JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS
Volume 28, Number 1, 2012

DOI: 10.1089/jop.2010.0181

Functional and Anatomic Response of the Retina and the Choroid to Intravitreal Bevacizumab for Macular Edema

Raimondo Forte, Gilda Cennamo, Maria Angelica Breve, Elisabetta Chiariello Vecchio, and Giuseppe de Crecchio

Abstract

Purpose: This study evaluated the rate of change of best corrected visual acuity (BCVA), central retinal sensitivity, and retinal and choroidal thickness in patients with macular edema after intravitreal bevacizumab.
Methods: This was a prospective, nonrandomized, interventional study. Thirty-four consecutive eyes (34 patients) with macular edema were included in the study. Choroidal neovascularization was present in 21 cases, stage 1 retinal angiomatous proliferation in 6 cases, branch retinal vein occlusion in 4 cases, and diabetic edema in 3 cases. Evaluation of BCVA (Early Treatment Diabetic Retinopathy Study [ETDRS] logarithm of the minimum angle of resolution [LogMAR]), central retinochoroidal thickness (RCT) at standardized A-scan, combined optical coherence tomography/microperimetric assessment of central retinal thickness (RT), central scotoma, and fixation behavior was performed during 12 months after treatment. Choroidal thickness was considered as the difference between RCT and RT. All patients received two initial intravitreal bevacizumab injections (1.25 mg/0.05 mL) at a 1-month interval.
Results: BCVA and RT during follow-up were significantly better than at baseline. BCVA was improved of 0.32 ± 0.3 LogMAR ($P < 0.001$) at month 1, 0.18 ± 0.4 LogMAR ($P = 0.05$) at month 6, and 0.14 ± 0.2 ($P = 0.09$) at month 12. RT was reduced by 172.9 ± 192.8 μm ($P < 0.001$) at month 1, 157.7 ± 134.2 μm ($P = 0.003$) at month 6, and 164.3 ± 122.3 ($P = 0.002$) at month 12. Mean retinal sensitivity significantly increased during the first month; it decreased afterward, but an improvement if compared with baseline was present at each visit during follow-up. In 23.5% of cases, a choroidal thinning was present during follow-up, and in this group visual acuity at baseline and final visual improvement were significantly greater if compared with patients showing a choroidal thickening.
Conclusion: Intravitreal bevacizumab for macular edema determines significant functional and anatomic improvement at the 12-month follow-up. Visual acuity at baseline and following treatment could be influenced by the choroidal involvement.

Introduction

Vascular endothelial growth factor (VEGF) has been shown to play a major role in stimulating angiogenesis and vascular permeability in age-related macular degeneration (AMD) patients,[1] and in determining retinal edema in branch and central retinal vein occlusion (BRVO, CRVO),[2] diabetic retinopathy,[3] and retinal angiomatous proliferation (RAP).[4] Recently, several clinical case series and noncontrolled studies from multiple investigators have described the pharmacologic inhibition of all VEGF isoforms with intravitreal bevacizumab as well as an improvement in visual acuity after the intravitreal use of bevacizumab for AMD-related choroidal neovascularization (CNV), diabetic macular edema, retinal angiomatous proliferation, and CRVO.[5–9] The early effects of bevacizumab in macular edema, notwithstanding the etiology of the edema, were recently investigated by other authors.[10] Herein, we report the 12-month anatomic and functional response in macular edema from different etiologies after intravitreal bevacizumab, and we focus on the changes of choroidal thickness.

Eye Department, University Federico II, Naples, Italy.

Materials and Methods

Patient selection

Intravitreal bevacizumab was investigated in 34 consecutive eyes (34 patients) with newly diagnosed macular edema from CNV secondary to AMD (21 eyes), stage 1 RAP (6 eyes), diabetic macular edema (3 eyes), and BRVO (4 eyes) from December, 2007, to June, 2008. Stage 1 RAP was intended as an intraretinal neovascularization (capillary proliferation within the retina), according to the classification suggested by Yannuzzi et al.[4] Exclusion criteria were clinically relevant opacities of the optic media and low-quality images obtained with optical coherence tomography (OCT). Furthermore, eyes with an anteroposterior axis shorter than 22 mm and longer than 23 mm at immersion A-scan echography were excluded because the maximum threshold for normality of macular retinochoroidal thickness has been calculated to be 1.5 mm in emmetropic eyes only.[11] At baseline assessment and during following visits (7 days, 1 month, 2 months, 3 months, and 6 months after first injection), investigations included best-corrected central visual acuity (BCVA), fluorescein angiography (FA), indocyanine green angiography (ICGA) in case of CNV and RAP, OCT, and central microperimetry (MP). A-scan standardized echography was performed at baseline, and after 1 month, 2 months, 6 months, and 12 months from injection. Bevacizumab (0.05 mL solution prepared from Avastin 100 mg/4 mL; Avastin™ from Genentech, Inc., South San Francisco, CA) was administered intravitreally in all patients through the pars plana according to standard procedures[12] at baseline and after 1 month. Each patient was informed of the off-label status of bevacizumab, and informed consent was obtained. Approval by the ethics committee of the eye clinic was obtained. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Study end points

