A Prospective Randomized Trial of Intravitreal Bevacizumab Versus Ranibizumab for the Management of Diabetic Macular Edema

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• PURPOSE: To compare visual acuity and spectral-domain optical coherence tomography (SDOCT) outcomes associated with intravitreal (IV) bevacizumab vs IV ranibizumab for the management of diabetic macular edema (DME).

• DESIGN: Prospective randomized trial.

• METHODS: Forty-eight patients (63 eyes) with center-involved DME were randomly assigned to receive 1.5 mg (0.06 cc) IV bevacizumab or 0.5 mg (0.05 cc) IV ranibizumab at baseline and monthly if central subfield thickness was greater than 275 μm.

• RESULTS: Forty-five patients (60 eyes) completed 48 weeks of follow-up. At baseline, mean ± standard error best-corrected visual acuity (BCVA) (logMAR) was 0.60 (20/80) ± 0.05 in the IV bevacizumab group and 0.63 (20/85) ± 0.05 in the IV ranibizumab group. A significant improvement in mean BCVA was observed in both groups at all study visits ($P < .05$); this improvement was significantly greater in the IV ranibizumab group compared with the IV bevacizumab group at weeks 8 ($P = .032$) and 32 ($P = .042$). A significant reduction in mean central subfield thickness was observed in both groups at all study visits compared with baseline ($P < .05$), with no significant difference in the magnitude of macular thickness reduction between groups. The mean number of injections was significantly higher ($P = .005$) in the IV bevacizumab group (9.84) than in the IV ranibizumab group (7.67).

• CONCLUSIONS: IV bevacizumab and IV ranibizumab are associated with similar effects on central subfield thickness in patients with DME through 1 year of follow-up. IV ranibizumab is associated with greater improvement in BCVA at some study visits, and the mean number of injections is higher in the IV bevacizumab group. (Am J Ophthalmol 2013;156: 502–510. © 2013 by Elsevier Inc. All rights reserved.)

MACULAR EDEMA IS THE LEADING CAUSE OF decreased visual acuity in patients with diabetic retinopathy.[1,2] Laser photocoagulation has been the standard-of-care treatment for diabetic macular edema (DME) for decades, based on the Early Treatment Diabetic Retinopathy Study (ETDRS) and other more recent clinical trials.[3–6] However, because visual acuity improvement post laser is observed infrequently, and because of the frequent recurrence or persistence of DME after laser treatment, there is a need for better treatments for the management of DME (especially for diffuse DME involving the foveal center, since focal DME not involving the foveal center may have a good prognosis after focal laser treatment).[3,4,6–8] Care must be taken, however, because the terms "diffuse" and "focal" DME have not been defined consistently in the literature; these terms have referred to a variety of diverse parameters (clinical and angiographic) itemized differently by various authors.[7–9] In addition, the definition of center- and non-center-involved DME may vary; the Diabetic Retinopathy Clinical Research Network (DRCRnet) has defined non-center-involved DME as "a baseline central subfield thickness <250 microns and a baseline photograph assessment of retinal thickness at the center of the macula graded as none or questionable."[7] Moreover, the parameters of a "normal" central subfield threshold may vary depending on the optical coherence tomography (OCT) machine employed.[10]

Among pharmacologic treatments currently available for DME, antiangiogenic agents such as bevacizumab and ranibizumab have been reported to be associated with visual acuity improvement and favorable remodeling of the macular architecture in patients with DME.[11–16] Ranibizumab has been evaluated in phase III prospective randomized clinical trials and reported to be associated with better visual acuity outcomes compared to focal/grid laser in patients with DME.[12,13] To our knowledge and based on a Medline search, there is no published study comparing intravitreal (IV) bevacizumab and IV ranibizumab for the treatment for DME. We conducted a randomized, prospective study to compare the visual

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acuity and spectral-domain optical coherence tomography (SDOCT) outcomes associated with IV bevacizumab vs IV ranibizumab for the management of DME.

METHODS

THE CURRENT STUDY IS A PROSPECTIVE RANDOMIZED CLINical trial registered at ClinicalTrials.gov (NCT01487629). The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board, Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, and all participants gave written informed consent before entering into the study. All patients evaluated in the Retina Section of the Department of Ophthalmology, School of Medicine of Ribeirão Preto of the University of Sao Paulo with center-involved DME in at least 1 eye between July 1, 2010 and August 31, 2011 were invited to participate in the study.

• **PATIENT ELIGIBILITY AND BASELINE EVALUATION:** *Inclusion criteria*. Inclusion criteria were as follows: (1) center-involved DME, defined as a central subfield thickness >300 μm on SDOCT, despite at least 1 session of macular laser photocoagulation performed at least 3 months previously; (2) best-corrected ETDRS visual acuity (BCVA) measurement between 0.3 logMAR (Snellen equivalent: 20/40) and 1.6 logMAR (Snellen equivalent: 20/800); (3) signed informed consent.

