Intravitreal Bevacizumab and Ranibizumab for Age-Related Macular Degeneration

A Multicenter, Retrospective Study

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Objective: To compare visual acuity (VA) outcomes after bevacizumab or ranibizumab treatment for AMD.

Design: Comparative, retrospective case series.

Participants: We followed 452 patients in a retrospective study of exudative AMD treated with anti-vascular endothelial growth factor drugs; 324 patients were treated with bevacizumab and 128 patients with ranibizumab.

Methods: All treatment-naïve patients who received either bevacizumab or ranibizumab were followed for 1 year. Baseline characteristics and VA were recorded using standard descriptive statistics.

Main Outcome Measures: Visual acuity.

Results: At 12 months, the distribution of VA improved in both groups with 22.9% of bevacizumab and 25.0% of ranibizumab attaining ≥20/40. Improvement in vision was observed in 27.3% of the bevacizumab group and 20.2% of the ranibizumab group. The mean number of injections at 12 months was 4.4 for bevacizumab and 6.2 for ranibizumab. There were 8 (2%) deaths in the bevacizumab group and 4 (3%) in the ranibizumab group. Two patients developed endophthalmitis in the bevacizumab group and the ranibizumab group. The bevacizumab group had slightly worse acuity at baseline, but both groups showed improvement and stability of vision over time.

Conclusions: Both treatments seem to be effective in stabilizing VA loss. There was no difference in VA outcome between the 2 treatment groups. Because the study is a nonrandomized comparison, selection bias could mask a true treatment difference. Results from the Comparison of the Age-related Macular Degeneration Treatment Trials will provide more definitive information about the comparative effectiveness of these drugs.

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Age-related macular degeneration (AMD) is the leading cause of severe vision loss in patients >60 years of age.[1] Because most cases of vision loss are due to the exudative form, the current treatments are targeted toward the treatment of neovascularization. In 2006, the United States Food and Drug Administration approved the use of ranibizumab (Lucentis; Genentech, South San Francisco, CA) for the treatment of exudative AMD. Before its approval, many ophthalmologists already were using bevacizumab (Avastin; Genentech), a drug very similar to ranibizumab. Bevacizumab is approved for the systemic treatment of certain cancers, but is not approved for injection into the eye. This "off-label" use of the drug has been reported to be effective at treating exudative AMD.[2–6] Although the safety and efficacy of ranibizumab is well established,[7,8] the cost per injection is high. However, bevacizumab is inexpensive, but it has not been well studied. The current study compares the efficacy of bevacizumab or ranibizumab in treating exudative AMD.

Methods

The study was conducted at Kaiser Permanente Southern California, which provides comprehensive prepaid medical care to 3.1 million residents of Southern California. This care is delivered by >6000 physicians working in 11 medical centers. The study population was composed of all persons, ≥18 years of age who have exudative AMD. Patients with choroidal neovascularization owing to conditions other than AMD were excluded. Only eyes with newly diagnosed choroidal neovascularization were eligible, and second eyes that subsequently developed choroidal neovascularization were excluded from the study.

Each of the 11 departments of ophthalmology maintained a log of all patients who received treatment with an anti-vascular endothelial growth factor agent. Using these logs, clinical information from patients with exudative AMD was used to create a registry. This registry was then used to identify all patients who had no prior treatment and who received a single anti-vascular endothelial growth factor agent. For eyes that were started on 1 therapy and then switched to another, visual acuity (VA) information was included until therapy was changed. Information after the change was not used. Charts of 100 randomly identified patients from the registry were reviewed by 2 reviewers to confirm inclusion and exclusion criteria. All 100 charts were found to meet the criteria. Age was determined at entry to the study. Race and socioeconomic status were obtained from geocoding using the patient's address and corresponding census block. Geocoding is a method to determine a person's race and socioeconomic status using census data. This method has been used and validated in a number of studies.[9]

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Visual acuity was abstracted from the chart at baseline and at 3-month intervals. To investigate the change during follow-up and perform statistical testing, Snellen acuities were converted into the logarithm of the mean angle of resolution (logMAR). This conversion is necessary to change the nonnormal distribution of the Snellen acuities into one that is normally distributed and testable statistically. Although the Snellen chart, when compared with the logMAR (Early Treatment Diabetic Retinopathy Study) chart, has different number of letters per line and different number of lines for the same change in acuity, this conversion was necessary to allow statistical testing. Analysis of change was conducted in a paired fashion; the change was computed not by group, but by eye. For example, logMAR change was based on computing the change between baseline and at 3, 6, 9, and 12 months by eye. These changes were then summarized for each time point.

