SHORT-TERM EFFECTIVENESS OF INTRAVITREAL BEVACIZUMAB VERSUS RANIBIZUMAB INJECTIONS FOR PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Purpose: To compare the effectiveness of three consecutive intravitreal injections of bevacizumab (Avastin) and ranibizumab (Lucentis) in patients with treatment-naïve neovascular age-related macular degeneration.

Methods: This is a retrospective comparative study of qualifying consecutively treated patients (n = 176) with new-onset subfoveal choroidal neovascularization presenting at 6 retina referral centers. Patients were treated with 3 consecutive monthly injections of ranibizumab (0.5 mg) or 3 injections of bevacizumab every 6 weeks (1.25 mg) as determined by physician and patient preference. Ophthalmologic evaluations included monthly visual acuity measurements, ocular examinations, and optical coherence tomography imaging at each visit.

Results: A 29.2% reduction in the mean central foveal thickness measurement through optical coherence tomography was found in the ranibizumab-treated patients versus a 20.9% reduction in the bevacizumab-treated patients ($P \leq 0.02$). Fifty-three percent of ranibizumab-treated patients had returned to a central foveal thickness of <200 μm by the completion of 3 injections compared with 35% of patients treated with bevacizumab ($P \leq 0.07$). No ocular or systemic adverse events were reported in either group.

Conclusion: Short-term effectiveness of ranibizumab treatment, as measured by incremental improvement in optical coherence tomography parameters, was significantly greater than bevacizumab treatment, suggesting that there is a difference in the biologic activities of ranibizumab and bevacizumab.

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Over the past several years, significant and rapid changes have taken place in regard to the treatment of neovascular age-related macular degeneration (AMD). Vascular endothelial growth factor-A has been implicated to play a major role in the pathogenesis of the neovascular complications of the disease.[1–4] The beneficial effects of blocking vascular endothelial growth factor-A were first demonstrated by the use of pegaptanib sodium (Macugen), which works by selectively binding the vascular endothelial growth factor-A_{165} isoform.[5,6]

In contrast to pegaptanib sodium, ranibizumab (Lucentis, Genentech, South San Francisco, CA) is a nonselective vascular endothelial growth factor-A inhibitor.[7,8] In 2 randomized pivotal Phase III clinical trials (MARINA and ANCHOR), ranibizumab stabilized (loss of $\leq$15 letters) 94.6% (MARINA) and 96.4% (ANCHOR) of patients after 1 year of treatment (primary end point; $P < 0.001$ vs. sham for MARINA, $P < 0.001$ vs. verteporfin photodynamic therapy for ANCHOR).[9,10] Patients treated with ranibizumab in the MARINA and ANCHOR trials were noted to

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have a 33.8% and 40.3% rate of 3-line improvement in visual acuity at 1 year, respectively ($P < 0.001$ vs. sham for MARINA, $P < 0.001$ vs. verteporfin photodynamic therapy for ANCHOR).[9,10]

The results of the MARINA trial were reported at the annual meeting of the American Society of Retina Specialists in July 2005 (Joan W. Miller and C. Y. Chung, July 2005, Montreal, Canada). At that same meeting, Dr. Philip Rosenfeld reported the results of his treatment of patients with neovascular AMD with systemic intravenous bevacizumab (Avastin) as well as experience with off-label intravitreal injections of 1.25 mg bevacizumab.[11,12] In the time interval between the presentation of the MARINA data at the American Society of Retina Specialists meeting and the final U.S. Food and Drug Administration approval of ranibizumab in June 2006,[13] several retrospective case series also suggested that intravitreal injections of bevacizumab were efficacious over the short term in patients with neovascular AMD.[12,14,15] In the absence of commercially available ranibizumab, individual clinicians began to offer off-label intravitreal bevacizumab injections to patients with neovascular AMD. The use of off-label intravitreal bevacizumab injections for treating neovascular AMD remains a common clinical practice in the United States and elsewhere even after the approval of ranibizumab by the Food and Drug Administration for treating this condition. Despite the worldwide acceptance of intravitreal bevacizumab into clinical practice, there have been no published comparative studies between the treatment effects of intravitreal bevacizumab and ranibizumab.

Given the widespread use of both ranibizumab and bevacizumab, it is important to understand if there are any differences between these two treatments in neovascular AMD. Although a large head-to-head clinical trial sponsored by the National Eye Institute evaluating the efficacy of ranibizumab and bevacizumab is currently enrolling (Comparative Age-related Macular Degeneration Treatments Trials), clear results will not be available for at least 2 years.[16] This study was designed in an attempt to determine whether there is a difference in the short-term effectiveness, as measured by anatomic changes, between ranibizumab and bevacizumab in treatment-naïve patients with neovascular AMD treated with a similar dosing regimen.