Exclusion criteria. Exclusion criteria were: (1) vitreomacular traction on SDOCT; (2) proliferative diabetic retinopathy needing panretinal photocoagulation (PRP) or anticipated to need PRP in the next 12 months; (3) macular capillary dropout on fluorescein angiography; (4) history of glaucoma or ocular hypertension (defined as an intraocular pressure higher than 22 mm Hg); (5) an ocular condition (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (eg, retinal vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc); (6) systemic corticosteroid therapy; (7) any condition that, in the opinion of the investigator, might preclude follow-up throughout the study period.

Each patient received a detailed ophthalmologic examination including measurement of BCVA according to the standardized ETDRS refraction protocol using a retroilluminated Lighthouse for the Blind distance visual acuity test chart (using modified ETDRS charts 1, 2, and R; Precision Vision, IL), as well as applanation tonometry, undilated and dilated slit-lamp biomicroscopic examination, indirect fundus examination, and fluorescein angiography using high-resolution angiography (HRA; Heidelberg Engineering, Heidelberg, Germany).

Fourier-domain OCT evaluation (Spectralis Eyetracker Tomographer, HRA-OCT; Heidelberg Engineering) was performed in all patients, and retinal thickness measurements were acquired using a standard 20 × 15-degree raster scan protocol consisting of 19 horizontal sections (each computed out of 25 frames) with a distance of 240 μm between each horizontal scan, covering a square of 20 × 15 degrees on the retina and centered on the foveal region. Follow-up mode was used to reduce test-retest variability. In order to optimize the accuracy of OCT data, automatic delineation of the inner and outer boundaries of the neurosensory retina generated by OCT built-in software was verified for each of the scans. Central subfield thickness values were calculated automatically as the average thickness of a central macular region 1000 μm in diameter centered on the patient's foveola by built-in Heidelberg software using retinal map analysis.

• **INTRAVITREAL INJECTION:** If both eyes were eligible for treatment and the patient agreed to treat both eyes with anti-VEGF therapy, 1 eye received the randomized treatment according to a computer-generated sequence and the contralateral eye received the other anti-VEGF agent on the next day; thus, if an eye was randomized to the ranibizumab group, the contralateral eye was allocated to the bevacizumab group. All injections were performed using topical proparacaine drops under sterile conditions (eyelid speculum and povidone-iodine). Before the injection was performed, the eyelids were scrubbed with 10% povidone-iodine, and 5% povidone-iodine drops were applied to the conjunctiva. The time between application of 5% povidone-iodine solution to the conjunctiva and administration of the intravitreal injection was 2 minutes. Povidone-iodine was applied to the conjunctiva directly over the intended injection site.[17–20] Care was taken in all cases to insure that the needle did not touch the lids or lashes. Bevacizumab (1.5 mg/0.06 cc; F. Hoffmann- La Roche Ltd., Basel, Switzerland) or ranibizumab (0.5 mg/0.05 cc; Novartis Pharma Stein AG, Stein, Switzerland) was injected into the vitreous cavity using a 29-gauge 0.5-inch needle inserted through the inferotemporal pars plana 3.0-3.5 mm posterior to the limbus.[21] After the injection, central retinal artery perfusion was confirmed with indirect ophthalmoscopy. Patients were instructed to instill 1 drop of 0.3% ciprofloxacin into the injected eye 4 times daily for 1 week after the procedure.

• **RETREATMENT PROTOCOL:** Retreatment with the originally assigned treatment was performed monthly if central subfield thickness was greater than 275 μm.

• **RESCUE THERAPY:** If, after 3 consecutive injections, there was not a reduction in central subfield thickness of at least 10% or an increase in BCVA of at least 5 letters compared with baseline, the patient could, at the discretion of the treating ophthalmologist, receive focal/grid laser

photocoagulation or continue to receive the same intravitreal medication for an additional 3 consecutive visits.

• **FOLLOW-UP EXAMINATIONS AND OUTCOME MEASURES:** Patients were scheduled for follow-up examinations at monthly intervals. At these visits, patients' BCVA was determined after ETDRS refraction, and they underwent complete ophthalmic examination using the same procedures as at baseline, with the exception of fluorescein angiography, which was performed only at the final follow-up visit. Examiners (E.T., F.P.P.A., R.P.) were masked regarding which treatment drug was used for each patient. Throughout the study, a single masked, certified examiner performed BCVA measurements prior to any other study procedure. Patients, OCT technicians, and fundus photographers were also masked to treatment group. Outcome measures include changes in ETDRS BCVA, changes in central subfield thickness, and occurrence of complications.