The primary study end point was the rate of change of visual acuity and central retinal thickness (RT) at OCT. Secondary study end points were: (1) changes of retinal sensitivity, location and stability of fixation as measured with combined spectral OCT/MP; (2) changes of central choroidal thickness considered as the difference between central retinochoroidal thickness as measured with A-scan standardized echography and RT in the 3-mm-diameter Early Treatment of Diabetic Retinopathy Study (ETDRS) central ring as measured with OCT. Choroidal thickness was first evaluated in all evaluated eyes as one single group; afterward it was evaluated in 21 eyes with a choroidal origin of the edema (COE, including CNV) and in 13 eyes with a retinal origin of the edema (ROE, including stage 1 RAP, diabetic macular edema, BRVO).

Assessment of visual function

Best corrected visual acuity. BCVA was measured after refraction using the ETDRS logarithm of the minimum angle of resolution (LogMAR) scale.

Microperimetry. Fundus-related microperimetry was performed using the spectral domain scanning laser ophthalmoscope (SD-SLO)/OCT (Ophthalmic Technologies Inc., Toronto, Canada). SD-SLO/OCT includes an automated tracking system to compensate in real time for any eye movement. In the SD-SLO/OCT system, the map of retinal sensitivity can be automatically overlapped on the OCT retinal thickness topographic map to associate each sensitivity value with a thickness value. To obtain a point-to-point overlapping, the software takes highly detectable features on the two maps (generally represented by vascular bifurcations) as a point of reference. We used a stimulus size equivalent to a Goldmann III test spot (size = 26 arc/min), with a stimulus intensity ranging from 16 dB to 0 dB (10–400 apostilbs) and a grid of 29 stimuli covering the central 8° area (centered on the fovea). A 4-2-1 double-staircase strategy was used, and results were reported in decibels. The area was classified as dense (or absolute) scotoma when maximum stimulus intensity was not seen. The recorded fixation pattern was classified into three categories for fixation location (central, poor central, predominantly eccentric) and fixation stability (stable, relatively unstable, unstable).[13] In this study, retinal sensitivity changes in the 8° central area, location and stability of fixation were measured at each visit.

Assessment of retinal and choroidal morphology

Optical coherence tomography. To evaluate central retinal thickness, SD-SLO/OCT was used. Spectral domain OCTs provide an improved acquisition speed and less artefacts if compared with time domain OCTs.[14] For this study, we evaluated the mean retinal thickness in the 3-mm-diameter central ring of the ETDRS map.

Echographic examination. Macular retinochoroidal thickness (RCT) was measured with standardized A-scan echography at T-minus sensitivity. Ultrasonography was performed using a Cinescan S Ophthalmic Ultrasound System (Quantel Medical S.A., Clermont-Ferrand, France) with 8-MHz standardized A-scan probes. To perform A-scan echography, the probe was positioned at the corneal apex and was maintained parallel to the optic axis at T-minus sensitivity, to measure macular RCT in a repeatable and accurate way.[11] For each patient, the mean distance between the retinal and the scleral spike in the macula after five repeated measurements was considered as indicative of macular RCT. A RCT of 1.5 mm was considered as the maximum threshold for normality in the macular area, as stated in previous reports.[11,15]

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (version 15.0, SPSS Inc., Chicago, IL). Repeated measures analysis of variance (ANOVA) with Dunnett correction for multiple comparisons was used to compare follow-up to baseline data within a treatment group. The Spearman correlation coefficient (rho) was used to measure the strength of correlation between BCVA, retinal sensitivity, and anatomic changes. Results were considered significant if the P value was < 0.05.

