Intravitreal Bevacizumab for Subfoveal Choroidal Neovascularization in Age-Related Macular Degeneration at Twenty-four Months: *The Pan-American Collaborative Retina Study*

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Purpose: To report the 24-month anatomic and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) response after primary intravitreal bevacizumab (IVB) (Avastin; Genentech Inc., San Francisco, CA) (1.25 or 2.5 mg) in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

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

Participants: We reviewed the clinical records of 180 consecutive patients (207 eyes) with subfoveal CNV secondary to AMD at 9 centers from 8 countries.

Methods: Patients were treated with at least 1 injection of IVB 1.25 mg (124 eyes [59.9%]) or 2.5 mg (83 eyes [40.1%]). Patients underwent ETDRS BCVA testing, ophthalmoscopic examination, optical coherence tomography (OCT), and fluorescein angiography (FA) at baseline and 1-, 3-, 6-, 12-, and 24-month visits.

Main Outcome Measures: Changes in BCVA and OCT.

Results: The mean age of our patients was 74.3±7.5 years. The mean number of IVB injections per eye was 5.1 (range, 1–24 injections). In the 1.25 mg group, baseline BCVA improved from 20/235 (logarithm of the minimum angle of resolution [logMAR] 1.07) to 20/172 (logMAR 0.92) at 24 months ($P<0.0001$). Similar BCVA changes were observed in the 2.5 mg group. At baseline, the mean central macular thickness (CMT) by OCT in the 1.25 mg group was 308.4±127.52 μm, which was reduced to 269.35±97.92 μm, 262.1±94.81 μm, 264.03±97.06 μm, 245.91±89.52 μm, and 249.27±89.14 μm at 1, 3, 6, 12, and 24 months, respectively ($P<0.0001$). Similar changes were observed in the 2.5 mg group. In the 2.5 mg group, systemic complications included 2 new cases (2.6%) of arterial hypertension, 1 case (1.3%) of stroke, and 1 case (1.3%) of death.

Conclusions: Primary IVB at a dose of 1.25 or 2.5 mg seems to provide stability or improvement in BCVA, OCT, and FA in subfoveal CNV secondary to AMD at 24 months. Our results show no significant difference regarding BCVA with IVB at doses of 1.25 or 2.5 mg.

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

Advanced age-related macular degeneration (AMD) can be classified into 2 forms: a non-neovascular form (geographic atrophy of the retinal pigment epithelium [RPE] involving the center of the macula) and a neovascular form characterized by choroidal neovascularization (CNV). Choroidal neovascularization in AMD is characterized by the accumulation of serous fluid in the retina or under the retina, blood under the retina, or RPE caused by the increased permeability of newly formed capillaries. Each of these can lead to severe vision loss.[1] The neovascular form is responsible for 80% to 90% of cases of severe vision loss due to AMD.[2–6]

There is evidence that vascular endothelial growth factor (VEGF) plays a major role in ocular neovascularization and the pathogenesis of AMD. Vascular endothelial growth factor has been shown to be an endothelial cell-specific mitogen in vitro and an angiogenic inducer in a variety of in vivo models.[7–11] Vascular endothelial growth factor has been shown to increase vascular permeability, induce vascular endothelial cell proliferation, and promote endothelial cell survival. It also serves as a chemotactic factor for leukocytes. All these properties are thought to be important in its role as an angiogenic factor.[7] Inhibition of VEGF, and

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thereby inhibition of angiogenesis and vascular permeability, can be an effective treatment for a variety of ocular diseases, including neovascular AMD.[10–16]

Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA) is a full-length humanized antibody that binds to all subtypes of VEGF and is successfully used in cancer therapy as a systemic drug.[17] Recent studies have demonstrated the usefulness of intravitreal injections of bevacizumab in the reduction of macular edema secondary to central vein occlusion and of vascular permeability and retinal neovascularization in fibrovascular proliferation secondary to proliferative diabetic retinopathy and CNV secondary to AMD.[18–24]

This retrospective study reports the 24-month anatomic and best-corrected visual acuity (BCVA) response after primary intravitreal bevacizumab (IVB) in patients with subfoveal CNV secondary to AMD. To our knowledge, this is the largest study with the longest follow-up to compare 1.25 and 2.5 mg IVB in exudative AMD. In addition, there are no studies published on the outcomes of 2.5 mg of IVB in AMD at 24 months.

Patients and Methods

We reviewed the clinical records of consecutive patients with CNV secondary to AMD who were treated with off-label IVB between September 2005 and July 2007 at 9 institutions in Venezuela, Brazil, Puerto Rico, Peru, Colombia, Costa Rica, Spain, and Argentina. A total of 207 eyes of 180 consecutive patients with subfoveal CNV secondary to AMD, a mean age of 74.3±8 years, and 24 months of follow-up were identified and included for this analysis. Institutional review board/ethics committee approval and patients' signed informed consent were obtained for this study at all 9 institutions. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients.