• **STATISTICAL ANALYSIS:** BCVA and central subfield thickness measured at each follow-up visit were compared with baseline BCVA and central subfield thickness values for within- and between-group comparisons, which were performed using multiple analysis of variance (MANOVA) for repeated measurements. Proportions of eyes with central subfield thickness ≤275 μm were compared using the likelihood ratio χ^2 test. In addition, a multivariate analysis comparing BCVA and central subfield thickness outcomes in the IV bevacizumab group and IV ranibizumab group was performed, taking into account number of injections, baseline BCVA, and central subfield thickness as effects.

A statistically significant effect was defined if $P < .05$, and a trend towards significance was reported if $P < .1$. Statistical analyses were performed using JMP 10.0.0 (2010; SAS Institute Inc, Cary, North Carolina, USA) software.

• **SAMPLE SIZE:** Sample size and powering were based on a previous clinical trial on bevacizumab use for diabetic macular edema,[14] where a mean change observed in central subfield thickness from baseline was −130 μm with a standard deviation of 122 μm. Therefore, to have 80% power to detect a difference of 50 μm between central subfield thickness change found in both groups, the sample size required in each group was 25 eyes. Thirty eyes per treatment group were required if one assumed a 10% dropout rate. With this sample size, there is a 20% chance for a failure to detect a true mean difference of at least 50 μm between the treatment groups (type I error), or for an incorrect conclusion that a difference of at least 50 μm exists between the treatment groups (type II error).

RESULTS

A TOTAL OF 48 PATIENTS WITH CENTER-INVOLVED DME IN at least 1 eye were identified during the study period. Forty-five patients (60 eyes; IV ranibizumab: 28 eyes, IV bevacizumab: 32 eyes) were included in the outcomes analyses; all patients were included in the safety analyses. The 3 patients excluded from the outcomes analyses consisted of 1 patient in the IV ranibizumab group who developed *Staphylococcus aureus* endophthalmitis after the first injection (this patient chose to exit the study and he did not complete any further study visits); 1 patient in the IV bevacizumab group who developed advanced posterior subcapsular cataract, which precluded adequate SDOCT images, after the ninth follow-up visit; and 1 patient from the IV bevacizumab group who missed 3 consecutive follow-up visits.

Another patient in the IV ranibizumab group developed *Streptococcus mitis* endophthalmitis after the 44-week study visit, but he completed all study visits and his data were included in the analysis. One patient in the IV bevacizumab group developed transient inferior vitreous hemorrhage attributable to acute posterior vitreous detachment at week 36 and was also maintained in the analysis.

Fifteen patients with bilateral DME received IV ranibizumab in 1 eye and IV bevacizumab in the other eye, and 30 patients received unilateral treatment. Forty percent of eyes (24/60) had proliferative diabetic retinopathy treated with PRP at least 6 months before the initial evaluation. Mean duration of DME estimated by the patients' reported duration of decreased vision was 37.3 months and 38.1 months in the IV bevacizumab and IV ranibizumab groups, respectively. The time interval between the last anti-VEGF or steroid treatment and study enrollment was at least 6 months. In the bevacizumab group, the number of eyes that had received IV triamcinolone, bevacizumab, or ranibizumab prior to entering the current study was 1, 3, and 2 eyes, respectively; in the ranibizumab group, the number of eyes that had received IV triamcinolone, bevacizumab, or ranibizumab prior to entering the current study was 2, 3, and 2 eyes, respectively. Baseline characteristics are summarized in Table 1.

• **OUTCOME MEASURES:** *Best-corrected visual acuity*. At baseline, mean BCVA (logMAR) ± standard error (SE) was 0.60 (Snellen equivalent: 20/80) ± 0.05 and 0.63 (Snellen equivalent: 20/85) ± 0.06 in the IV bevacizumab and IV ranibizumab groups, respectively ($P = .680$). Intragroup significant improvement in mean BCVA compared with baseline was observed at all study follow-up visits ($P < .05$). Maximum mean BCVA improvement occurred at weeks 44 and 48 (−0.23 ± 0.02 logMAR: ∼2.5 ETDRS lines) in the IV bevacizumab group and at week 48 (−0.29 ± 0.04 logMAR: ∼3 ETDRS lines) in the IV ranibizumab group. There was a significantly greater mean improvement in BCVA in the IV ranibizumab group compared with the IV bevacizumab group at weeks 8 ($P = .0318$) and 32 ($P = .0415$), with a trend towards significance at weeks 28, 36, and 40 ($P < .10$) (Table 2, and Figure 1, Top).