Patients and Methods

Subjects

A total of 69 eyes of 69 patients treated with bevacizumab and 107 eyes of 107 patients treated with ranibizumab were included for review and analysis. Informed consent was obtained from all patients treated with bevacizumab injections regarding its potential benefits as well as its local and systemic risks. Investigational Review Board approval was obtained through the Quorum Investigational Review Board committee for the retrospective analysis of this data; subjects did not consent to be prospectively randomized. The patients' records were obtained and reviewed only to record necessary clinical data. All subject data were masked for identity to maintain Health Insurance Portability and Accountability Act compliance.

Inclusion Criteria

Retina centers were included in the study if their standard method of treating patients followed the study protocol: treatment with antivascular endothelial growth factor agents for a minimum of three consecutive injections, baseline fluorescein angiography and optical coherence tomography (OCT) evaluations, and OCT evaluation after completion of the third consecutive injection. Consecutively treated patients with subfoveal choroidal neovascularization resulting from AMD, as determined by fluorescein angiography, between January 1, 2006, and November 1, 2006, from the identified retina centers were reviewed for potential enrollment in this trial. Based on surgeon preference, patients must have been treated with a dosing regimen of 3 monthly treatments of 0.5 mg intravitreal ranibizumab or 3 1.25-mg injections of intravitreal ranibizumab dosed every 6 weeks.

The following criteria were required to be met for a patient to be included in this study.

1. No previous treatment for neovascular AMD in the study eye.
2. Baseline visual acuity between 20/40 and 20/320.
3. Either minimally classic/occult with no classic choroidal neovascularization measuring <12 disk areas and with at least 50% of the lesion area having choroidal neovascularization or predominantly classic choroidal neovascularization measuring $<5{,}400$ μm in greatest linear diameter.
4. Fluorescein angiography at baseline (before treatment).
5. Optical coherence tomography at baseline and after three treatments.

Consecutive records of 452 patients were reviewed. All included patients that received three consecutive injections of either ranibizumab or bevacizumab.

Treatment Protocols

Treatment of all patients was performed as an induction protocol of three consecutive injections followed by treatment at the discretion of the physician. For bevacizumab injections, a 0.12-mL aliquot of commercially prepared bevacizumab (25 mg/mL) was placed in a tuberculin syringe by a compounding pharmacy. All eyes were prepared in a standard fashion using 5% povidone–iodine, a sterile lid speculum, and postoperative antibiotics. Bevacizumab (1.25 mg, 0.05 mL) was injected intravitreally through the pars plana 3.5 mm posterior to the limbus. For the ranibizumab-treated patients, the same protocol was followed with 0.5 mg (0.05 mL) of ranibizumab delivered through a 30-gauge needle attached to a tuberculin syringe.

Patient Assessment

Baseline fluorescein angiography was performed on all patients and interpreted by the treating physician for lesion size and leakage characteristics. Optical coherence tomography studies were carried out at baseline and at each successive follow-up visit. Retinal thickness was assessed by OCT (Stratus III OCT, Carl Zeiss, Dublin, CA) using 6 diagonal fast and slow 6-mm scans. The retinal thickness of the 1-mm central retina was obtained through fast macula scan. Macular volume was measured by determining the volume between 2 computer-generated lines based on data points from 6 consecutive 6-mm radial line scans centered on the macula, the first that traces the inner surface of the retina and the second that traces the top surface of the retinal pigment epithelium.

Main Outcome Measures

The primary outcome measure for this analysis was the reduction in the mean central foveal thickness (center subfield thickness as measured on the Stratus III OCT) 1 month after the third consecutive injection. Secondary measures included the change in macular volume measured by OCT and the percentage of patients who had normalization of their macular thickness to <200 μm.

Statistical Methods

SAS programming language (SAS Institute, Cary, NC) was used for all analyses. For continuous variables, medians for baseline, final values, change, and percent change were compared between bevacizumab and ranibizumab treatment groups using Wilcoxon rank sum tests. The significance of within-group change and percent change were tested using signed rank sum tests. Frequencies were compared between treatment groups using chi-square tests. The accepted level of significance for all comparisons was $P < 0.05$. Because the sample size required to detect a difference between treatment groups was determined a priori, no subgroup analyses (e.g., outcomes based on lesion type at baseline) were performed because the sample size did not provide the required power to detect any such differences.