Eyes with subfoveal CNV secondary to AMD regardless of size, composition (classic or occult), and visual acuity (VA) were included. Exclusion criteria included patients (eyes) with CNV secondary to AMD previously treated with laser photocoagulation, intravitreal triamcinolone, macular surgery, or photodynamic therapy, and patients with a history of glaucoma, diabetic retinopathy, and macular disorders other than AMD. Eyes in patients with a history of uncontrolled hypertension and recent thromboembolic events were not usually injected with bevacizumab, but this decision was left to the discretion of the treating physician.

Each patient underwent BCVA measurement with Early Treatment Diabetic Retinopathy Study (ETDRS) charts and ophthalmic examination, including slit-lamp biomicroscopy. Baseline central retinal characteristics were measured by optical coherence tomography (OCT) (Stratus OCT, Carl Zeiss, Dublin, CA) using 6 diagonal slow 6-mm radial line scans (software version 4.0) through a dilated pupil. A retina specialist performed the scans. The retinal thickness of the 1-mm central retina was obtained using the macular thickness map for our calculations. The scans were reviewed, and manual caliper-assisted measurements were used in case of delineation errors.

The dose of 1.25 or 2.5 mg of bevacizumab was determined by the treating physician. If a patient received one of the doses at baseline, the same dose was delivered throughout the study. 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) of 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, and patients were instructed to administer topical antibiotics for 7 days.

All patients were given detailed postinjection instructions, evaluated at 1 week of the injection, and asked to call promptly if any pain or significant changes in vision occurred. In addition, patients were examined at 2 weeks and 1 month after the first injection and monthly thereafter. At 1, 3, 6, 12, and 24 months after the initial injection, ophthalmic examination included OCT. Only patients with a minimum of 24 months of follow-up were included in this consecutive series. Fluorescein angiography (FA) was performed at the discretion of the examiner and not at every postinjection evaluation.

Patients received reinjections when there was a recurrence or persistence. Recurrence was defined as any decrease from the prior visit BCVA associated with an increase of subretinal fluid, macular edema, or RPE detachment on OCT or FA after complete or partial resolution in previous follow-up visits. Persistence was defined as no improvement in BCVA and OCT or FA findings from baseline. Because the optimal treatment dose or interval with IVB is unknown, treatment intervals and dose were also chosen by the treating physician. However, most patients were usually treated at 4- to 6-week interval visits if necessary.

All data were collected in a Microsoft Excel 2003 spreadsheet (Microsoft Corporation, Redmond, WA) and analyzed using SPSS V13.0 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-ups. Patients' ETDRS BCVAs were transferred from their records and converted to a logarithm of the minimum angle of resolution (logMAR) scale for analysis. Repeated-measures analysis of variance was used to compare mean values to analyze mean retinal thickness and logMAR VA statistically. An increase or decrease in BCVA was considered to have occurred if there was a change of 2 or more ETDRS lines of BCVA. Main outcome measures included changes in BCVA and central macular thickness (CMT) measured by OCT.

Results

A total of 128 patients (71.1%) were Hispanic, and 52 patients (28.9%) were Caucasian. Patients had a mean age of 74.3±8 years (range, 54–93 years), and 66.1% were female (61 men and 119 women). All eyes were followed for 24 months. A summary of the demographics and baseline characteristics of our patients is shown in Table 1.

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. By 1 month, the mean BCVA improved from 20/257 (logMAR 1.11±0.47) to 20/196 (logMAR 0.99±0.5), a difference that was statistically significant ($P<0.0001$). This improvement in BCVA was maintained throughout the 3-, 6-, 12-, and 24-month follow-ups. At 3 months, mean BCVA was 20/180, logMAR 0.95±0.49 ($P<0.0001$). At 6-months, mean BCVA was 20/192, logMAR 0.98±0.52 ($P<0.0001$). At 12 months, mean BCVA was 20/192, logMAR 0.98±0.55 ($P<0.0001$). At 24 months, mean BCVA was 20/184, logMAR 0.95±0.52 ($P<0.0001$). At 24 months, BCVA analysis by subgroups demonstrated that 89 eyes (43%) remained stable, 90 eyes (43.5%) improved ≥2 ETDRS lines of BCVA, and 28 eyes (13.5%) had a decrease of ≥2 ETDRS lines of BCVA (Fig 1) because of increased lesion size, subretinal fibrosis, RPE rip, or RPE atrophy.