Standard descriptive statistics were used to describe the baseline characteristics. *t*-tests or the Wilcoxon rank–sum test were used to compare continuous variables. The chi-square test or the Fisher exact test was used to compare categorical variables. All analyses were performed on the Statistical Analyses System (SAS Inc., Cary, NC). The study was reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board.

Results

From August 2005 to June 2008, 452 patients were entered into a registry of patients with exudative AMD treated with anti-vascular endothelial factor drugs. A total of 324 patients were treated with bevacizumab and 128 patients with ranibizumab. Table 1 shows the baseline characteristics of both groups. The ranibizumab group was slightly older, but had slightly better VA (mean VA, 20/160).

Of the 324 patients treated with bevacizumab, by 1 year, 8 (2.5%) patients had died, 37 (11.4%) were lost to follow-up, and 74 (22.8%) had changed treatments. Of the 128 patients in the ranibizumab group, 4 (3.1%) had died, 16 (12.5%) were lost to follow-up, and 4 (3.1%) had changed treatments. In most cases, the reason for patients changing treatment could not be determined. Endophthalmitis was seen in 2 patients treated in the bevacizumab group and 2 in the ranibizumab group. Only 1 case from each treated group was culture positive; both of these cases grew out *Staphylococcus epidermidis*. All 4 cases responded well to treatment with return to baseline vision within 1 month.

Table 1. Baseline Characteristic of Patients Treated with Bevacizumab and Ranibizumab

Demographic	Bevacizumab Group (n = 324)	Ranibizumab Group (n = 128)
Age (yrs)		
Mean (standard deviation)	78.2 (9.3)	81.8 (7.0)
<50	0.9%	0.0%
50–64	8.0%	1.6%
65–74	23.2%	15.6%
75–84	44.1%	49.2%
≥85	23.8%	33.6%
Gender		
Female	56.5%	60.9%
Male	43.5%	39.1%
Vision		
≤20/200	40.1%	33.6%
>20/200 to <20/40	46.3%	54.7%
≥20/40	13.6%	11.7%
Mean visual acuity (log mean angle of resolution)	0.9	0.8
Race (Geocoded)		
Asian	10.9%	7.8%
African American	2.9%	3.5%
Native American	0.4%	0.6%
Non-Hispanic white	52.1%	59.2%
Hispanic	30.8%	25.3%
Other	2.8%	3.7%