Table 1. Baseline Characteristics

	Bevacizumab	Ranibizumab	*P**
Age, years	79.6 ± 9.8	78.3 ± 8.8	0.27
No. subjects	69	107	
Gender, %			
Male	33.3	43.5	
Female	66.7	56.5	0.28
Lesion composition			
Occult	72.6%	78.8%	
Classic†	24.5%	20.0%	
RAP	0	1.2%	
Fibrosis	2.0%	0	0.41
Area of lesion, unit	5.0 ± 3.9	6.2 ± 4.5	0.15
GLD	3.3 ± 0.9	3.4 ± 1.8	0.30
VA			
Mean	20/100	20/100	
Median	20/80	20/80	
Range	20/40–20/320	20/30–20/320	0.84
Central foveal thickness, μm	308 ± 80	310 ± 82	0.71
Volume, mm^3	7.4 ± 0.9	7.7 ± 0.9	0.003

*Wilcoxon rank sum test *P* values. Chi-square test *P* values for comparison of frequencies.

†Includes both minimally classic and predominantly classic lesions.

GLD, greatest linear diameter; RAP, retinal angiomatous proliferation; VA, visual acuity.

Results

The ranibizumab-treated and bevacizumab-treated patients had similar baseline characteristics of age, sex, lesion composition, visual acuity, and OCT measurements (Table 1). Occult lesions were the most predominant with 78.8% and 72.6% of ranibizumab- and bevacizumab-treated subjects having this lesion type, respectively. Classic lesions comprised 20.0% and 24.5% of the ranibizumab- and bevacizumab-treated groups, respectively. In the ranibizumab group, 1.2% had retinal angiomatous proliferation lesions, and in the bevacizumab group, 2.0% had fibrosis. There was a small but significant difference noted between the baseline volumes of the lesions, with the ranibizumab group having a slightly larger baseline volume of 7.7 ± 0.09 mm^3. No additional baseline characteristics were measured because the sample

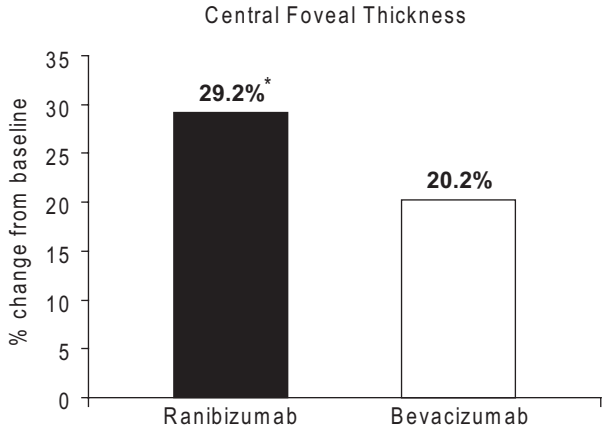

Fig. 1. The percent change in central foveal thickness from baseline for ranibizumab and bevacizumab. *$P \leq 0.02$.

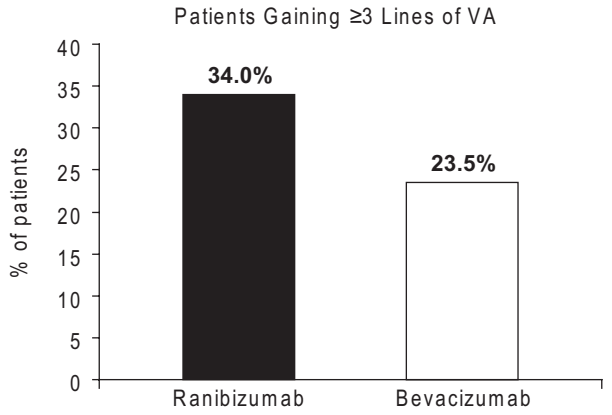

Fig. 2. The percent of subjects who gained ≥3 lines of visual acuity from baseline after 3 doses of ranibizumab or bevacizumab. The difference was not significant ($P \leq 0.14$).

size did not provide enough power to detect significant differences. Evidence of a greater reduction of central foveal thickness as measured by OCT was noted in patients treated with ranibizumab versus those treated with bevacizumab. After 3 treatments, although both groups demonstrated a statistically significant reduction from the baseline central foveal thickness measure ($P \leq 0.0001$ for both treatments), the ranibizumab-treated patients experienced a greater (29.2%) decrease in this parameter as compared with the bevacizumab-treated group (20.2%; $P \leq 0.02$; Figure 1). Analyzing the central foveal thickness data according to the relative increase in thickening (the difference between the actual central foveal thickness measure and a "normal" central foveal thickness of 200 μm) showed a greater improvement in resolution of thickening in the ranibizumab-treated group versus the bevacizumab-treated group, although this difference was not significant ($P \leq 0.07$).