Table 1. Patients' Demographics and Baseline Characteristics

	IVB Dose		
	1.25 mg	*2.5 mg*	*P Value*
No. of eyes	124	83	
Male/female (n)	78/46	60/23	
Mean age (y)	74.4±7.9	75.02±7.7	0.58
CNV type (C/O/PC)	55/36/33	23/39/21	
Baseline BCVA (logMAR)	1.07±0.48	1.15±0.45	0.2
Baseline CMT (μm)	308.39±127.52	416.17±111.91	>0.001

BCVA = best-corrected visual acuity; C = classic; CMT = central macular thickness; CNV = choroidal neovascularization; IVB = intravitreal bevacizumab; logMAR = logarithm of the minimum angle of resolution; O = occult; PC = predominantly classic.

Optical coherence tomography results were available for all cases at 1, 3, 6, 12, and 24 months. At 1 month, the mean CMT decreased from 349.6±131.32 μm to 272.24±87.48 μm ($P<0.001$), and this overall improvement continued throughout the 24-month follow-up. At the 3-, 6-, 12-, and 24-month follow-ups, mean CMTs were 262.46±84.14 μm, 259.1 ±84.37 μm, 252.67±81.77 μm, and 251.25±79.86 μm, respectively, a statistically significant difference from baseline at all time points ($P<0.0001$) (Figs 2 and 3).

All eyes received an intravitreal injection at the initial visit; however, recurrences were treated at the discretion of the treating physician according to our definition. There were a total of 1050 IVB injections performed in the 24 months of follow-up. The mean number of IVB injections per eye was 5.1±3.2 (range, 1–24). A total of 9.2% of eyes (19/207) received 1 injection, 9.2% of eyes (19/207) received 2 injections, 10.1% of eyes (21/207) received 3 injections, 20.3% of eyes (42/207) received 4 injections, 15% of eyes (31/207) received 5 injections, 15.4% of eyes (32/207) received 6 injections, 5.8% of eyes (12/207) received 7 injections, 4.8% of eyes (10/207) received 8 injections, 1.9% of eyes (4/207) received 9 injections, 3.4% of eyes (7/207) received 10 injections, and 4.8% of eyes (10/207) received more than 10 injections. A total of 124 cases (59.9%) were treated with a dose of IVB of 1.25 mg, and 83 cases (40.1%) were treated with a dose of 2.5 mg.

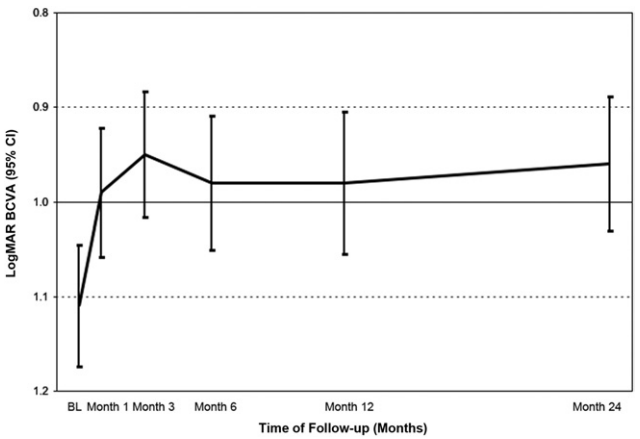

Figure 1. Changes in BCVA after IVB. The BCVA improved at 1 month from logMAR 1.11 to 0.99, a difference that was statistically significant ($P<0.0001$); this level of BCVA was maintained throughout 3, 6, 12, and 24 months of follow-up. BCVA = best-corrected visual acuity; BL = baseline; CI = confidence interval; IVB = intravitreal bevacizumab; logMAR = logarithm of the minimum angle of resolution.

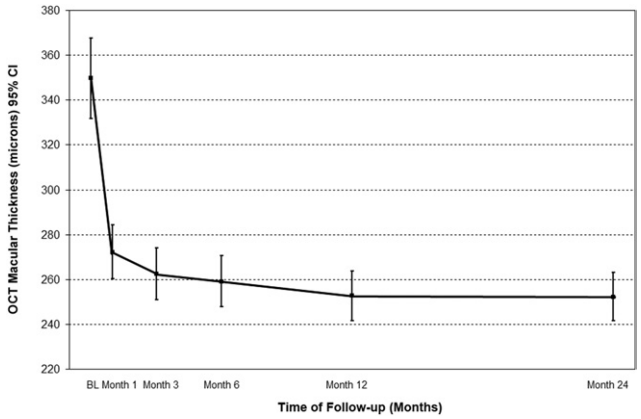

Figure 2. Changes in CMT with OCT during follow-up after IVB. Mean CMT at 1 month decreased from 349.6±131.32 μm to 272.24±87.48 μm ($P<0.001$), and this overall improvement continued throughout the 24 months of follow-up. At 3, 6, 12, and 24 months of follow-up, CMTs were 262.46±84.14 μm, 259.1±84.37 μm, 252.67±81.77 μm, and 251.25±79.86 μm, respectively ($P<0.001$). BL = baseline; CI = confidence interval; CMT = central macular thickness; IVB = intravitreal bevacizumab; OCT = optical coherence tomography.

