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CLINICAL STUDY

Bevacizumab *vs* ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial

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Abstract

Purpose **To report 1-year visual and anatomic outcomes of a prospective, double-masked randomised clinical trial comparing bevacizumab with ranibizumab for the treatment of age-related macular degeneration (AMD).**

Methods **Patients who met inclusion criteria were randomised 2:1 to bevacizumab or ranibizumab. All subjects and investigators (except for the pharmacist responsible for study assignments) were masked to treatment arms. Visual acuity was taken on Early Treatment Diabetic Retinopathy Study chart. Patients were given either bevacizumab or ranibizumab every month for the first 3 months, followed by an optical coherence tomography-guided, variable-dosing treatment schedule. Main outcomes measured included visual acuity, foveal thickness, and total number of injections over the 1-year treatment period.**

Results **In total, 15 patients received bevacizumab and 7 patients received ranibizumab. The average pre-operative visual acuity was 34.9 letters in the bevacizumab group, and 32.7 letters in the ranibizumab group. At 1-year follow-up, mean vision was 42.5 letters in the bevacizumab group, and 39.0 letters in the ranibizumab group. Two-tailed *t*-test failed to showed statistical significance between the two groups ($P = 0.5$). Patients in the bevacizumab group underwent an average of eight injections, whereas patients in the ranibizumab group underwent a mean of four injections ($P = 0.001$).**

Conclusion **The 1-year outcomes of a prospective, double-masked, randomised clinical trial comparing bevacizumab with ranibizumab failed to show a difference in visual and anatomic outcomes between the two treatments for choroidal neovascularisation in AMD. Total injections given over the treatment period were significantly different between the two groups. Further studies with larger sample sizes are warranted.**

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness over the age of 50 in developed Western countries.[1,2] Although non-exudative (dry) AMD can lead to severe vision loss, exudative (wet) AMD is often more visually devastating with a higher risk of blindness. Vision loss occurs in wet AMD from choroidal neovascularisation (CNV) affecting the foveal centre, which, prior to the advent of recent therapies, often led to legal blindness for most of those it affected.

Recent data have shown that angiogenic growth factors, particularly vascular endothelial growth factor (VEGF), have a key role in the formation of CNV in macular degeneration.[3–8] Therapies that inhibit active forms of VEGF

have been shown to be effective in the treatment of wet AMD. Pegaptanib sodium (Macugen; Eyetech, Palm Beach Gardens, FL, USA) was the first of such treatments that was found to be a safe and effective for wet AMD, and it received approval by the US Food and Drug Administration (FDA) in 2004.[9,10] About 2 years later, ranibizumab (Lucentis; Genentech, San Francisco, CA, USA) was approved by the FDA for the treatment of CNV in wet AMD. The Minimally Classic/Occult Trial of the anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularisation in AMD (ANCHOR) studies, both of which were multicentre, randomised, double-masked trials, established the superiority of ranibizumab to any prior FDA-approved treatments.[11–13]

Before the approval of ranibizumab by the FDA in 2006, vitreo-retinal specialists began using bevacizumab (Avastin; Genentech) in small doses as a local intraocular injection to treat wet AMD. Both ranibizumab and bevacizumab inhibit all biologically active forms of VEGF.[14] As a recombinant humanised monoclonal IgG1 antibody, with a molecular weight of 149 kDa, bevacizumab was approved by the FDA in 2004 for treatment of metastatic cancer of the colon or rectum as an intravenous infusion. Philip Rosenfeld of the University of Miami pioneered the off-label use of bevacizumab in the eye, after early data using Avastin intravenously suggested its efficacy in treatment of wet AMD.[15–17] Within 6 months, the use of intravitreal Avastin for treatment of macular degeneration spread all over the world.[18]

Although both ranibizumab and bevacizumab have independently been shown to be effective for the treatment of wet AMD, as far as the authors are aware, a randomised, prospective trial comparing the two drugs head to head has not yet been completed. The purpose of this article is to report 1-year visual and anatomic outcomes of a prospective, double-blinded, randomised controlled trial comparing bevacizumab with ranibizumab.