The macular volume of patients treated with 3 doses of ranibizumab decreased by 11.9%, whereas the macular volume of patients treated with 3 doses of bevacizumab decreased by only 8.0% ($P \leq 0.009$). The reduction in the relative increase in macular volume was also noted to be greater in the ranibizumab-treated group than the bevacizumab-treated group ($P \leq 0.007$).

On average, both ranibizumab- and bevacizumab-treated patients were noted to have a significant ($P \leq 0.0001$) but similar increase in their mean visual acuity from baseline after 3 treatments. For the ranibizumab group, the change was 7 letters, and for the bevacizumab group, the change was 4 letters ($P = 0.64$). There was a trend toward a greater increase in the gain of ≥3 lines of visual acuity in the ranibizumab group (34.0%) versus the bevacizumab group (23.5%; $P \leq 0.14$), although this difference was not significant (Figure 2).

Discussion

Given the widespread use of both ranibizumab and bevacizumab, it is reasonable to assume that there is a general perception of equivalence between the two biologic agents. Although the results of the ANCHOR and MARINA trials were from large randomized, prospective, controlled, double-masked clinical trials of treatment-naïve subjects with up to 2 years follow-up,[9,10] most bevacizumab data are based on uncontrolled case series and small prospective studies.[17–19] Often bevacizumab data are obtained from retrospective studies and include subjects with varying durations of disease activity and/or previous treatments for neovascular AMD.[20,21] Many of these case series have shown visual acuity results similar to that of the MARINA and ANCHOR trials. For example, Falkenstein et al[20] recently reported a mean gain of 15 letters in a consecutive series of 18 eyes treated with bevacizumab at 6-week intervals. In contrast, however, Emerson et al[18] found only a 4-letter gain at 3 months in 78 patients treated with ranibizumab on an as-needed basis. Despite the widely available Level II evidence to support the efficacy of bevacizumab in neovascular AMD, the ability to compare this evidence with data from randomized clinical trials is limited. To the best of our knowledge at the time of writing this article, this is the first direct comparison of the treatment effectiveness of ranibizumab and bevacizumab.

In this study, we attempted to compare two similarly treated and reasonably matched cohorts of patients treated with ranibizumab and bevacizumab in a "standard of care" protocol. Our main goal was to provide insight into the short-term biologic activity of

bevacizumab and ranibizumab by using OCT as a surrogate measure for visual acuity. In an attempt to limit bias, we determined a specific hypothesis and calculated the sample size to assess this with the appropriate power a priori. To further limit potential bias, we carefully identified qualifying consecutively treated patients during a predetermined study period and eliminated patients who did not fit the fixed entry criteria (selected to approximate those used in the MARINA and ANCHOR trials).[9] Given the variability of treatment dosing regimens after the three consecutive injections, we elected to evaluate the short-term (after three consecutive injections) efficacies of these two pharmacologic agents to directly compare the biologic response of the neovascular process involved in AMD.

Although the ranibizumab and bevacizumab treatment groups had slightly different dosing intervals (every 4 weeks vs. every 6 weeks), there is precedent for this type of comparison. Oncology drugs are often compared directly in clinical trials although they may have different dosing regimens.[22–24] Although different dosing schedules were used, all patients received three consecutive injections of either ranibizumab or bevacizumab and were all evaluated 1 month after the third injection. This study did not attempt to directly compare monthly dosing of ranibizumab with bevacizumab, and therefore, results comparing monthly dosing between these two treatments may be different; however, we believe that the difference in central foveal thickness measurements found in our study suggests that there is a difference in biologic activity between ranibizumab and bevacizumab. This conclusion is supported by the difference in pharmacokinetic properties for ranibizumab and bevacizumab, which provides a scientific rationale suggesting a need for less frequent dosing (e.g., every 6 weeks) of bevacizumab.[25,26]

In conclusion, our results imply that there is a distinct difference in the short-term biologic activity between ranibizumab and bevacizumab. In nearly every parameter measured by OCT, the ranibizumab-treated patients were noted to have a significantly greater effect from the treatment as compared with bevacizumab-treated patients. Although the literature provides only variable results regarding the association between OCT and visual acuity, a modest correlation has been determined between central foveal thickness and visual acuity in several studies.[27–29] In addition, OCT is used as a standard of practice in making treatment decisions for patients with neovascular AMD. Furthermore, in regard to sample size, detecting a difference in OCT measurements was much more reasonable than for detecting visual acuity differences. Another potential contention with the data presented here could be that there are often errors in central foveal thickness and volume calculations made by OCT. Although this is a valid observation, the level of error in OCT measurements, especially considering the well-matched baseline characteristics, should have been similar in both groups, and the study was specifically powered to detect a difference in this variable.