A total of 188 eyes (90.8%) received a second injection at a mean of 9.3±7.8 weeks, 169 eyes (81.6%) received a third injection at a mean of 11.9±11.5 weeks, 148 eyes (71.5%) received a fourth injection at a mean of 12.3±10.3 weeks, 106 eyes (51.2%) received a fifth injection at a mean of 10.9±9.1 weeks, 75 eyes (36.2%) received a sixth injection at a mean of 9.92±5.8 weeks, 43 eyes (20.8%) received a seventh injection at a mean of 9.10±5.2 weeks, 31 eyes (15%) received an eighth injection at a mean of 8.45±4.2 weeks, 21 eyes (10.1%) received a ninth injection at a mean of 8.57±4.8 weeks, 17 eyes (8.2%) received a tenth injection at a mean of 8.35±4 weeks, and 10 eyes (4.8%) received 10 or more injections at a mean of 7.42±3.2 weeks.

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

At 1 month, BCVA improved in the 1.25 mg group from 20/235 (logMAR 1.07) at baseline to 20/196 (logMAR 0.99), a difference that was statistically significant ($P=0.002$). This improvement was maintained throughout the 3-, 6-, 12-, and 24-month follow-ups. The mean BCVA at 24 months was 20/172 (logMAR 0.92), a statistically significant difference from baseline BCVA ($P<0.0001$).

Similar BCVA changes were observed in the 2.5 mg group. At 1 month, BCVA improved from 20/285 (logMAR 1.15) at baseline to 20/196 (logMAR 0.99), a difference that was statistically significant ($P<0.0001$). This improvement was maintained throughout the 3-, 6-, 12-, and 24-month follow-ups. The mean BCVA at 24 months was 20/205 (logMAR 1.01), a statistically significant difference from baseline BCVA ($P=0.002$) (Table 2; Fig 4).

At 24 months, BCVA analysis by subgroups demonstrated that in the 1.25 mg group, 54 eyes (43.5%) remained stable, 54 eyes (43.5%) improved ≥2 ETDRS lines of BCVA, and 16 eyes (12.9%) decreased ≥2 ETDRS lines of BCVA. In the 2.5 mg group, 35 eyes (42.2%) remained stable, 36 eyes (43.4%) improved ≥2 ETDRS lines of BCVA, and 12 eyes (14.5%) decreased ≥2 ETDRS lines of BCVA.

The mean CMT (by OCT) at baseline in the 1.25 mg group was 308.4±127.52 μm, which was significantly reduced to a mean of 269.35±97.92 μm, 262.1±94.81 μm, 264.03±97.06 μm, 245.91±