Results

No patient was lost to follow-up. There were 16 males and 18 females with a mean age of 71 ± 8.9 years (range, 43–91 years). Time from diagnosis ranged between 7 days and 40

Table 1. Baseline Characteristics (Mean ± Standard Deviaton) of 34 Eyes Presenting with Macular Edema

	n	Age (years)	BCVA ETDRS LogMAR	RT (μm)	RCT (mm)	CT (mm)
All cases	34	71 ± 9	1.12 ± 0.6	502.2 ± 232	2.0 ± 0.3	1.49 ± 0.3
Choroidal neovascularization	21	70.6 ± 8.6	1.07 ± 0.5	443.1 ± 151.9	2 ± 0.3	1.55 ± 0.2
RAP	6	73.3 ± 4.2	0.98 ± 0.8	646 ± 451.6	2.05 ± 0.3	1.4 ± 0.3
DME	3	76.6 ± 6.3	1.08 ± 0.1	410.3 ± 109.7	1.94 ± 0.2	1.53 ± 0.2
BRVO	4	65.7 ± 15.8	1.35 ± 0.8	657.2 ± 117.1	2.07 ± 0.2	1.41 ± 0.3

BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LogMar, logarithm of the minimum angle of resolution; RT, central retinal thickness; RCT, central retino-choroidal thickness; CT, central choroidal thickness; RAP, retinal angiomatous proliferation; DME, diabetic macular edema; BRVO, branch retinal vein occlusion.

days (mean 18.3 days). Baseline characteristics are summarized in Table 1.

No adverse events were observed during follow-up. All patients received both injections. All scheduled examinations were performed during the visits, except for MP, which was not accepted by all patients at each visit to conclude the examination. Functional and anatomic changes during follow up are shown in Table 2 and Table 3.

Visual changes

Mean BCVA progressively increased during the first month; it decreased afterward, but a significant improvement if compared with baseline was present at each visit during follow-up (Table 3, Fig. 1).

Retinal sensitivity

Mean retinal sensitivity increased significantly during the first month; it decreased afterward, but an improvement if compared with baseline was present at each visit during follow-up. Low correlation was found between BCVA and retinal sensitivity during follow-up (Table 3, Fig. 1).

Location and stability of fixation

During follow-up, the number of eyes with predominantly central fixation was always greater than at baseline, although a constant improvement was not present. Stability of fixation progressively improved during the first 2 months, whereas fixation became progressively more unstable between month 3 and month 12. However, during follow-up, both location and stability of fixation were always better than at baseline.

Retinal thickness–choroidal thickness

A significant improvement of mean retinal thickness in the 3-mm-diameter central ring was present at each visit (Table 2, Fig. 1). Retinal thickness was reduced by 172.9 ± 192.8 μm, $P < 0.001$ at month 1, by 157.7 ± 134.2 μm, $P = 0.003$ at month 6, and by 164.2 122.2, $P = 0.01$ at month 12. Correlation (Spearman rho) between central RT and BCVA during follow-up was 0.4 ($P < 0.001$). RCT at baseline was increased, and it significantly improved during follow-up.

Among all patients, choroidal thickness increased during the first month from injection, decreased during the second month, and increased again between month 3 and month 12. However, choroidal thickness changes were not statistically significant (Table 2). A choroidal thinning was present between baseline and month 12 in 8 cases (23.5%), whereas a choroidal thickening was detected in 26 cases (77.5%) (Fig. 2). If compared with patients who presented with a choroidal thickening during follow-up, those who showed reduction of choroidal thickness presented at baseline a significantly better visual acuity (0.81 ± 0.49 vs. 1.21 ± 0.62, $P = 0.04$), a lower retinal thickness (380.5 ± 162.4 μm vs. 546.4 ± 240.5 μm, $P = 0.3$) and a greater choroidal thickness (1.75 ± 0.25 mm vs. 1.39 ± 0.22 mm, $P = 0.1$). Although in the group enjoying choroidal thinning during follow-up, the latter was progressive, in the group presenting with choroidal thickening, the choroid thickened during the first month, improved to values better than at baseline during the second month, and thickened again between month 2 and month 12. In both the group presenting with choroidal thinning and the group presenting with choroidal thickening, an improvement of BCVA and RT was present during follow-up. However, after 12 months, patients with a reduction of choroidal thickness showed a greater improvement of VA ($P = 0.007$) and RT ($P = 0.09$) if compared with patients with choroidal thickening (Fig. 2).

Evaluation according to the origin of the edema

Between the group of 21 eyes with a COE (including choroidal neovascularization) and the group of 13 eyes with a ROE (including stage 1 RAP, retinal vein occlusion, and diabetic macular edema), no significant difference in BCVA, retinal sensitivity, and location and stability of fixation at baseline and during follow-up was present. At baseline, retinal and choroidal thickening were present in both groups. Significantly greater retinal thickening was present in the group with a ROE ($P = 0.02$), whereas a greater choroidal thickening was present in eyes with a COE, although this difference was not significant ($P = 0.8$). During follow-up, a significant retinal and choroidal thinning when compared to baseline was present in both groups, and the differences at each visit between the two groups were not significant.