Materials and methods

This is a prospective, double-blinded, randomised clinical trial at the Veterans Affairs (VA) Boston Healthcare System Hospital in Massachusetts, which is the outpatient tertiary care referral centre for vitreo-retinal care for veterans in the New England area. The VA Boston provides health care for eligible veterans, and its pharmacy dispenses all medications. The costs of the study medications were covered by the Boston VA Healthcare System Pharmacy Department, which typically administers all medications to the VA patients. The authors certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Patients were enrolled by a 2 : 1 randomisation to either the bevacizumab (2) or the ranibizumab (1) arm of the study. All subjects were assigned a study number. To obtain blinding of treatment assignments, the Research Pharmacist at the VA Hospital Pharmacy was responsible for randomisation, tracking and ensuring the correct study drug was administered to each patient at each visit, and dispensing the same volume of each drug in identical 1 ml syringes. As the only investigator with knowledge of subject assignments, the Research Pharmacist was, in turn, masked to all visual and anatomic outcomes to treatment. All other investigators, as well as other physicians, residents, and office personnel who may have inadvertently come in contact with study subjects, were masked to treatment assignments.

Patients were evaluated and determined to meet eligibility criteria by one of three vitreo-retinal specialists (MS, EF, and SN). Key inclusion criteria included age greater than 50, presence of a symptomatic CNV, confirmed by intravenous fluorescein angiogram (FA) and optical coherence tomography (OCT) (Stratus; Carl Zeiss Meditec, Inc., Dublin, CA, USA) affecting the foveal centre, ability to provide informed consent, and a cooperative patient willing to commit to regular clinic appointments and follow-up. The original protocol approved by the institutional review board specified a baseline visual acuity between 20/40 and 20/200 to meet inclusion criteria. However, this was later amended to include all baseline visual acuities equal to or better than 20/400.

Key exclusion criteria included previous treatment for wet AMD within the past 1 year, presence of subretinal haemorrhage that is greater than 50% of the size of the lesion on FA, presence of advanced glaucoma, any coexisting macular disease causing decreased vision, history of malignant or uncontrolled hypertension, intraocular inflammation, history of thromboembolic phenomena, inability to provide informed consent, and participation in another concurrent ophthalmic clinical trial.

All subjects received a full ophthalmic examination with dilated fundus examination, FA, and OCT. Blood pressure was measured at baseline and on all follow-up visits. After being informed of the risks and benefits of the study, and potential alternatives to treatment, patients who wished to enrol signed the IRB-approved study consent before entering the study. Informed consent was also obtained on all subsequent treatment visits requiring injections.

Once the patient received a diagnosis, and eligibility criteria were met, the patient was enrolled and treatment

was initiated either the same day or within 1 week of diagnosis. Baseline visual acuity and follow-up visions were obtained with Early Treatment Diabetic Retinopathy Study (ETDRS) chart. As the examination rooms in the clinical care area did not have the capacity to measure visual acuity at 4 m, without violating the Health Insurance Portability and Accountability Act, ETDRS vision was obtained at 2 m for all study subjects, instead of the usual 4 m recommended by ETDRS protocol. Vision was recorded in the same, consistent fashion for all study subjects in both treatment arms. Visual acuity was expressed and recorded in total ETDRS letters, and translated to 10/x, at baseline exam and all follow-up visits. When calculating and reporting outcomes for mean visual acuities, vision was converted to LogMar equivalents.[19]

Patients were given intravitreal injection of bevacizumab or ranibizumab every month for the first 3 months (at months 0, 1 and 2). Following the third injection, decision to administer further treatment was guided primarily by OCT changes, and secondarily by visual acuity changes and clinical examination. Following the third injection at month 2, patients returned monthly and underwent visual acuity measurements obtained by ETDRS chart, OCT, and clinical examination. If patients showed a qualitative increase in intraretinal fluid or subretinal fluid by OCT, then additional injection with study medication was administered. Any significant worsening of visual acuity, or increase in fluid or haemorrhage on clinical examination, led to a repeat FA and possible re-injection based on the results.