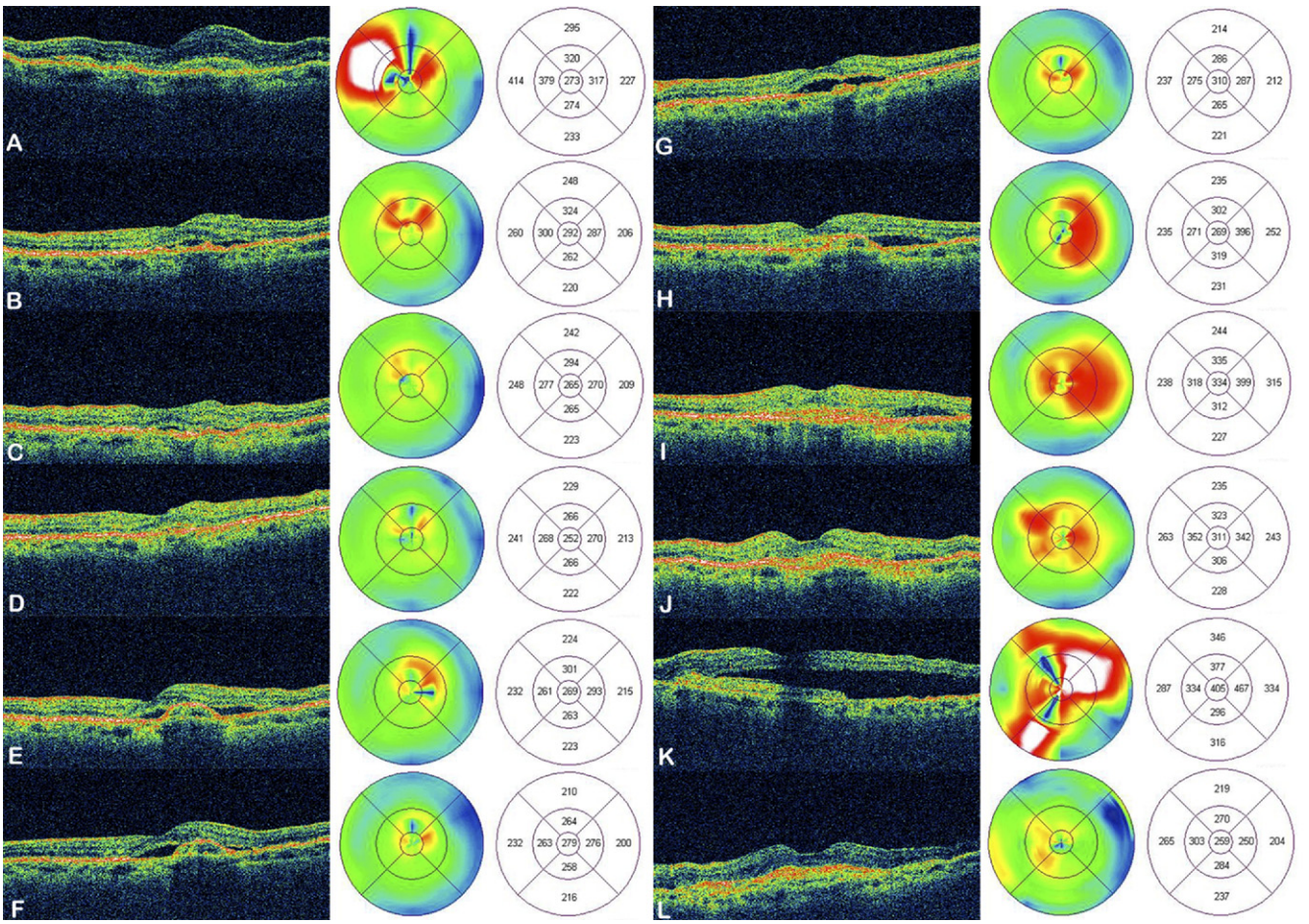

Figure 3. Sequential OCT scans of a 68-year-old woman with 1-month history of vision loss to 20/400 in her left eye. She was diagnosed with subfoveal CNV. **A,** An OCT scan before treatment demonstrated a localized fusiform thickening and duplication of the highly reflective external band (RPE/choriocapillaris complex) corresponding to CNV. The retinal map analysis revealed a CMT of 273 μm. The patient was offered IVB at a dose of 2.5 mg. **B,** One month after the injection, VA improved to 20/40. An OCT scan demonstrated improvement of macular architecture with mild residual subretinal fluid (SRF). **C,** Two months after the injection, VA decreased to 20/50 and the OCT scan showed SRF with a CMT of 265 μm. She received a second injection of IVB at a dose of 2.5 mg at this point. **D,** Three months after the first injection, the OCT scan showed total reabsorption of SRF and an improvement in CMT to 252 μm; her VA improved to 20/32. **E,** Six months after the first injection, VA decreased to 20/80, and an OCT scan demonstrated the reappearance of SRF associated with a retinal pigment epithelial detachment and a CMT of 269 μm. She received a third injection of IVB. **F,** Eight months after the first injection, her VA returned to 20/32 but with only partial resolution of the SRF and pigment epithelial detachment. She received a fourth injection of IVB. **G, H,** Twelve and 15 months after the first injection, OCT demonstrated SRF associated with a pigment epithelial detachment with a VA of 20/40. A fifth IVB injection was given. **I, J,** The OCT scans at 18 and 19 months showed significant improvement and almost complete restoration of foveal anatomy; central foveal thicknesses were 334 and 311 μm, respectively, and VA was maintained at 20/40. **K,** At 21 months after the first injection, there was a decrease in VA to 20/200, and OCT showed central elevation with loss of the foveal contour and reappearance of SRF associated with diffuse thickening of the RPE/choriocapillaris complex in the area corresponding to CNV and subretinal fibrosis with a CMT of 405 μm. A sixth IVB injection was given at this time. **L,** Twenty-four months after the first injection, VA improved to 20/160 and OCT showed improvement in CMT to 259 μm with complete reabsorption of SRF and normalization of the foveal anatomy. The external highly reflective band (including the RPE/choriocapillaris complex) demonstrated a fusiform thickening corresponding to subretinal fibrosis. CMT = central macular thickness; CNV = choroidal neovascularization; IVB = intravitreal bevacizumab; OCT = optical coherence tomography; RPE = retinal pigment epithelium; VA = visual acuity.

89.52 μm, and 249.27±89.14 μm at 1, 3, 6, 12, and 24 months, respectively, after the initial treatment ($P<0.0001$). Similar changes were observed in the 2.5 mg group: The mean CMT at baseline was 411.17±111.91 μm, which was significantly reduced to a mean of 276.54±69.35 μm, 262.1±65.58 μm, 251.73±60.49 μm, 262.76±67.86 μm, and 254.19±63.93 μm at 1, 3, 6, 12, and 24 months after the initial treatment, respectively ($P<0.0001$) (Fig 5).