TABLE 1. Baseline Characteristics of Patients Treated With Intravitreal Bevacizumab Versus Ranibizumab for the Management of Diabetic Macular Edema

Baseline Characteristics	Bevacizumab Group	Ranibizumab Group
Age (years) (mean + SE)	63.8 ± 8.8	63.7 ± 9.0
Sex (male/female)	13/19	14/14
Race (black/Hispanic/white)	4/4/24	6/4/18
Duration of diabetes (years) (mean + SD)	16.2 ± 8.0	15.9 ± 8.0
Phakic	23	21
Pseudophakic	9	7
Treatment regimen: no insulin	13	13
Treatment regimen: insulin	19	15
HbA1c (mean ± SD)	8.6 ± 1.3	8.7 ± 2.0
Systolic blood pressure (mm Hg) (mean ± SD)	139.3 ± 16.5	143.1 ± 20.1
Diastolic blood pressure (mm Hg) (mean ± SD)	78.6 ± 11.2	80.5 ± 11.9
Grid photocoagulation sessions (n) (mean ± SD)	1.41 ± 0.87	1.51 ± 0.78
Moderate or severe nonproliferative diabetic retinopathy	19	17
Diabetic retinopathy treated with PRP	13	11

HbA1c = glycosylated hemoglobin A1c; PRP = panretinal photocoagulation.

TABLE 2. Mean and Standard Error for Best-Corrected Visual Acuity and Central Subfield Thickness in the Intravitreal Bevacizumab and Intravitreal Ranibizumab Groups for the Management of Diabetic Macular Edema, During 48-Week Follow-up Period

	Best-Corrected Visual Acuity (logMAR)			Central Subfield Thickness (μm)		
Week	IV Bevacizumab	IV Ranibizumab	*P*[a]	IV Bevacizumab	IV Ranibizumab	*P*
0	0.60 ± 0.05	0.63 ± 0.06		451.7 ± 22.3	421.9 ± 23.1	
4	0.48 ± 0.06	0.53 ± 0.06	.6613	385.3 ± 20.9	328.9 ± 18.0	.2615
8	0.48 ± 0.06	0.46 ± 0.06	.0318	357.2 ± 17.6	313.9 ± 15.2	.4407
12	0.45 ± 0.05	0.46 ± 0.05	.1893	347.3 ± 17.5	309.3 ± 18.0	.5106
16	0.42 ± 0.05	0.43 ± 0.06	.2481	347.6 ± 17.7	316.8 ± 14.5	.6035
20	0.41 ± 0.05	0.42 ± 0.06	.2590	343.6 ± 20.5	304.0 ± 17.9	.4934
24	0.41 ± 0.05	0.40 ± 0.05	.1457	342.8 ± 18.4	300.4 ± 12.4	.4584
28	0.43 ± 0.06	0.40 ± 0.05	.0659	352.1 ± 20.1	293.9 ± 13.9	.2839
32	0.41 ± 0.06	0.36 ± 0.04	.0415	351.1 ± 19.5	295.6 ± 15.5	.3091
36	0.40 ± 0.06	0.36 ± 0.04	.0543	344.5 ± 20.6	287.7 ± 14.7	.3173
40	0.39 ± 0.06	0.35 ± 0.04	.0635	354.0 ± 21.5	291.2 ± 10.4	.2315
44	0.36 ± 0.05	0.34 ± 0.04	.1326	339.8 ± 19.5	281.2 ± 14.3	.2843
48	0.36 ± 0.05	0.34 ± 0.04	.1886	329.7 ± 19.3	280.9 ± 12.6	.4865

IV = intravitreal.
[a]Dark gray background highlights $P < .05$; light gray background highlights $P < .10$.

With respect to the proportion of eyes losing or gaining ≥10 or ≥15 ETDRS letters, no significant difference between IV bevacizumab and IV ranibizumab groups was observed ($P > .05$).

In the IV bevacizumab group, the proportion of eyes losing ≥10 ETDRS letters was 6% at week 16 and from weeks 28-40, and 3% at weeks 12, 20, and 24. The proportion of eyes in the IV bevacizumab group that lost ≥15 letters was 3% at weeks 32 and 36. In the IV ranibizumab group, a loss of ≥10 ETDRS letters was not observed at any follow-up visit. A gain of ≥10 ETDRS letters was observed in 45% and 44% of eyes in the IV bevacizumab and IV ranibizumab groups, respectively, at week 16, and in 61% and 68% in the 2 groups, respectively, at week 48. A gain of ≥15 letters was observed in 15% and 16% of eyes in the IV bevacizumab and IV ranibizumab groups, respectively, at week 16, and in 39% and 48% in the 2 groups, respectively, at week 48 (Figure 1, Bottom).

