizumab (Avastin). Retina 2006; 26:257–61.
47. Early Treatment Diabetic Retinopathy Study Research Group. Focal photocoagulation treatment of diabetic macular edema: relationship of treatment effects to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Arch Ophthalmol 1995;113:1144–55.
48. Chieh JJ, Roth DB, Liu M, et al. Intravitreal triamcinolone acetonide for diabetic macular edema. Retina 2005;25: 828–34.
49. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
50. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317:703–13.
51. Strom C, Sander B, Klemp K, et al. Effect of ruboxistaurin on blood-retinal barrier permeability in relation to severity of leakage in diabetic macular edema. Invest Ophthalmol Vis Sci 2005;46:3855–8.
52. Campochiaro PA, C99-PKC412–003 Study Group. Reduction of diabetic macular edema by oral administration of the kinase inhibitor PKC412. Invest Ophthalmol Vis Sci 2004; 45:922–31.
53. Miyamoto K, Ogura Y. Pathogenetic potential of leukocytes in diabetic retinopathy. Semin Ophthalmol 1999;14:233–9.
54. Miyamoto K, Khosrof S, Bursell S, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. Proc Natl Acad Sci U S A 1999;96:10836–41.
55. Vermes I, Steinmetz ET, Zeyen LJ, van der Veen EA. Rheological properties of white blood cells are changed in diabetic patients with microvascular complications. Diabetologia 1987; 30:434–6.
56. Schröder S, Palinski W, Schmid-Schönbein GW. Activated monocytes and granulocytes, capillary nonperfusion, and neovascularization in diabetic retinopathy. Am J Pathol 1991;139: 81–100.
57. McLeod DS, Lefer DJ, Merges C, Lutty GA. Enhanced expression of intracellular adhesion molecule-1 and P-selectin in the diabetic human retina and choroid. Am J Pathol 1995;147: 642–53.
58. Antonetti DA, Barber AJ, Khin S, et al, Penn State Retina Research Group. Vascular permeability in experimental diabetes is associated with reduced endothelial occludin content: vascular endothelial growth factor decreases occludin in retinal endothelial cells. Diabetes 1998;47:1953–9.
59. Soheilian M, Ramezani A, Bijanzadeh B, et al. Intravitreal bevacizumab (Avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. Retina 2007;27:1187–95.
60. Kumar A, Sinha S. Intravitreal bevacizumab (Avastin) treatment of diffuse diabetic macular edema in an Indian population. Indian J Ophthalmol 2007;55:451–5.
61. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115:1447–59.
62. Schachat AP. A new look at an old treatment for diabetic macular edema. Ophthalmology 2008;115:1445–6.
63. Schachat AP, Chambers WA, Liesegang TJ, Albert DA. Safe and effective. Ophthalmology 2003;110:2073–4.

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[1] Retina and Vitreous Service, Clinica Oftalmológica Centro Caracas, Caracas, Venezuela.

[2] Instituto Nacional de Investigación en Oftalmología (INIO), Medellin, Colombia.

[3] Instituto de Cirugia Ocular, San Jose, Costa Rica.

[4] Instituto da Visão, Departamento de Oftalmologia, Universidade Federal de São Paulo, São Paulo, Brazil.

[5] OFTALMOS, Universidad de Buenos Aires, Facultad de Medicina, Buenos Aires, Argentina.

[6] Instituto Docente de Especialidades Oftalmológicas (IDEO), Maracaibo, Venezuela.

[7] Centro de Oftalmología Bonafonte Barcelona, Spain.

[8] MACULA D&T Diagnóstico, Tratamiento & Rehabilitación Visual, Lima, Peru.

[9] Consorcio Hospital, General Universitario de Valencia, Valencia, Spain.

[10] Fundacion Oftalmologica Nacional, Universidad del Rosario, Bogota, Colombia.

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Correspondence:
J. Fernando Arevalo, MD, FACS, Clinica Oftalmologica Centro Caracas, Edif. Centro Caracas PH-1, Av. Panteon, San Bernardino, Caracas 1010, Venezuela. E-mail: arevalojf2020@gmail.com.

Appendix 1. The Pan-American Collaborative Retina Study Group (PACORES)

L. Wu (PI), T. Evans, Instituto de Cirugia Ocular, San Jose, Costa Rica; J. F. Arevalo (PI), J. G. Sanchez, R. A. Garcia-Amaris, D. G. Zeballos, J. V. Espinoza, Clinica Oftalmologica Centro Caracas and the Arevalo-Coutinho Foundation for Research in Ophthalmology, Caracas, Venezuela; M. Farah (PI), M. Maia, F. B. Aggio, Instituto da Visão, Departamento de Oftalmologia, Universidade Federal de São Paulo, Sao Paulo, Brazil; V. Morales-Canton (PI), H. Quiroz-Mercado, J. Fromow-Guerra, J. L. Guerrero-Naranjo, Asociación para Evitar la Ceguera en México, Mexico City, Mexico; F. J. Rodriguez (PI), G. Figueroa, R. Infante, D. Medina, Fundacion Oftalmologica Nacional, Universidad del Rosario, Bogota, Colombia; M. H. Berrocal (PI), V. Cruz-Villegas, University of Puerto Rico, San Juan, Puerto Rico; F. Graue-Wiechers (PI), D. Lozano-Rechy, V. Robledo, J. L. Rodriguez-Loaiza, Fundacion Conde Valenciana, Mexico City, Mexico; J. A. Roca (PI), G. Reategui, Clínica Ricardo Palma, Lima, Peru; M. J. Saravia (PI), M. Martinez-Cartier, Hospital Universitario Austral, Buenos Aires, Argentina; M. Avila (PI), Departamento de Oftalmologia, Universidade Federal de Goiás, Goiânia, Brazil; R. A. Costa (PI), J. Cardillo, Hospital de Olhos de Araraquara, and the Universidade de Sao Paulo, Sao Paulo, Brazil; J. Verdaguer (PI), C. Carpentier, J. I. Verdaguer, L. Filsecker, G. Sepúlveda, Fundacion Oftalmologica Los Andes, Santiago de Chile, Chile; A. Alezzandrini (PI), F. Sanchez, C. Marini, B. Garcia, OFTALMOS, Catedra de Oftalmologia, Universidad de Buenos Aires, Buenos Aires, Argentina.

PI = principal investigator.