There was no statistically significant difference in BCVA between the eyes that received 1.25 mg of IVB and the eyes that received 2.5 mg of IVB at any time point during the study. There was a statistically significant difference in the reduction in CMT in favor of the 2.5 mg group between baseline and 1 month of follow-up ($P<0.001$) and between baseline and 24 months of follow-up ($P<0.0001$) compared with the 1.25 mg group. However, there was a higher frequency of injections in the 2.5 mg group compared with the 1.25 mg group (6.61±3.75 vs 4.04±2.25 injections; $P<0.0001$).

The injection of IVB was well tolerated in all patients. In the 1.25 mg group, there were no systemic complications. Ocular complications included uveitis in 1 eye (0.8%), endophthalmitis in

Table 2. Best-Corrected Visual Acuity in Eyes Injected with Doses of 1.25 and 2.5 mg of Intravitreal Bevacizumab at 24-Month Follow-up

	Subgroup 1.25 mg		Subgroup 2.5 mg	
	BCVA	*LogMAR*	*BCVA*	*LogMAR*
Baseline	20/235	1.07±0.48	20/285	1.15±0.45
1 mo	20/196	0.99±0.5	20/196	0.99±0.51
3 mos	20/180	0.95±0.5	20/180	0.95±0.49
6 mos	20/192	0.98±0.51	20/192	0.98±0.52
12 mos	20/188	0.97±0.54	20/205	1.01±0.56
24 mos	20/172	0.92±0.52	20/205	1.00±0.53

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.

1 eye (0.8%), cataract progression in 1 eye (0.8%), and transient increased intraocular pressure in 1 eye (0.8%). In the 2.5 mg group, systemic complications included 2 new cases (2.6%) of arterial hypertension, 1 stroke (1.3%), and 1 death (1.3%). Ocular complications included uveitis in 1 eye (1.2%), endophthalmitis in 1 eye (1.2%), and an RPE rip in 1 eye (1.2%).

Discussion

The majority of eyes that were treated with primary IVB at doses of 1.25 or 2.5 mg showed anatomic and functional improvement at 24 months. Both leakage and macular thickening caused by CNV were significantly reduced. At 1 month, the mean CMT measurements decreased from 349.6±131.32 μm to 272.24±87.48 μm ($P<0.001$), and this overall improvement continued throughout the 24-month follow-up. In addition, 43.5% of consecutive eyes gained ≥2 lines of ETDRS at the 24-month time point. However, 13.5% of the eyes in this study lost ≥2 lines of ETDRS because of increased lesion size, subretinal fibrosis, RPE rip, or RPE atrophy.

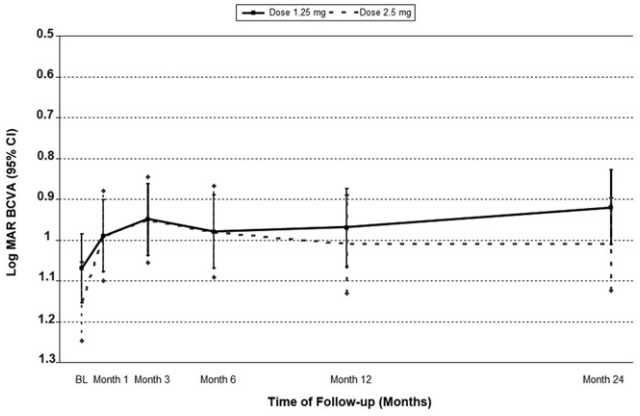

Figure 4. Changes in BCVA between doses of 1.25 mg (*continuous line*) and 2.5 mg (*dotted line*) of IVB. In the 1.25 mg group, at 1 month BCVA improved from logMAR 1.07 to 0.99, a difference that was statistically significant ($P=0.002$). This improvement was maintained throughout the 3, 6, 12, and 24-month follow-ups. The mean 24-month BCVA was logMAR 0.92 ($P<0.0001$), a statistically significant difference from baseline BCVA. Similar BCVA changes were observed in the 2.5 mg group; at 1 month BCVA improved from logMAR 1.15 to 0.99 ($P<0.0001$), a difference that was statistically significant. This improvement in BCVA was maintained throughout the 3-, 6-, 12-, and 24-month follow-ups. The mean 24-month BCVA was logMAR 1.01 ($P=0.002$), a statistically significant difference from baseline BCVA. BCVA = best-corrected visual acuity; BL = baseline; CI = confidence interval; IVB = intravitreal bevacizumab; logMAR = logarithm of the minimum angle of resolution.