Central subfield thickness. At baseline, mean ± SE central subfield thickness was 451 ± 22 μm and 421 ± 23 μm at baseline in the IV bevacizumab and IV ranibizumab groups, respectively ($P = .4062$) (Figure 2, Top). Intragroup significant reduction in central subfield thickness

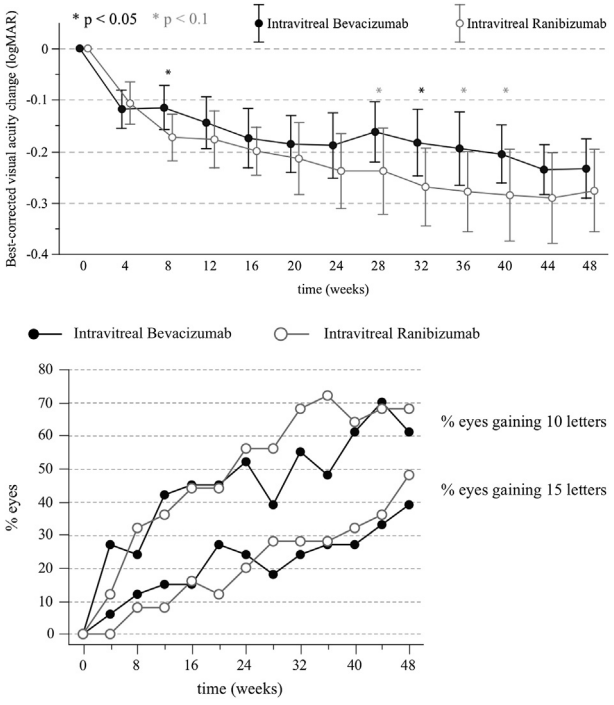

FIGURE 1. Best-corrected visual acuity in intravitreal (IV) bevacizumab vs ranibizumab for the management of diabetic macular edema. (Top) Best-corrected visual acuity (BCVA) plotted against follow-up visit for IV bevacizumab vs ranibizumab for the management of diabetic macular edema. Points represent the mean BCVA change in logMAR and error bars the 95% confidence limits at each study follow-up visit compared with baseline. The magnitude of BCVA improvement was significantly higher in the IV ranibizumab group compared with the IV bevacizumab group at weeks 8 ($P = .03$) and 32 ($P = .04$), with a trend towards significance at weeks 28 ($P = .06$), 36 ($P = .05$), and 40 ($P = .06$). (Bottom) Proportion of eyes treated with IV bevacizumab (black circles) and ranibizumab (open circles) gaining ≥10 or ≥15 ETDRS letters: No statistically significant difference was observed between groups for gain of ≥10 or ≥15 letters at any study visit.

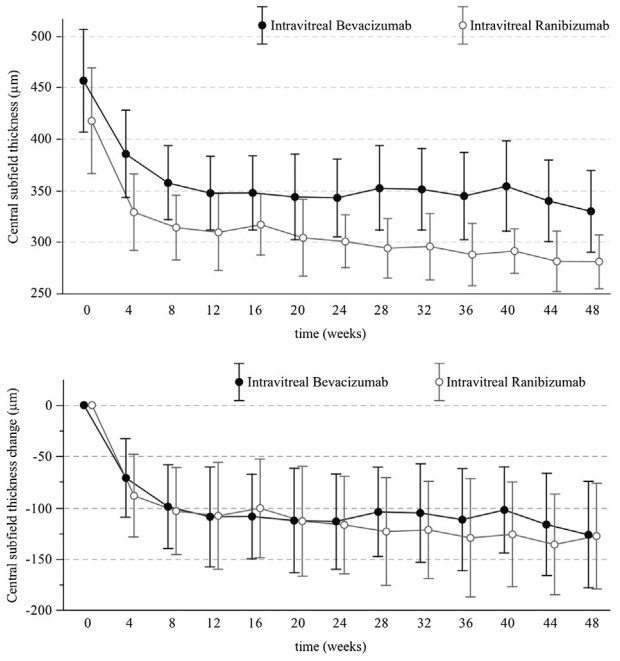

FIGURE 2. Intravitreal (IV) bevacizumab vs ranibizumab for the management of diabetic macular edema. (Top) Circles represent the mean and error bars the 95% confidence limits for central subfield thickness at each study visit. The mean central subfield thickness in the IV ranibizumab group was lower than the central subfield thickness in the IV bevacizumab group at all follow-up visits, although the difference between the 2 groups was not statistically significant. (Bottom) Mean change in central subfield thickness (μm) ± 95% confidence limits at each study follow-up visit compared with baseline. There was no significant difference between the IV bevacizumab group and IV ranibizumab group in the magnitude of central subfield thickness change at any of the study follow-up visits.