OCT-guided, variable-dosing therapy, implemented after month 2, was opted for several reasons. The investigators felt it was prudent to study a treatment regimen based on current practice patterns of many vitreo-retinal specialists at the time the study commenced. Moreover, preliminary results of the PrONTO and PIER studies seemed to indicate that OCT-guided, variable-dosing treatment shows more merit than fixed quarterly dosing intervals.[20,21]

Injections were administered using standard sterile technique. Treatment site was always marked before patients were brought to the procedure room. The treated eye was prepped with 5% povidone iodine solution, flushed copiously into the conjunctival fornices, with additional solution painted around the eyelids for skin preparation. Following subconjunctival injection with 2% lidocaine and one drop of antiobiotic solution (Vigamox, Alcon Laboratories, Fort Worth, TX, USA), 0.05 ml of either bevacizumab or ranibizumab was injected into the intravitreal space of every subject. Post-operative intraocular pressure (IOP) was checked within one-half hour of injection, and IOP-lowering agents were administered if IOP was significantly elevated (>30 mm Hg). Patients were treated with topical antibiotics for 4 days after injection.

Safety assessments were performed at scheduled clinic visits. Specific assessments for ocular and systemic adverse events were performed at each visit, such as blood pressure, ocular surface symptoms, gastrointestinal symptoms, and specific questions related to thromoembolic disease. Patients were examined for ocular adverse events, such as corneal abrasion, cataracts, inflammation, endophthalmitis, and vascular occlusions. Patients were seen at 1-week follow-up after each injection to assess for adverse events.

The primary outcome measured was visual acuity and central foveal thickness. Total number of injections received during the treatment period was also monitored. The mean visual acuities and mean central foveal thickness were compared by using a two-tailed *t*-test with 95% confidence intervals. With the aide of two independent statisticians, the total sample size estimate to obtain statistical significance, with 2 : 1 randomisation of bevacizumab to ranibizumab, was calculated at 135. With a sample of 90 in the new treatment group (bevacizumab) and 45 in the usual care group (ranibizumab), power to detect a real, moderate effect size difference is 0.79 ($P = 0.05$, two-tailed).[22]

Results

From April 2007 to February 2009, 28 patients were enrolled in the study. This relatively low number of patients enrolled over a 2-year period was likely due to two reasons. A larger than expected number of potential study participants was previously treated with visudyne or other anti-angiogenesis agents within the past 12 months, thus disqualifying them from the study. There was also a lower volume of AMD patients who presented to the VA and met inclusion criteria than initially anticipated. Both of these factors contributed to low enrolment. All those who met inclusion criteria were offered enrolment in the study, and a relatively high number (estimated 80%) consented to participation. After enrolment, three patients voluntarily dropped out of the study after receiving only one injection at month 0, stating that they could not return for frequent follow-up visits due to long distance of travel (two received bevacizumab and one received ranibizumab). A fourth patient relocated to another state after month 7 and he had received bevacizumab. Two patients died (one due to complications related to meckel cell carcinoma and the other due to unknown causes), and they both received bevacizumab.