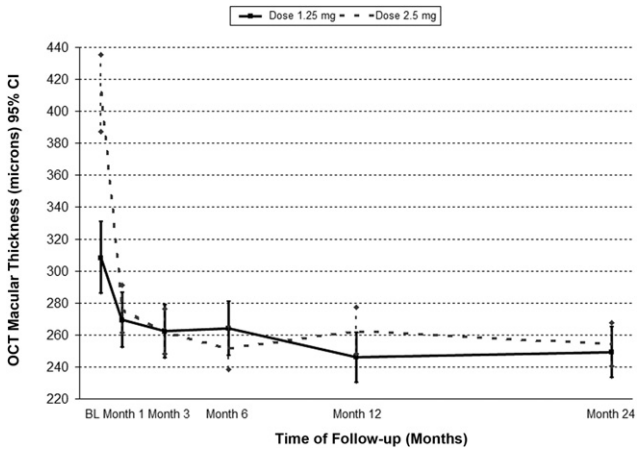

Figure 5. Changes in macular thickness with OCT during follow-up between doses of 1.25 mg (*continuous line*) and 2.5 mg (*dotted line*) of IVB. In the 1.25 mg group, the mean CMT decreased from 308.4±127.52 μm at baseline to 269.35±97.92 μm, 262.10±94.81 μm, 264.03±97.06 μm, 245.91±89.52 μm, and 249.27±89.14 μm at 1, 3, 6, 12, and 24 months, respectively ($P<0.0001$). In the 2.5 mg group, the mean CMT decreased from 411.17±111.91 μm at baseline to 276.54±69.35 μm, 262.1±65.58 μm, 251.73±60.49 μm, 262.76±67.86 μm, and 254.19±63.93 μm at 1, 3, 6, 12, and 24 months, respectively ($P<0.0001$). BL = baseline; CI = confidence interval; CMT = central macular thickness; IVB = intravitreal bevacizumab; OCT = optical coherence tomography.

Bevacizumab is a humanized monoclonal antibody to VEGF that was designed for intravenous administration and approved by different regulatory agencies to treat metastatic colorectal cancer.[24] The amount of human retinal penetration for a full-length anti-VEGF antibody is not currently known. However, full-thickness retinal penetration of IVB was observed in an animal model.[25,26] In addition, IVB does not seem to be toxic to the retina in albino rabbits at a concentration up to 2.5 mg.[27] Immunohistochemical studies have demonstrated good penetration of the retinal layers after an intravitreal injection of bevacizumab.[27] A series of 9 patients treated with IVB for neovascular AMD who were studied with pretreatment and posttreatment multifocal electroretinography or Ganzfeld electroretinography showed improved visual function and no evidence of toxicity.[26]

Bakri et al[28] reported 4 cases of uveitis after intravitreal injections of bevacizumab to treat CNV associated with AMD. Two patients presented with pain and red eye associated with iritis, and 2 patients presented with vitritis several days after IVB. Two studies[29,30] reported patients who developed an acute RPE tear after IVB. In an open-label, uncontrolled clinical study of 4303 injections of 1.25 or 2.5 mg of IVB, our group previously reported systemic adverse events in 18 patients (1.5%).[31] These included 7 cases (0.59%) of acutely elevated systemic blood pressure,

6 (0.5%) cerebrovascular accidents, 5 (0.4%) myocardial infarctions, 2 (0.17%) iliac artery aneurysms, 2 (0.17%) toe amputations, and 5 deaths (0.4%). Ocular complications included 7 cases (0.16%) of bacterial endophthalmitis, 7 (0.16%) tractional retinal detachments, 4 cases (0.09%) of uveitis, and 1 case (0.02%) each of rhegmatogenous retinal detachment and vitreous hemorrhage. Bevacizumab seems to be safe and well tolerated during the first 12 months.[31]

Michels et al[19] and Rosenfeld et al[32] were the first to report the use of systemic bevacizumab and IVB in the treatment of AMD. In a small series, intravenous administration of 5 mg/kg of bevacizumab at 2-week intervals produced a significant reduction in retinal thickening and improvement in VA.[19] There is, however, a small but significant risk of thromboembolic events, such as stroke and myocardial infarction with systemic administration of bevacizumab.[16] Therefore, the intravitreal administration of bevacizumab is an attractive option to reduce systemic exposure. Numerous reports of IVB in patients with CNV from AMD have shown promise.[10,32,33]

To date, clinical experience with bevacizumab is limited to retrospective case series and unpublished data. Avery et al[20] recently reported on IVB in 81 eyes with unresponsive CNV secondary to AMD. Spaide et al[33] reported on IVB in 266 eyes with unresponsive and nontreated CNV secondary to AMD. Both studies demonstrated a significant decrease in macular thickness and improvement in VA. Yoganathan et al[24] reported significant improvement in vision in a retrospective review of 50 eyes of 48 patients with untreated and previously treated CNV secondary to AMD with a median length of follow-up of 34 weeks. These studies reaffirmed the short-term biologic effect of IVB on CNV secondary to AMD.