Discussion

In this study we prospectively evaluated the anatomic and functional changes after bevacizumab for macular edema, the choroidal response to bevacizumab, and the influences of the choroidal involvement on visual changes. Other authors have evaluated the early effects of bevacizumab on macular edema from different origins.[10] To our knowledge, this is the first reported prospective evaluation of these effects during 12 months and the first attempt to describe the choroidal long-term changes after intravitreal bevacizumab.

Table 2. Functional and Anatomic Changes During 12 Months after Intravitreal Bevacizumab for Macular Edema

	Baseline	*7 days*	*1 month*	*2 months*	*3 months*	*6 months*	*12 months*
BCVA (ETDRS LogMAR, mean ± SD)	1.12 ± 0.6	0.96 ± 0.49 ($P = 0.03$)	0.8 ± 0.42 ($P < 0.001$)	0.85 ± 0.5 ($P = 0.001$)	0.91 ± 0.48 ($P = 0.02$)	0.94 ± 0.48 ($P = 0.05$)	0.98 ± 0.36 ($P = 0.05$)
RT μm, mean ± SD)	502.2 ± 232	353.16 ± 201.6 ($P < 0.001$)	329.22 ± 189.1 ($P < 0.001$)	347.8 ± 199.2 ($P = 0.001$)	358.9 ± 186.7 ($P < 0.001$)	344.45 ± 163.2 ($P = 0.003$)	338.21 ± 145.3 ($P = 0.01$)
RCT (mm, mean ± SD)	2.01 ± 0.29	—	1.91 ± 0.28 ($P = 0.05$)	1.76 ± 0.21 ($P = 0.005$)	—	1.91 ± 0.36 ($P = 0.05$)	1.86 ± 0.24 ($P = 0.05$)
CT (mm, mean ± SD)	1.49 ± 0.28	—	1.57 ± 0.28 ($P = 0.2$)	1.42 ± 0.3 ($P = 0.4$)	—	1.57 ± 0.3 ($P = 0.6$)	1.56 ± 0.2
MP fixation stability *(n)*	Stable 5 RU 25 U 1	Stable 6 RU 21 U 2	Stable 6 RU 24	Stable 8 RU 22 U 1	Stable 5 RU 17	Stable 2 RU 19	Stable 1 RU 19 U 1
MP fixation location *(n)*	PC 9 POC 14 PE 8	PC 15 POC 11 PE 3	PC 12 POC 11 PE 7	PC 16 POC 11 PE 4	PC 10 POC 9 PE 3	PC 12 POC 6 PE 3	PC 12 POC 6 PE 3

BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LogMar, logarithm of the minimum angle of resolution; RT, central retinal thickness; RCT, central retinochoroidal thickness; CT, central choroidal thickness; MP, microperimetry; *P*, statistical significance compared with baseline; RU, relatively unstable; U, unstable; PC, prevalently central; POC, poor central; PE, prevalently eccentric.

Table 3. Changes in Best Corrected Visual Acuity and Retinal Sensitivity (Decibels) During 12 Months after Intravitreal Bevacizumab for Macular Edema

	BL-7 days	*BL-1M*	*BL-2M*	*BL-3M*	*BL-6M*	*BL-12 M*
ΔBCVA	−0.16 ± 0.3 ($P = 0.03$)	−0.32 ± 0.3 ($P < 0.001$)	−0.27 ± 0.3 ($P < 0.001$)	−0.21 ± 0.4 ($P = 0.002$)	−0.18 ± 0.4 ($P = 0.05$)	−0.14 ± 0.2 ($P = 0.08$)
ΔdB	1.3 ± 2.5 ($P = 0.01$)	2.1 ± 2.5 ($P < 0.001$)	0.25 ± 1.9 ($P = 4$)	0.7 ± 1.7 ($P = 0.07$)	0.58 ± 1.6 ($P = 0.1$)	0.78 ± 0.8 ($P = 0.09$)
Spearman Correlation ΔBCVA-ΔdB	−0.2 ($P = 0.2$)	0.1 ($P = 0.5$)	−0.03 ($P = 0.8$)	−0.3 ($P = 0.1$)	−0.1 ($P = 0.5$)	−0.2 ($P = 0.1$)

BL, baseline; M, month; BCVA, best corrected visual acuity; dB, decibels.