Hence, 22 patients completed their 1-year follow-up appointment. Out of these, 15 patients received

Table 1 Patient demographics distribution participating in bevacizumab *vs* ranibizumab injections for AMD

Characteristics	*Bevacizumab*	*Ranibizumab*
Gender		
Male	15	6
Female	0	1
Mean age	78	80
Median age	82	79
Race		
White	15	7
Other	0	0
Baseline vision		
Mean (ETDRS letters)	34.9	32.7
Range	12–60	4–66
Mean (Snellen)	20/100	20/110
Average injections.	8	4
Given *P*-value: 0.0009		
Classic lesions	3	1
Predominantly occult lesions	2	1
Occult lesions	10	5

Abbreviation: ETDRS, Early Treatment Diabetic Retinopathy Study.

bevacizumab and 7 patients received ranibizumab. Table 1 outlines the patient baseline demographics. As enrolment reflected the patient demographics of a Veterans Hospital, all but one subject were male. Mean age for patients in the bevacizumab and ranibizumab group was 78 and 80 respectively. All subjects were of Caucasian descent. None of the subjects received treatment for wet AMD within the past 1 year prior to enrolment in the study. One subject in the bevacizumab group received combination therapy with visudyne and triamcinolone acetonide 3 years prior to enrolment in this study, whereas one subject in the ranibizumab group received therapy with pegaptanib sodium ending 13 months prior to enrolment. Out of 15 patients, 8 (53%) patients in the bevacizumab group were symptomatic for 1 weeks to 2 months before presentation, whereas the remaining subjects were either asymptomatic or had symptoms for an unknown duration. In the ranibizumab group, four out of seven (57%) subjects were symptomatic for 1 week to 2 months prior to presentation, whereas the remaining three were asymptomatic or had symptoms for an unknown duration. Three patients (20%) in the bevacizumab group had classic or predominantly classic CNV (greater than 50% classic component), whereas the remaining patients (80%) had occult or predominantly occult lesions (greater than 50% occult component). In the ranibizumab group, one (14%) subject had classic CNV, whereas six subjects (86%) had occult or predominantly occult lesions.

Table 2 outlines, in detail, the visual outcomes for each subject at baseline and at 1 year. Data were organised within the table by baseline ETDRS vision, from lowest to highest. The final three columns in Table 2 show total letters improved, lines improved, and total number of injections required for each subject. Table 3 summarises the mean and median visual and anatomic (central foveal thickness) outcomes for each group.

Baseline visions and central macular thickness (CMT) at month 0 were not statistically significant between the two groups ($P = 0.80$ and 0.26, respectively). In the bevacizumab group, 3/15 (20%) had a baseline visual acuity of 20/100 or worse and in ranibizumab group 2/7 (28%) had a baseline vision of 20/100 or worse.

The results in Table 2 illustrate that one subject (in the ranibizumab group) showed a loss of greater than 15 letters on the ETDRS chart at 1 year. Five patients in the bevacizumab group and one patient in the ranibizumab group showed 15 letters or greater improvement in visual acuity. In the bevacizumab group, the pre-operative visual acuity was 34.9 ± 14.5 (mean $\pm$ SD) letters (range 12–60 letters, see Table 2). At the 1-year follow-up visit, the mean post-operative vision was 42.5 ± 13.7 letters, (range 15–58 letters), leading to an improvement of 7.6 letters (or 1.5 lines of vision). In the ranibizumab group, the pre-operative vision was 32.7 ± 20.9 (range 4–66 letters, see Table 2), with a mean post-operative visual acuity at 1 year of 39.0 ± 10.1 (range 30–55) letters, leading to an improvement of 6.3 letters (or 1.5 lines of vision). The difference in visual acuity change from baseline to 1-year follow-up between the two groups was 1.3 ± 14.9 (95% confidence interval 0.64–15.5) letters and was not statistically significant ($P = 0.74$).

The CMT measured by OCT showed a greater change in the ranibizumab group of $-91\,\mu$m compared with the change in thickness in the bevacizumab group of $-50\,\mu$m. The largest percent change in foveal thickness occurred during the first 3 months, during which ranibizumab showed a more robust response than bevacizumab, anatomically, to the first three injections. The mean difference in change from baseline to 1-year CMT between the two groups was 77.45 ± 150.6 (mean $\pm$ SD) and was not statistically significant ($P = 0.29$).