compared with baseline was observed at all study follow-up visits ($P < .05$). Maximum mean central subfield thickness reduction occurred at week 44 (−136 ± 23 μm) in the IV ranibizumab group and at week 48 (−126 ± 25 μm) in the IV bevacizumab group (Table 2, and Figure 2, Bottom). There was no difference in mean central subfield thickness reduction between the IV bevacizumab and IV ranibizumab groups at any of the study follow-up visits. However, there was a significantly higher proportion of eyes with a central subfield thickness ≤275 μm in the IV ranibizumab group compared with the IV bevacizumab group at weeks 4 ($P = .0029$; likelihood ratio), 28 ($P = .0077$), 36 ($P = .0028$), and 44 ($P = .0292$) (Figure 3).

Number of intravitreal injections. The mean (± standard error of the mean; SEM) number of injections in the IV bevacizumab group was 9.84 ± 0.55, which was significantly ($P = .005$; Wilcoxon) higher than the mean (± SEM) number of injections in the IV ranibizumab group (7.67 ± 0.60 injections). In the IV bevacizumab group, 16 eyes received 12 injections, while only 4 eyes from the IV ranibizumab group were treated with 12 injections (Figure 4).

Rescue therapy. Two eyes from 2 different patients received rescue laser therapy: 1 from the IV ranibizumab group at week 32 and the other from the IV bevacizumab group at week 36. An additional 8 patients (8 eyes) from the IV bevacizumab group and 3 patients (3 eyes) from the IV ranibizumab group met the criteria for rescue therapy during the study period and these patients elected to be treated with 3 additional consecutive injections of their originally assigned treatment. The number of eyes that met the criteria for rescue therapy during the study period was significantly higher in the IV bevacizumab group (n = 9) compared with the IV ranibizumab group (n = 4) ($P = .042$; paired t test).

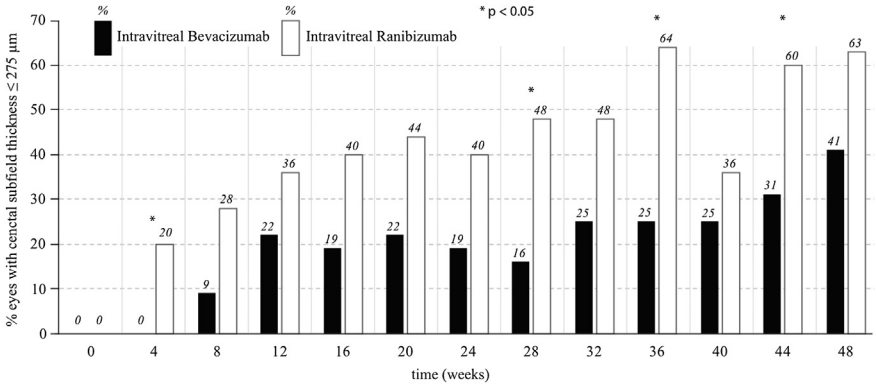

FIGURE 3. Proportion of eyes with diabetic macular edema treated with intravitreal (IV) bevacizumab (black bars) and ranibizumab (white bars) with central subfield thickness ≤275 µm. The proportion was significantly higher in the IV bevacizumab group at weeks 4 ($P = .029$), 28 ($P = .007$), 36 ($P = .0028$), and 44 ($P = .029$) (likelihood ratio) when compared with the IV ranibizumab group.

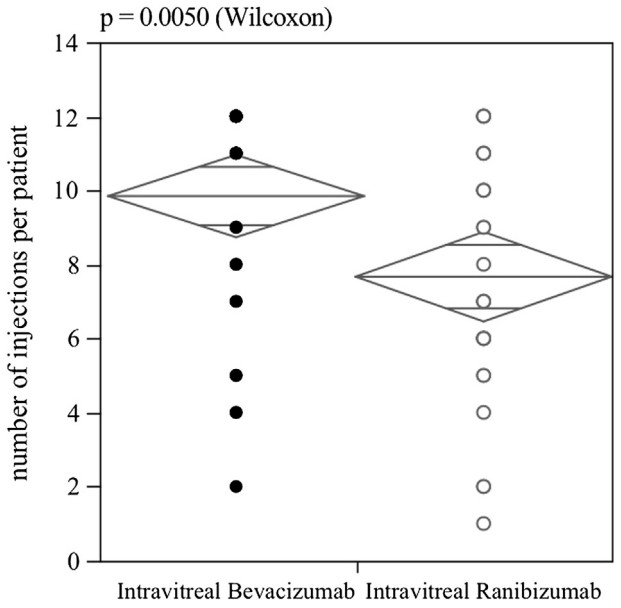

FIGURE 4. Mean diamond plots summarizing the distribution of number of intravitreal (IV) injections of bevacizumab and ranibizumab for management of diabetic macular edema after 48 weeks. The center horizontal line represents the mean, and the superior and inferior lines represent the 95% and 5% confidence limits, respectively. The mean number of injections (± standard error) was 9.84 ± 0.55 and 7.67 ± 0.60 in the IV bevacizumab group and IV ranibizumab group, respectively ($P = .005$; Wilcoxon).