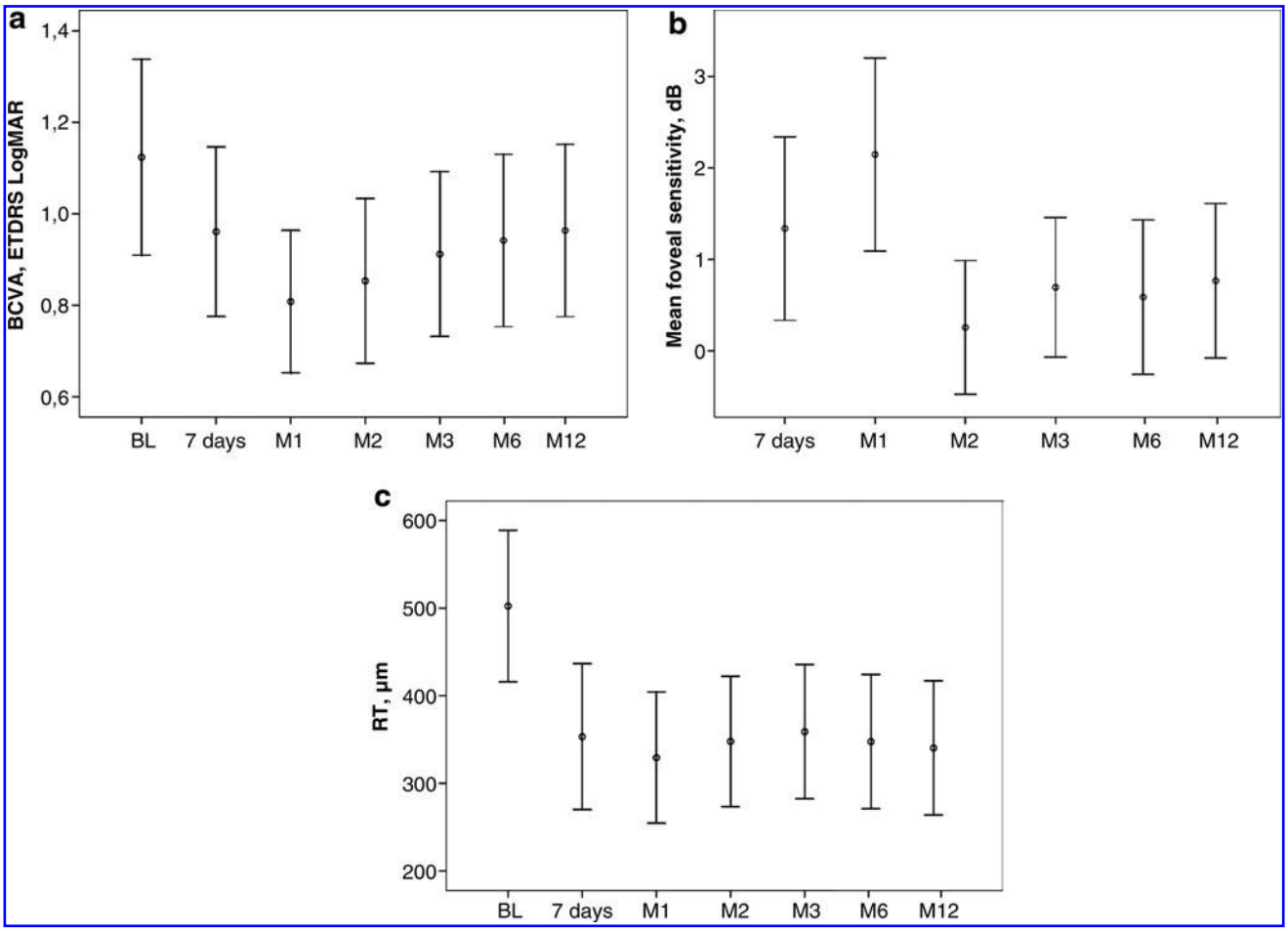


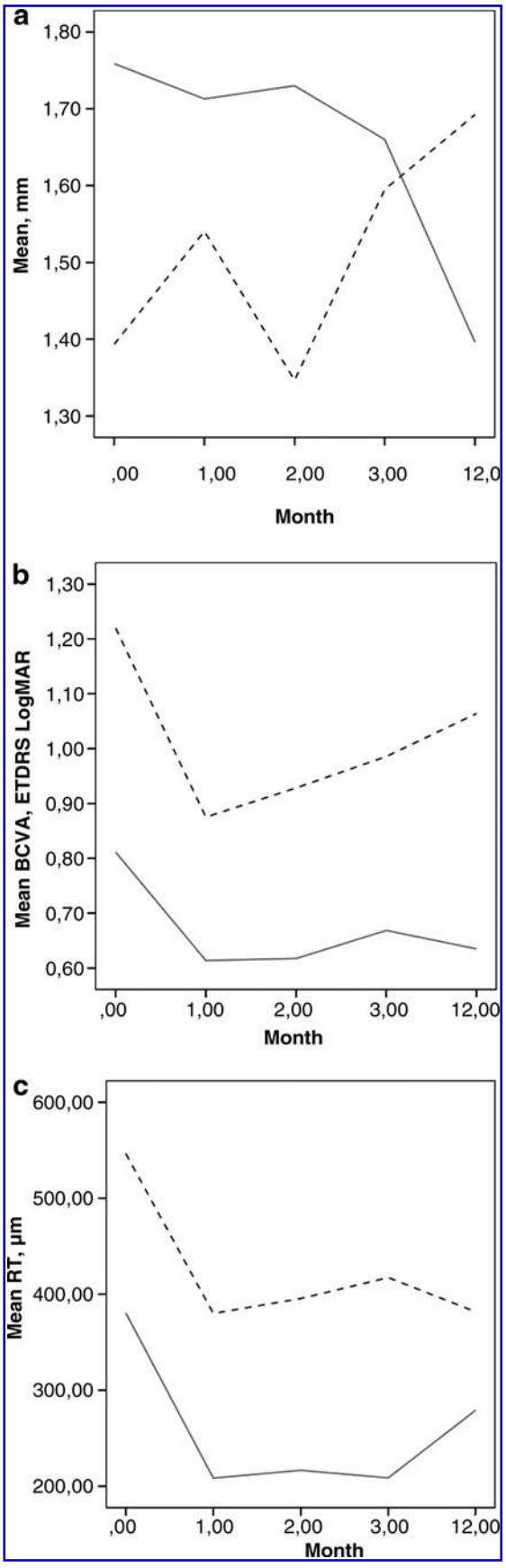
FIG. 1. Functional and anatomic changes during 12 months after intravitreal bevacizumab for macular edema (means and 95% confidence interval). (**a**) Changes of best corrected visual acuity (BCVA), (**b**) mean sensitivity in the central 8° area compared with baseline, and (**c**) mean central retinal thickness (RT). ETDRS, Early Treatment of Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution; BL, baseline; M, month.

During 12 months, an overall improvement of visual function and RT was obtained. Visual acuity showed the greatest improvement during the month after the first injection, afterward it slowly worsened, although it was always significantly better than at baseline. A significant improvement in BCVA and a reduction in central retinal thickness due to the treatment with bevacizumab have been reported in CNV from AMD,[9,16] in RAP,[17] diabetic macular edema,[5] and retinal vein occlusions.[6,8,18,19] According to our data, the general visual trend seems to show a greater effectiveness of the first of the two injections, and a possible reason could be the reported tachyphylaxis and decreased bioefficacy of bevacizumab after repeated injections.[20]

In this study, a combined spectral domain OCT/MP was used. Retinal sensitivity, location, and stability of fixation improved during follow-up, although a low correlation was found with BCVA. Combined spectral domain OCT/MP allows a live real-time evaluation of both morphologic and functional retinal features in every single retinal point. In eyes with macular edema associated with retinal vein occlusion, a long-lasting rapid improvement in macular sensitivity has been recently reported after intravitreal injection of bevacizumab.[21] Previous studies have suggested the hypothesis that fixation instability inversely correlates to visual acuity.[22,23] Our results agree with this hypothesis, although a strong correlation was not found.

A significant reduction of the mean retinal thickness in the 3-mm-diameter central ring as measured with OCT was present during follow-up. As for visual acuity, the greatest improvement of RT was present during the month following the first injection. As also reported by other authors,[24] we found no strong correlation between the increase of BCVA and the reduction of central RT.

To measure the central choroidal thickness, we used a method that has been previously validated.[10,11] Among all evaluated eyes, choroidal thickness increased during the first month, reduced between month 1 and month 2, and increased again during the following months to values greater than baseline. However, these changes were not significant. In 77.5% of cases, a choroidal thickening was present between baseline and month 12. In this group, a choroidal thinning was present between month 1 and month 2, and it could represent either a late response to the first injection or a response to the cumulative effect of the two injections. Interestingly, patients that showed a choroidal thinning during follow-up presented with a better VA and RT at baseline. Both the group with choroidal thinning and the group with choroidal thickening during follow-up showed improvement of VA



and RT if compared with baseline. Nevertheless, patients with a choroidal thinning showed a significantly greater visual improvement. These findings likely suggest a role of choroidal involvement in determining the final visual outcome.