Figure 1 illustrates, in a line graph, the change in ETDRS letters in the bevacizumab and ranibizumab groups from baseline to 12-month follow-up. The line graphs show little difference in outcomes between the two groups at 1 year, with similar gains in letters and lines of vision on ETDRS chart. Figure 2 describes the change in central foveal thickness over the same time period. From 0 to 3 months, there is a greater improvement in central foveal thickness in the ranibizumab group compared with the bevacizumab group, and after 3 months, central foveal thickness is maintained for the remainder of the follow-up period in both groups.

Table 2 Visual outcomes at baseline and at 1 year for bevacizumab and ranibizumab for the treatment of AMD

	AGE	*ETDRS letters baseline*	*Snellen baseline*	*LogMar baseline*	*ETDRS 1 year*	*Snellen 1 year*	*LogMar 1 year*	*Letters improved*	*Lines improved*	*# Inj*
Bevacizumab										
1	57	12	20/320	1.2	54	20/40	0.3	+42	8	7
2	75	16	20/250	1.1	22	20/200	1.0	+6	1	7
3	83	18	20/200	1.0	33	20/100	0.7	+15	3	10
4	83	23	20/160	0.9	15	20/250	1.1	−8	−2	3
5	72	27	20/160	0.9	49	20/50	0.4	+21	4	9
6	66	27	20/160	0.9	58	20/32	0.2	+31	6	7
7	89	28	20/125	0.8	34	20/100	0.7	+6	1	6
8	88	35	20/100	0.7	42	20/80	0.6	+7	1	11
9	80	42	20/80	0.6	29	20/125	0.8	−13	−3	4
10	84	43	20/64	0.5	58	20/32	0.2	+15	3	9
11	83	44	20/64	0.5	35	20/100	0.7	−9	−2	8
12	82	47	20/64	0.5	52	20/50	0.4	+5	1	8
13	85	50	20/50	0.4	54	20/40	0.3	+4	1	9
14	64	52	20/50	0.4	49	20/50	0.4	−3	−1	12
15	78	60	20/32	0.2	54	20/40	0.3	−6	−1	4
Ranibizumab										
1	73	4	20/400	1.3	32	20/125	0.8	+28	6	3
2	80	18	20/200	1.0	30	20/125	0.6	+12	2	3
3	88	24	20/160	0.9	33	20/100	0.7	+9	2	5
4	78	28	20/125	0.8	30	20/125	0.8	+2	0	3
5	73	37	20/100	0.7	45	20/64	0.5	+8	2	4
6	89	52	20/50	0.4	55	20/40	0.3	+3	1	3
7	79	66	20/25	0.1	48	20/50	0.4	−18	−4	6

Table 3 Summary of visual acuity and anatomic outcomes between bevacizumab and ranibizumab treatment groups

	ETDRS vision at baseline		*ETDRS vision at 1 year*		*Lines improved*	*Letters improved*	*Change in CMT (μm)*
	Mean	*Median*	*Mean*	*Median*			
Bevacizumab							
ETDRS letters	34.9	35	42.5	49	1.5	7.6	−50
Snellen equivalent	20/100	20/100	20/70	20/50			
Ranibizumab							
ETDRS letters	32.7	28	39	33	1.5	6.3	−91
Snellen equivalent	20/110	20/125	20/80	20/100			
Statistical analysis	$P=0.8$	—	$P=0.5$	—	—	$P=0.74$	$P=0.29$

Subjects receiving bevacizumab underwent a mean of eight injections (range 3–8, median 7) over 12 months, whereas those in the ranibizumab group underwent four injections (range 3–6, median 4). The difference between these two groups was statistically significant ($P=0.001$).

There were no major ocular adverse effects reported in any subjects who completed the 1-year follow-up visit. Minor adverse events included subconjunctival haemorrhage, transient post-injection pain, and elevated IOP, controllable with topical medication, immediately after the injection period. There were no subjects with anterior chamber inflammation, vitreous haemorrhage, retinal detachment, or endophthalmitis. No systemic adverse events, such as elevated blood pressure, thromoembolic disease, or stroke were found in those who completed 1-year follow-up.