Multivariate analysis. A multivariate analysis comparing BCVA and central subfield thickness outcomes between the IV bevacizumab and IV ranibizumab groups, taking into account number of injections, baseline BCVA, and central subfield thickness, demonstrated a statistically significant influence of baseline BCVA on follow-up BCVA ($P < .001$) but no other significant differences between groups ($P = .051$) across follow-up time ($P = .490$) regarding these 2 outcomes.

Adverse events. There was no significant change in mean intraocular pressure compared with baseline at any of the study follow-up visits in either group ($P < .05$). In the IV bevacizumab group, 1 patient experienced clinically significant cataract progression that prevented a clear view of the fundus after his ninth visit and another patient developed transient vitreous hemorrhage after an acute posterior vitreous detachment.

There were 2 patients who developed endophthalmitis in the IV ranibizumab group (both patients were treated unilaterally) and 1 patient, also in the IV ranibizumab group, who experienced increased blood pressure, controlled with oral antihypertensive agents. Additionally, 1 patient developed transient worsening of renal function. This patient, who had the right eye treated with ranibizumab and the left eye treated with bevacizumab, had a serum creatinine level of 2.0 mg/dL at baseline and, during the study, his creatinine level increased to 2.9 mg/dL; at the last study visit, his creatinine level had returned to 2.0 mg/dL. No patient experienced myocardial infarction, stroke, or gastrointestinal bleeding throughout the study period.

DISCUSSION

IN THE PRESENT STUDY, BOTH GROUPS ACHIEVED SIGNIFICANT improvement in BCVA compared with baseline at all study visits ($P < .05$). At week 48, there was a mean BCVA improvement of 0.23 logMAR (~11 letters) and 0.27 logMAR (~13 letters) in the IV bevacizumab and IV ranibizumab groups, respectively. Similarly, DRCR.net[12] reported a mean BCVA improvement of 8.2 letters in patients with DME treated with IV ranibizumab plus prompt laser and 8.4 letters in patients treated with IV ranibizumab plus deferred laser after 1 year of follow-up. More recently, the RISE and RIDE[13] studies also showed significant improvements in BCVA associated with IV ranibizumab treatment for DME. In the RISE

study, the IV ranibizumab 0.5 mg group demonstrated a mean improvement of 12 letters in BCVA at 1 year, and in the RIDE study, the IV ranibizumab 0.5 mg group demonstrated a mean improvement of 11 letters in BCVA at 1 year. Similarly, the BOLT[14] study reported a significant mean improvement in BCVA after anti-VEGF treatment for DME; eyes treated with IV bevacizumab gained a mean of 5.6 letters at 1 year of follow-up.

Although both groups achieved a significant improvement in mean BCVA, IV ranibizumab eyes demonstrated significantly greater BCVA gains when compared with IV bevacizumab eyes at weeks 8 and 32 and a trend toward significance at weeks 28, 36, and 40. This difference between the groups at these time points during follow-up may be attributable to lower central subfield thickness values in the IV ranibizumab group compared with the IV bevacizumab group at these periods (Figure 2, Top) and, consequently, a significantly higher proportion of patients with a central subfield thickness ≤275 μm in the IV ranibizumab group (Figure 3). Correspondingly, the proportion of IV bevacizumab eyes that met the criterion for rescue therapy was significantly higher in the IV bevacizumab group compared with the IV ranibizumab group. Despite significant differences between groups in BCVA at weeks 8 and 32, it is important to note that because the sample size calculation for this study was based on the difference between treatment groups with respect to central subfield thickness, conclusions regarding BCVA are limited: the lack of a significant difference between treatment groups with respect to BCVA at some study visits does not necessarily indicate that both anti-VEGF treatments have an equivalent effect on BCVA. In other words, a significant difference between groups may have been detected at other study visits if the study had been conducted with a sample size based on differences in BCVA rather than on differences in central subfield thickness.