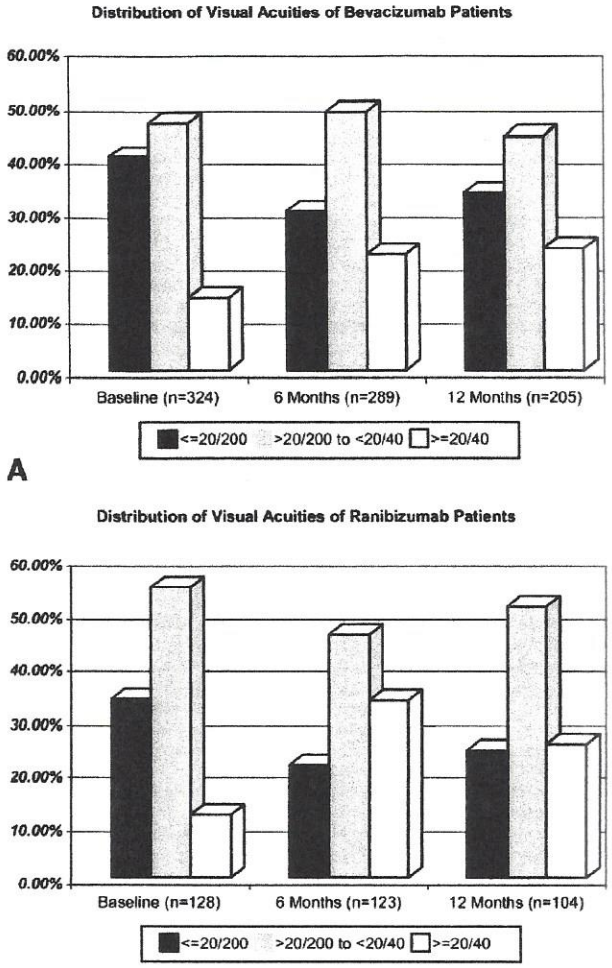

Figure 1. Distribution of visual acuity at baseline and after initial injection. A, Distribution for eyes treated with bevacizumab. B, Distribution for eyes treated with ranibizumab.

With follow-up, the distribution of visual acuities improved for both groups (Fig 1). At 1 year, the proportion of patients with VA ≥20/40 increased in the bevacizumab group from 13.6% at baseline to 22.9% at 12 months, and from 11.7% at baseline to 25.0% in the ranibizumab group. Although the bevacizumab group had slightly worse VA at the start, both groups showed improvement from baseline and stability of vision over time (Fig 2). Figure 3 shows a scatter plot of the VA at baseline and at 12 months after the first injection. We also looked at the number of eyes at each follow-up interval that had doubling of the visual angle and improvement of VA. Table 2 shows doubling of the visual angle (3-line loss of Early Treatment Diabetic Retinopathy Study acuity

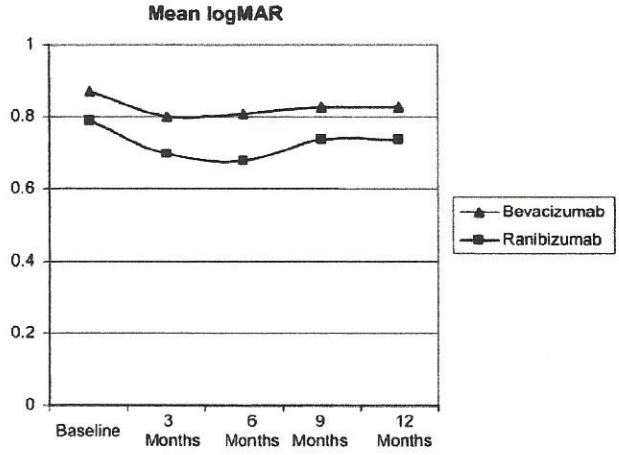

Figure 2. Mean visual acuity expressed in logarithm of mean angle of resolution (logMAR) units. Snellen visual acuity of 20/200 is 1.0 logMAR units, and 20/100 is 0.7 and 20/20 is 0.0 logMAR units. (See Methods for a more detailed explanation.)

or loss of logMAR ≥ 0.3) in 17.6% of the bevacizumab group and 15.4% of the ranibizumab group ($P = 0.6$). Improvement of vision (3-line gain on the Early Treatment Diabetic Retinopathy Study chart or logMAR ≥ 0.3 [e.g., 20/80 to 20/40] was observed in 27.3% of the bevacizumab group and 20.2% of the ranibizumab group (Table 3; $P = 0.2$).

There was a difference in the mean number of injections for each group. The bevacizumab group received a mean of 4.4 injections over 12 months, whereas the ranibizumab group had a mean of 6.2 injections in the same time period (Table 4). Visual acuity outcomes from eyes that received a bevacizumab injection every 4 weeks were compared with all ranibizumab eyes treated every 4 weeks (Table 5). There were no differences between the 2 groups.