Discussion

Our study aims to offer 1-year results of a randomised, double-masked, single centre clinical trial comparing bevacizumab with the current gold standard ranibizumab. With 22 subjects and a 2:1 randomisation, early results of this trial suggest that at 1 year, visual

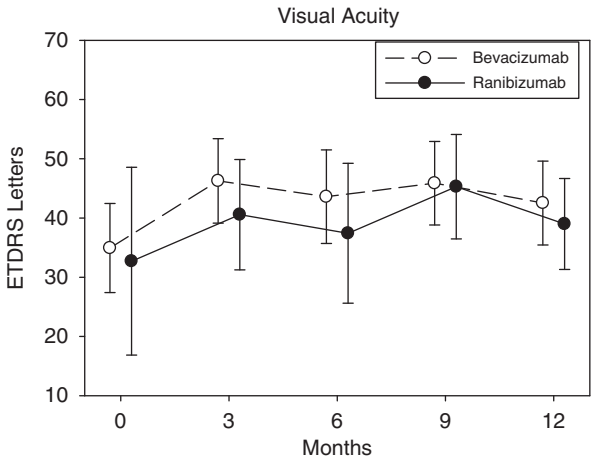

Figure 1 Visual outcomes at baseline and months 3, 6, 9, and 12. This figure compares bevacizumab with ranibizumab for the treatment of exudative age-related macular degeneration. Change in average letters seen on ETDRS chart from baseline was plotted over a period of 12 months. Both groups demonstrate a steep increase in letters gained in the first 3 months of treatment followed by a plateau. The error bars extend two SDs on both sides of the line.

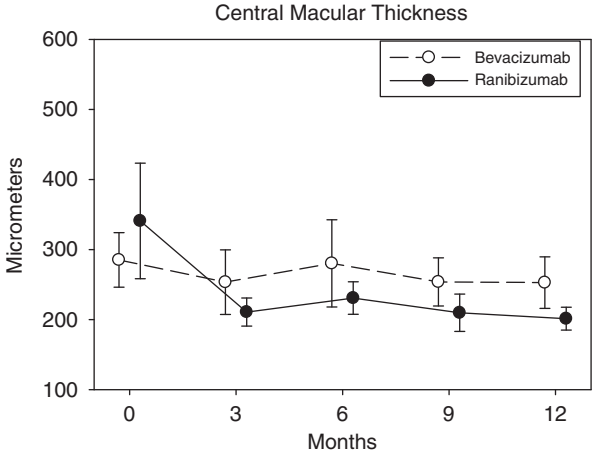

Figure 2 Change in central macular thickness (CMT) at baseline and months 3, 6, 9 and 12. This compares bevacizumab with ranibizumab for the treatment of exudative age-related macular degeneration. Ranizumab group shows the most decrease in CMT, especially in the first 3 months after treatment. This trend is not seen in bevacizumab group. The error bars extend two SDs on both sides of the line.

outcomes of bevacizumab compared with ranibizumab failed to show a difference between the two groups. Out of 15 patients, 10 (66%) in the bevacizumab group showed improvement or stabilisation of vision, whereas 6 of 7 patients (85%) in the ranibizumab group remained stable or improved. Overall mean visual outcomes showed no statistically significant difference between the two groups on two-tailed *t*-test with 95% confidence interval. Both groups had a significant gain in visual acuity in the first 3 months of the study when they received monthly injections. But from month 3 to month 12, the change in visual acuity at 3-month intervals within each group was greater in the bevacizumab group than in the ranibizumab arm.

As to anatomic outcomes, change in central foveal thickness after treatment was not significant in the two treatment arms. The results were similar to visual outcomes, where no significant difference between the two groups could be established due to the small sample size.