Chan and Duker[30] recently reported an alternative method of reporting changes in OCT thickness. With the understanding that a return to "normal" thickness provides a floor for how much the central foveal thickness measurement can change, they proposed the term standardized change in macular thickness. The standardized change in macular thickness is derived by dividing the absolute change in central foveal thickness (initial minus the final) by the potential maximum reduction in central foveal thickness (initial central foveal thickness minus the normal central foveal thickness of 200 μm). In a similar fashion, our results demonstrated a significantly greater percentage of patients in the ranibizumab group than that of the bevacizumab group that had returned to a normal central foveal thickness of $\leq$200 μm.

It is important to keep in mind that the study was not powered to detect differences in visual acuity between the ranibizumab and bevacizumab groups. Based on a sample size of 43 ranibizumab and 78 bevacizumab patients, a sample size calculation was performed to determine the ability to detect a difference of 3 lines or more of visual acuity between the groups. We determined that a test with 80% power and $\alpha = 0.05$ would require a sample size of 50 and 90 in the ranibizumab and bevacizumab groups, respectively. The more likely scenario would be a small difference in improvements in visual acuity, for which a much larger sample size would be needed; on the basis of an a priori sample size calculation, we estimated that it would have required 2,654 patients in each arm of this study to detect a 1-letter difference in the mean change in visual acuity and 296 patients per group to detect a difference of 3 letters of mean visual acuity change between the 2 groups. Although the variance between groups may change based on the sample studied, this calculation provides guidance for investigators who intend to perform future studies to directly compare ranibizumab and bevacizumab.

Despite the lack of power to determine small changes in visual acuity between ranibizumab and bevacizumab, our results revealed a trend toward a greater number $\geq$3-line gainers in the ranibizumab group. Interpretation of comparative visual acuity results in a retrospective study requires important cave-

ats. For example, Boyer et al[31] recently reported a subgroup analysis of the patients treated in the MARINA trial and noted that baseline visual acuity, choroidal neovascularization lesion size, and age were the most important determinants of final visual acuity. In our study (Table 1), no statistically significant differences in these 3 parameters were noted, lending further credence to our results.

As previously mentioned, we attempted to control for the inherent bias that exists in retrospective trials by including practitioners who had experience in both treatment modalities by asking for consecutively treated patients and by designating specific study parameters (baseline visual acuity, consecutive enrollment, dates of enrollment, and so on). Because the treatment choice was left to the discretion of the patient and treating physician, some additional potential for bias does exist, but the standard clinical setting limited the possibility of controlling for this issue. However, the similarity in baseline characteristics between the two groups is reassuring and suggests that the groups were in fact well balanced. Another limitation in this study was the absence of a strict protocol to measure visual acuity. This fact in combination with the relatively short follow-up period, which did not allow enough time for large changes in visual acuity to occur in most patients, likely led to some of the variances in visual acuity that were noted in the two groups and may limit the interpretation of these visual acuity results.

A more precise determination of the differences between these two treatments may be established after the completion of currently planned randomized, controlled trials,[16] but in the interval before trial results become known, inferences can be made from retrospective studies such as this one with defined a priori hypotheses and study design. In addition, it may be important to consider that superiority can be divided into several parameters, including the biologic response or short-term ability to halt exudation, long-term visual acuity improvements, the length of the injection-free interval (period between successful induction and recurrence of exudation), and number of injections required per year to achieve visual acuity and exudation results.

Our results suggest that in at least one of these parameters, namely the biologic response or short-term ability to halt exudation, ranibizumab seems to be superior to bevacizumab. Furthermore, there is a trend suggesting that it may also provide superior visual acuity results. Although this study does not provide definitive proof that there are clinically significant differences in the visual acuity results of patients treated with ranibizumab or bevacizumab, it does seem to demonstrate a possible difference in the biologic activity of the two treatments. This result may be an important factor to consider clinically when deciding how to most appropriately treat patients with neovascular AMD.

Key words: ranibizumab, bevacizumab, Lucentis, Avastin, age-related macular degeneration (AMD), intravitreal injection, OCT.

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