Significant improvements in central subfield thickness compared with baseline were observed in both the IV bevacizumab and IV ranibizumab groups. At week 48, both groups demonstrated a mean central subfield thickness reduction compared with baseline of 120 μm. Similarly, the DRCR.net[12] reported a mean improvement in central subfield thickness of 131 μm and 137 μm in patients with DME treated with IV ranibizumab plus prompt or deferred laser, respectively, after 1-year follow-up. More recently, the RISE and RIDE[13] studies reported a mean central subfield thickness reduction at 1 year of 250 μm in patients with DME treated with IV ranibizumab. The greater absolute value of central subfield thickness reduction observed in the RISE and RIDE studies may be related to higher baseline central foveal thickness values and/or more constant VEGF blockage with monthly treatment compared to the DRCR.net study,[12] in which the mean number of injections was 8 per year, and the present study, in which the mean number of injections was 7.67 per year. It is also important to note that the multivariate analysis in the current study did not demonstrate any influence of baseline central subfield thickness on the number of injections in either study group. Treatment with IV bevacizumab has also been reported to be associated with favorable anatomic effects in patients with DME; the BOLT[14] study reported a mean central subfield thickness reduction at 1 year of 130 μm, which is very similar to the 120 μm reduction observed in the IV bevacizumab group of the present study.

Despite no significant difference in the magnitude of absolute central subfield thickness reduction between the IV bevacizumab and IV ranibizumab groups, there was a higher proportion of eyes with a central subfield thickness ≤275 μm in the IV ranibizumab group compared with the IV bevacizumab group at all study follow-up visits; at weeks 4, 28, 36, and 44, this difference was statistically significant. Since reinjections were guided by this anatomic parameter (central subfield thickness), IV bevacizumab eyes were treated with a significantly higher mean number of intravitreal injections (9.89) compared with IV ranibizumab eyes (7.67), yet achieved similar central subfield thickness and BCVA outcomes compared with IV ranibizumab eyes at week 48. It is also important to point out a possible crossover effect of bevacizumab in the contralateral eyes of the 15 patients treated bilaterally, which may have positively influenced central subfield reduction in ranibizumab-treated contralateral eyes. However, there also may have been a crossover effect of ranibizumab. This potential crossover effect represents a limitation for studies that permit bilateral anti-VEGF treatment.

The reinjection criterion (a central subfield thickness >275 μm) was based on data from patients with chronic DME that responded with favorable macular remodeling and were considered to demonstrate "no fluid" on OCT after intravitreal anti-VEGF treatment (L. Barroso et al, unpublished data, November 2012). It has been reported that for patients with chronic DME, a lower central subfield thickness threshold value should be established in comparison to normal population values,[22,23] probably because of some degree of central retinal atrophy related to previous laser or mild to moderate ischemia.[24] Consistent with the latter report, in the present study no patients with "no fluid" on OCT at week 48 had a central subfield thickness ≥275 μm. In addition, in the present study, among the 42 eyes that had any degree of concave foveal contour at week 48 despite some fluid on OCT, only 5 (12%) had a central subfield thickness >275 μm (L. Barroso et al, unpublished data, November 2012).

No difference in intraocular pressure between the 2 groups was observed throughout the study, and no significant change in intraocular pressure was observed at any study visit compared with baseline in either group. The results of the current study are consistent with data from other studies that reported no apparent association between intravitreal anti-VEGF injection and increase in

intraocular pressure,[25,26] and are in contrast to some studies that have suggested such an association.[27,28] There were 2 cases of endophthalmitis in the IV ranibizumab group among a total of 553 injections administered in the study. The DRCR.net[25] reported 3 cases of endophthalmitis out of a total of 3973 injections (0.08%) in ranibizumab arms. The RISE and RIDE studies,[13] taken together, reported a total of 4 endophthalmitis cases among a total of 10 584 injections administered. In the current study, all injections were performed in an ambulatory operating room, following recommended aseptic practices.[17–20] The relatively high endophthalmitis rate in our study may be related to patient-related characteristics, such as poor socioeconomic status and hygiene habits.[17] Finally, administering anti-VEGF to both eyes may increase the risk of systemic complications; in fact, 1 of these patients had transient increase in creatinine levels during the study.

In sum, in the current study, IV bevacizumab and IV ranibizumab were associated with improvement in mean BCVA and mean central subfield thickness in patients with center-involved DME at 48 weeks of follow-up when compared with baseline. Eyes in the IV bevacizumab group received a significantly higher number of injections than eyes in the IV ranibizumab group. During the study, eyes in the IV ranibizumab group experienced a faster recovery of BCVA compared with eyes in the IV bevacizumab group, which may be explained by the higher proportion of eyes in the IV ranibizumab group with a central subfield thickness <275 μm at intermediate-term study follow-up visits. To our knowledge and based on a Medline search, this is the first report comparing IV bevacizumab and IV ranibizumab for the treatment of DME. The current study is limited by a small sample size; larger prospective studies are warranted to confirm our preliminary findings.

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Biosketch

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Biosketch

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