Eyes with choroidal neovascularization were considered as a group with a COE, whereas the eyes with stage 1 RAP, BRVO, and diabetic edema were considered as a group with a ROE. In both groups, retinal sensitivity and choroidal thickness were not significantly different at baseline and during follow-up. Retinal thickness at baseline was greater in the group with a retinal origin of the edema, but no significant differences were present between the two groups during follow-up. This could suggest a minor role of the origin of the edema (whether retinal or choroidal) on functional and anatomical changes after intravitreal bevacizumab. On the other hand, the choroid was thickened also in eyes where the disease is supposed to start from the retina (as in stage 1 RAP, retinal vein occlusion, and diabetic edema). This could suggest a choroidal involvement in any of the diseases determining macular edema. However, whether choroidal involvement starts with retinal involvement or is a consequence of the retinal disease could not be stated.

A limitation of this prospective study is the small size of the studied population. However, the size of the subgroups was planned considering the prospective design of the study and to make an evaluation of change rates rather than raw measurement values, reducing the bias due to small group size. Furthermore, for statistics, the eyes were grouped in two groups only—eyes with a retinal origin of the edema and eyes with a choroidal origin of the edema.

In conclusion, bevacizumab injection for macular edema determines both functional and anatomic improvement at the 12-month follow-up. Although the effects on the neuroretina are more evident, a choroidal response can be detected and could represent a prognostic factor for final visual outcome.

Author Disclosure Statement

This study had no financial support and the authors have no proprietary interest. The study was performed with informed consent and following all the guidelines for experimental investigations required by the Institutional Review Board or Ethics Committee of which all authors are affiliated.

References

1. Ferrara, N. Molecular and biological properties of vascular endothelial growth factor. *J. Mol. Med*. 77:527–543, 1999.
2. Noma, H., Funatsu, H., Yamasaki, M., Tsukamoto, H., Mimura, T, Sone, T, Jian, K., Sakamoto, I., Nakano, K., Yamashita, H., Minamoto, A., and Mishima, H.K. Pathogenesis of

FIG. 2. Choroidal changes during 12 months after intravitreal bevacizumab for macular edema. (**a**) Changes of the mean choroidal thickness in the 3-mm-diameter central ring. Changes of mean best corrected visual acuity (BCVA) (**b**) and mean central retinal thickness (RT) (**c**) in the group with choroidal thickening and in the group with choroidal thinning. (Dashed line) Choroidal thickening; (solid line) choroidal thinning. ETDRS, Early Treatment of Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution.

macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. *Am. J. Ophthalmol.* 140:256–261, 2005.
3. Shimada, H., Akaza, E., Yuzawa, M., and Kawashima, M. Concentration gradient of vascular endothelial growth factor in the vitreous of eyes with diabetic macular edema. *Invest Ophthalmol. Vis. Sci.* 50:2953–2955, 2009.
4. Yannuzzi, L.A., Negrao, S., Iida, T., Carvalho, C., Rodriguez-Coleman, H., Slakter, J., Freund, K.B., Sorenson, J., Orlock, D, and Borodoker, N. Retinal angiomatous proliferation in age-related macular degeneration. *Retina* 21:416–434, 2001.
5. Haritoglou, C., Kook, D., Neubauer, A., Wolf, A., Priglinger, S., Strauss, R., Gandorfer, A., Ulbig, M., Kampik, A. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. *Retina* 26:999–1005, 2006.
6. Iturralde, D., Spaide, R.F., Meyerle, C.B., Klancnik J.M., Yannuzzi, L.A., Fisher, Y.L., Sorenson, J., Slakter, J.S., Freund, K.B., Cooney, M, and Fine, H.F. Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: A short-term study. *Retina* 26:279–284, 2006.
7. Gharbiya, M., Allievi, F., Recupero, V., Martini, D., Mazzeo, L., and Gabrieli, C.B. Intravitreal bevacizumab as primary treatment for retinal angiomatous proliferation: Twelve-month results. *Retina* 29:740–749, 2009.
8. Wu, L., Arevalo, J.F., Berrocal, M.H., Maia, M., Roca, J.A., Morales-Cantón, V., Alezzandrini, A.A., and Díaz-Llopis, M.J. Comparison of two doses of intravitreal bevacizumab as primary treatment for macular edema secondary to branch retinal vein occlusions: Results of the Pan American Collaborative Retina Study Group at 24 months. *Retina* 29:1396–1403, 2009.
9. Spaide, R.F., Laud, K., Fine, H.F., Klancnik J.M., Meyerle, C.B., Yannuzzi, L.A., Sorenson, J., Slakter, J., Fisher, Y.L., and Cooney, M.J. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 26:383–390, 2006.
10. Welch, D.E., Elmariah, H., Peden, M.C., Adams, S.G., Ratnakaram, R., and Kaushal, S. Short-term response of macular edema to intravitreal bevacizumab. *Br. J. Ophthalmol.* 93: 1033–1036, 2009.
11. Cennamo, G., Rosa, N., La Rana, A., Pasquariello, A., and Iaccarino, G. Macula study with standardized echography. *Acta Ophthalmol. Scand.* 74:178–181, 1996.
12. Aiello, L.P., Brucker, A.J., Chang, S., Cunningham, E.T., Jr., D'Amico, D.J., Flynn, H.W., Jr., Grillone, L.R., Hutcherson, S., Liebmann, J.M., O'Brien, T.P., Scott, I.U., Spaide, R.F., Ta, C., and Trese, M.T. Evolving guidelines for intravitreous injections. *Retina* 24:13–19, 2004.
13. Fujii, G.Y., De Juan, E., Humayun, M.S., Sunness, J.S., Chang, T.S., and Rossi, J.V. Characteristics of visual loss by scanning laser ophthalmoscope microperimetry in eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Am. J. Ophthalmol.* 136:1067–1078, 2003.
14. Forte, R., Cennamo, G.L., Finelli, M.L., de Crecchio, G. Comparison of time domain Stratus OCT and spectral domain SLO/OCT for assessment of macular thickness and volume. *Eye (Lond.)* 23:2071–2078, 2009.
15. Atta, H.R., and Byrne, S.F. The findings of standardized echography for choroidal folds. *Arch. Ophthalmol.* 106:1234–1241, 1988.
16. Bashshur, Z.F., Haddad, Z.A., Schakal, A., Jaafar R.F., Saab, M., and Noureddin, B.N. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: A one-year prospective study. *Am. J. Ophthalmol.* 145:249–256, 2008.
17. Kriechbaum, K., Michels, S., Prager, F., Georgopoulos, M., Funk, M., Geitzebnauer, W., and Schmidt-Erfurth, U. Intravitreal Avastin for macular oedema secondary to retinal vein occlusion: a prospective study. *Br. J. Ophthalmol.* 92: 518–522, 2008.
18. Ferrara, D.C., Koizumi, H., and Spaide, R.F. Early bevacizumab treatment of central retinal vein occlusion. *Am. J. Ophthalmol.* 144:864–871, 2007.
19. Schaal, S., Kaplan, H.J., and Tezel, T.H. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? *Ophthalmology* 115:2199–2205, 2008.
20. Yamaike, N., Tsujikawa, A., Sakamoto, A., Ota, M., Kotera, Y., Miyamoto, K., Kita, M., and Yoshimura, N. Retinal sensitivity after intravitreal injection of bevacizumab for the treatment of macular edema secondary to retinal vein occlusion. *Retina* 29:757–767, 2009.
21. Carpineto, P., Ciancaglini, M., Di Antonio, L., Gavalas, C., and Mastropasqua, L. Fundus microperimetry patterns of fixation in type 2 diabetic patients with diffuse macular edema. *Retina* 27:21–29, 2007.
22. Kube, T., Schmidt, S., Toonen, F., Kirchhof, B., and Wolf, S. Fixation stability and macular light sensitivity in patients with diabetic maculopathy: A microperimetric study with a scanning laser ophthalmoscope. *Ophthalmologica* 219:16–20, 2005.
23. Ladewig, M.S., Karl, S.E., Hamelmann, V., Helb, H-M., Scholl, H.P.N., Holz, F.G., and Eter, N. Combined intravitreal bevacizumab and photodynamic therapy for neovascular age-related macular degeneration. *Graefes Arch. Clin. Exp. Ophthalmol.* 246:17–25, 2008.
24. Koch, K.R., Muether, P.S., Hermann, M.M., Hoerster, R., Kirchhof, B., and Fauser, S. Subjective perception versus objective outcome after intravitreal ranibizumab for exudative AMD. Graefes Arch Clin Exp Ophthalmol. 2011 Sep 8. [epub ahead of print].

Received: December 2, 2010
Accepted: September 13, 2011

Address correspondence to:
Raimondo Forte, M.D., Ph.D.
Dipartimento di Scienze Oftalmologiche
Università Federico II
Via Pansini 5
80131 Naples
Italy

E-mail: raifor@hotmail.com