Patients in the bevacizumab group underwent statistically significant more injections than those in the ranibizumab group ($P = 0.001$). The reason for this is unclear and difficult to interpret. As a larger molecule with a longer half-life, one would intuitively expect patients receiving bevacizumab to undergo fewer injections. One possible reason for this may be a tachyphylactic response. Results from the Pan-American Collaborative Retina Study found, when comparing two doses of bevacizumab (1.25 *vs* 2.5 mg), that patients receiving the higher dose underwent more injections (Wu L *et al*, Comparison of two doses of primary intravitreal bevacizumab for subfoveal CNV in AMD at 24 months: Results from the Pan-American Collaborative Retina Study group. Association for Research in Vision and Ophthalmology, May 3, 2010). An alternative possibility is that patients in the ranibizumab group had a more robust and immediate response during the first 3 months than those in the bevacizumab group (Figure 2), and as OCT findings were the primary guide for re-treatment, the early and more dramatic change in foveal thickness in this treatment arm may have contributed to fewer injections over time.

Ranibizumab was the first therapy proven by several prospective, randomised, multicentre clinical trials to improve vision for patients with exudative AMD, with all lesion subtypes.[11–13] Alternatively, most of the evidence supporting the use of bevacizumab for treatment of AMD is derived from interventional case series and retrospective studies.[23–32] Bevacizumab was formulated for intravenous use by its manufacturer, and at this time, its use in the eye is entirely off-label. Hindsight has shown in retrospective reviews, non-comparative case series, and international safety surveys that bevacizumab given intravitreally at 1.25 mg appears to be safe and non-toxic to the eye, with seemingly minimal systemic and ocular adverse effects.[33–36]

The evidence to date supporting use of bevacizumab, in the treatment of AMD, uniformly lacks two key facets: (1) patient and investigator masking and (2) direct

comparison with ranibizumab (the current gold standard treatment in the United States) in a prospective manner. As far as the authors are aware, our study is the first trial to report 1-year data of a double-blinded, randomised, prospective trial comparing bevacizumab with ranibizumab. With the exception that total injections given to subjects over 1 year were significantly different between the two treatment arms, visual and anatomic outcomes at 1 year are similar to previously reported, early outcomes of this study at 6 months.[37] Further studies with a larger sample size are required to verify our results.

The strengths of this study are in its methodology. The prospective, double-blinded nature of this study helps minimise patient and investigator bias. Limitations are present, and include a small sample size and an almost entirely male patient population in a VA setting, not allowing the investigators to extrapolate these results to apply to female or non-Caucasian patients with AMD.

The socioeconomic implications in determining a difference in efficacy for the treatment of AMD are important to consider. In an environment where health care costs are soaring, comparative treatment trials will likely have a greater emphasis in the future. As the sample size in this study is small, and without power to detect a real, moderate difference in efficacy, results from this trial should be interpreted with care, and clinicians should be mindful of the limitations before contemplating changes in practice patterns. Larger comparative treatment trials are currently underway in the United States, Europe, and other parts of the world, and they will also help answer the question of safety and efficacy of bevacizumab compared with ranibizumab. In addition, results from research and development of newer anti-angiogenesis therapies, as well as more data on the effects of combination therapy, are expected to emerge soon.

Summary

What was known before

- Bevacizumab and ranibizumab are both used for the treatment of exudative age-related macular degeneration (AMD). Both drugs have been shown to be efficacious for the treatment of AMD, however, a head-to-head, randomised, double-masked clinical trial comparing these two drugs has not yet been completed.

What this study adds

- Our data failed to show a difference in visual and anatomic outcomes at 1 year. Additionally, patients in the bevacizumab group required a significantly higher number of injections than those treated with ranibizumab. As far as the authors are aware, this is the first study to describe 1-year outcomes of a prospective, randomised, double-masked clinical trial directly comparing bevacizumab with ranibizuamab.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

Design and conduct of study: MS, SN, EF, MD, and AH
Collection, management, analysis, interpretation of data: MS, SN, GA, and EA.
Preparation/review/approval of manuscript: MS, GA, EF, MD, and AH.
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