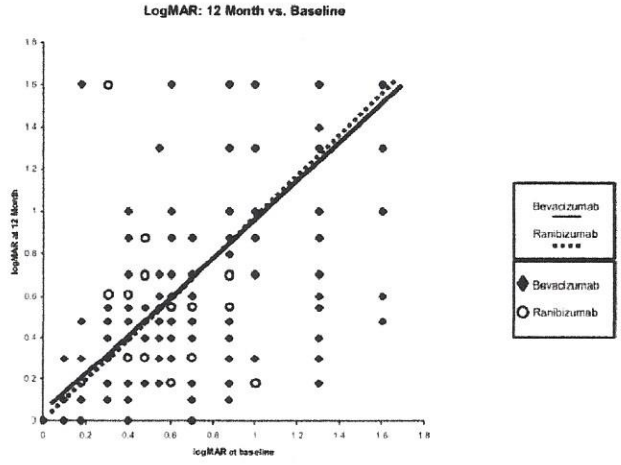

Figure 3. Scatter plot showing the baseline and 12-month visual acuity expressed in logarithm of mean angle of resolution (logMAR) units. Snellen visual acuity of 20/200 is 1.0 logMAR units, and 20/100 is 0.7 and 20/20 is 0.0 logMAR units. (See Methods for more detailed explanation.) Some points represent multiple observations. Using logMAR, a slope < 1.0 is consistent with improvement. The slope is 0.8 for the bevacizumab and 0.9 for ranibizumab treated groups; the difference between the 2 is not significant ($P = 0.36$).

Table 2. Improvement of Visual Acuity with Follow-up

logMAR Gain of ≥ 0.3	Baseline	3 Months	6 Months	9 Months	12 Months
Bevacizumab % (n)	Reference	20.1 (313)	26.6 (289)	26.8 (254)	27.3 (205)
Ranibizumab % (n)	Reference	19.7 (127)	23.6 (123)	20.0 (115)	20.2 (104)
P		0.9	0.5	0.2	0.2

logMAR = log of the mean angle of resolution.

Discussion

Visual acuity outcomes of eyes treated with bevacizumab and ranibizumab are reported in the current study. Comparing the mean VA, changes in VA, and VA loss and gain, there did not seem to be any great differences between the 2 agents. Some investigators have suggested that ranibizumab might act faster, but the current data did not seem to show any difference.

The current study did not specify a treatment protocol, because at the time of the study inception, there was no universal agreement on treatment frequency within the 11 practices of Kaiser Permanente Southern California or in the larger ophthalmic community. There was no financial incentive or disincentive for use of either agent. All patients were Kaiser Foundation Health Plan members and as such had no copay or coverage differences with either drug. Each of the 11 medical centers is free to set their own clinical practice and choice of the drug was dependent only on physician and patient choice. The results of the study represent real-world experience of the 2 drugs.

The sample size of the current study does not have sufficient power to determine whether there are any differences in safety. Rare systemic adverse events such stroke or other cardiovascular end points require the monitoring of large number of injections possible only through much larger studies. This is also true for ocular events such as endophthalmitis, vitreous hemorrhage, and retinal detachment. Recent studies have reported endophthalmitis to occur in about 0.02% of intravitreal injections of anti-vascular endothelial growth factor agents.[10,11] In our study, the frequency of endophthalmitis was 0.2% (2/905 injections) in the bevacizumab group and 0.3% (2/648 injections) in the

Table 3. Loss of Visual Acuity with Follow-up

logMAR Loss of ≥ 0.3	Baseline	3 Months	6 Months	9 Months	12 Months
Bevacizumab % (n)	Reference	10.2 (313)	16.6 (289)	15.4 (254)	17.6 (205)
Ranibizumab % (n)	Reference	9.5 (127)	12.2 (123)	16.5 (115)	15.4 (104)
P		0.8	0.3	0.8	0.6

logMAR = log of the mean angle of resolution.

Table 4. Mean Number of Injections

	Baseline	3 Months	6 Months	9 Months	12 Months
Avastin	1.00 (0.05)	2.44 (0.77)	3.28 (1.28)	3.91 (1.99)	4.41 (2.41)
n		313	289	254	205
Lucentis	1.00 (0.00)	3.48 (0.65)	5.05 (1.18)	5.63 (1.60)	6.23 (2.16)
n		127	123	115	104
P		<0.0001	<0.0001	<0.0001	<0.0001

Values are presented as mean (standard deviation).