We previously reported the 12-month anatomic and ETDRS BCVA response after primary IVB in patients with subfoveal CNV secondary to AMD at 12 months of follow-up. Sixty-three eyes of 63 consecutive patients were treated with at least 1 intravitreal injection of 1.25 or 2.5 mg of bevacizumab. The mean baseline BCVA was 20/320 (logMAR 1.2), and the mean 12-month BCVA was 20/200 (logMAR 1.0) ($P<0.001$). Central macular thickness at baseline by OCT had a mean of 389.2 ± 149.6 μm, which was significantly reduced to a mean of 281.0 ± 96.1 μm, 268.2 ± 82.6, μm, 262.6 ± 92.3 μm, and 241.3 ± 76.7 μm at 1, 3, 6, and 12 months, respectively, after initial treatment ($P<0.0001$). Our group concluded that primary IVB at a dose of 1.25 or 2.5 mg seems to provide stability or improvement in BCVA, OCT, and FA in subfoveal CNV secondary to AMD at 12 months.[34]

Our current 24-month data show that retinal thickening significantly and rapidly improved in the majority of cases. Our results also suggest a reduced risk of VA loss in eyes with CNV secondary to AMD treated with IVB (86.5% of eyes). Our data compare favorably with those of Yoganathan et al,[24] who analyzed untreated and previously treated CNV secondary to AMD. They found that 10 (71%) and 6 (43%) previously untreated eyes gained at least 5 and 15 letters of VA, respectively. We studied previously untreated CNV, and our visual data suggest corresponding improvement, with the mean final vision improving significantly from baseline. However, visual improvement depends on several factors other than retinal thickness, including chronicity, pigment epithelial atrophy, and the presence or absence of fibrosis. These factors were not specifically accounted for and may have influenced the visual outcomes.

A total of 188 eyes (90.5%) required reinjections (a second injection was performed at a mean of 9.3 ± 7.8 weeks), 169 eyes (81.64%) required a third injection at a mean of 11.9 ± 11.5 weeks, 148 eyes (71.5%) required a fourth injection at a mean of 12.3 ± 10.3 weeks, and 106 eyes (51.2%) required 5 or more injections. There was no statistically significant difference in BCVA between the 1.25 mg and 2.5 mg groups at any time point during the study. There was a statistically significant difference in the reduction in CMT in favor of the 2.5 mg group between baseline and 1-month follow-up ($P<0.001$) and between baseline and 24-month follow-up ($P<0.0001$) when compared with the 1.25 mg group, perhaps because the baseline CMT in the 2.5 mg group was statistically significantly higher. In addition, there was a higher frequency of injections in the 2.5 mg group compared with the 1.25 mg group ($P<0.0001$).

The optimum dosing sequence for IVB is still undetermined. The mean number of IVB injections in our study was rather low for 24 months. In addition, the interval between injections seems long, and this may have affected our functional outcomes. However, we elected to defer reinjections until there was a recurrence or persistence. It is possible that a different dosing schedule, such as a series of injections every 6 weeks for an extended period of time (3 or 4 times) followed by retreatment only for recurrences, may be superior to the method used in this study; however, we chose to err on the side of undertreatment until further safety data are available.

The ocular side effects of IVB in our study seem to be similar to those in previous reports. No systemic adverse events were seen in the 1.25 mg group. However, in the 2.5 mg group, systemic complications included 2 new cases (2.6%) of arterial hypertension, 1 stroke (1.3%), and 1 death (1.3%). These findings are consistent with a recent report by Modarres et al.[35] In a comparative prospective study of 86 patients followed for 5 months after IVB, they reported more complications in the 2.5 mg group than in the 1.25 mg group. In the 2.5 mg group, 3 cases of vitreous reaction and 1 case of massive subretinal hemorrhage were observed.[35]

Study Limitations

Our study included a limited number of patients and was nonrandomized, uncontrolled, and retrospective. In addition, although our statistical analysis demonstrated no difference between both doses used, our study was not powered to determine such a difference. Furthermore, we had no standardized adverse event form to collect our safety data. However, the results were promising and suggest the need for further investigation.

In conclusion, primary IVB at doses of 1.25 or 2.5 mg provides improvement in BCVA, OCT, and FA in subfoveal CNV secondary to AMD at 24 months. We identified no difference in outcomes between IVB at doses of 1.25 or 2.5

mg. The significant difference shown in the reduction in CMT between the 2 groups may be related to a higher retinal elevation at baseline in the 2.5 mg group or other unknown factors. We found low rates of systemic adverse events in both groups, although there were more in the higher dose group, but the difference was not significant. Unless data to support improved efficacy for the 2.5 mg dose become available, we favor the lower dose.

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Footnotes and Financial Disclosures

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*For a complete listing of participating members of the Pan-American Collaborative Retina Study Group, see Appendix 1 (available at http://aaojournal.org).

This article contains online-only material. The following should appear online-only: Appendix 1.

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