Table 6. Distribution of Enrollment Date by Treatment Group

Drug	2005, % (n)	2006, % (n)	2007, % (n)	Total, % (n)
Bevacizumab	11.1 (36)	67.6 (219)	21.3 (69)	100.0 (324)
Ranibizumab	0.0 (0)	45.3 (58)	54.7 (70)	100.0 (128)

Percentage of each treated group and the calendar year in which they received their first treatment.

ranibizumab group. Although the proportions in our study seem to be higher, only 1 case from each group was culture positive. In addition, the 95% confidence interval is 0.03% to 0.8% for bevacizumab and 0.04% to 1.0% for ranibizumab. These confidence intervals show that the 2 rates are equivalent and very close to the published rate.

At 1 year, the number of injections varied between the 2 groups (4.4 vs 6.2 for bevacizumab vs ranibizumab). This difference may be due in part to the belief that bevacizumab is a larger molecule and has a longer intraocular half-life. Interestingly, the number of injections is also greater during the first 6 months compared with the last 6 months. From baseline to 6 months, bevacizumab patients on average received 3.3 injections, and 1.1 injections during months 6 to 12. This may represent both physician's and patient's desires to stop treatment. This reduction of injections also seems to have reduced the VA.

The proportion of patients who did not have doubling of their visual angle was reported to be 94% in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration[4] and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration[5] studies, and only 85% in the current study's ranibizumab treated group. The slightly lower proportion may be explained by the following: First, the population in the current study is older; 34% of the current study's ranibizumab treated patients were ≥85 years compared with 10% to 21% in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration study and 31% to 36% in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration study. Second, the 2 Genentech studies excluded patients with vision <20/320, while the current study had 34% of patients with vision ≤20/200. The third reason is that patients enrolled in the ranibizumab group of the current study only received on average 6.2 injections, whereas the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration study averaged >11.

Table 5. One-Year Results of Eyes Treated with Bevacizumab Every 4 Weeks and with Ranibizumab Every 4 Weeks

	Bevacizumab	Ranibizumab	P
n	37	75	
Mean logMAR	0.74	0.72	0.85
Mean logMAR change	−0.06	−0.05	0.87
Proportion of eyes gaining logMAR 0.3	24.3%	20.0%	0.60
Proportion of eyes loosing logMAR 0.3	13.5%	13.3%	0.98

Visual acuity is expressed as the log of the mean angle of resolution (logMAR).

The strengths of the study are the large number of patients and long follow-up. Using a 2-sided test at an alpha of 0.05, the power to detect a 15% difference in improvement or worsening of vision is >85%. Financial barriers were not a factor: Patients had no copay differences and physicians had no financial incentives to use or not use either drug.

The weakness of the study is that it is an observational study and treatment assignment was not randomized. There was not a standardized protocol to guide injection frequency. Visual acuities were recorded using the Snellen chart and then converted to logMAR for certain analyses. In addition, because bevacizumab was available earlier, about 11% of the bevacizumab group was enrolled to 2005 compared with 0% for the ranibizumab group (Table 6). Although unlikely, the study cannot rule out the possibility that differences in management of our patients (other than the availability of the drugs) in 2005 compared with 2006 could also account for the results.

Another potential confounding factor is that some patients switched therapies during follow-up. Our study was an observational study and there were no criteria for changing drugs. The availability of ranibizumab most likely accounted for some of the changes observed in the bevacizumab group. To minimize the confounding from change in therapy, and to maximize the information in our data, the study included all eyes that had monotherapy at entry into the registry. In eyes where the therapy was changed, VA information was collected at entry up to include the visit at which therapy was changed. Visual acuity in the visit after the treatment change was not included. About 22.8% (74/324) of the bevacizumab and 3.1% (4/128) of the ranibizumab patients switched. One reason for the higher prevalence of change in the bevacizumab group might be the Food and Drug Administration's approval of ranibizumab.

In summary, the VA outcomes of bevacizumab and ranibizumab treatments for exudative AMD are reported in

a case series from a multicenter group practice. Both treatments seem to be effective in stabilizing VA loss. Although there were a large number of patients enrolled, the study was a nonrandomized comparison. Results from the Comparison of the Age-related Macular Degeneration Treatment Trials will provide more definitive information about the comparative effectiveness of these drugs.

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Footnotes and Financial Disclosures

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