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REVIEW

Comparative Review of Ranibizumab versus Bevacizumab in the Treatment of Neovascular Age-related Macular Degeneration

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Abstract: Age-related macular degeneration (AMD) is the leading cause of visual loss in the developed World in patients over age 55. Therapeutic advances in the dry (non-exudative) form of AMD have been very modest with a protective role demonstrated for supplemental anti-oxidant vitamin therapy in patients showing high risk characteristics for future progression. In contrast, a major advance in the treatment of the wet (exudative) form of AMD occurred with the introduction of anti-angiogenic molecules targeting Vascular Endothelial Growth Factor (VEGF)—specifically, ranibizumab (Lucentis) and bevacizumab (Avastin). A review of the therapeutic effect of these drugs in wet AMD is presented with a comparison of their results.

Keywords: AMD, age-related macular degeneration, ranibizumab, bevacizumab

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness among elderly patients in developed countries.[1,2] It affects more than 1.75 million individuals in the United States. Owing to the rapid aging of the US population, this number will increase to almost 3 million by 2020.[1] Visual acuity loss in patients with AMD can be secondary to atrophy of the retinal pigment epithelium (RPE), so called "dry AMD", or secondary to newly formed abnormal blood vessels growing under the retina, choroidal neovascularization (CNV), or "wet AMD".

Vascular Endothelial Growth Factor (VEGF) is a signaling protein important in vasculogenesis and angiogenesis. The gene for VEGF is on chromosome 6p12. VEGF binds to extracellular vascular endothelial growth factor receptors (VEGFR1 and VEGFR2), which are a tyrosine kinase family receptor. It is the binding to VEGFR2 that is important in ocular neovascularization. VEGF stimulates vascular endothelial cell growth (i.e. proliferation) and survival. VEGF also stimulates hyper-permeability of vessels and has been shown to play a major role in the development and persistence of CNV in wet AMD.[3–6]

Mechanism of Action/Metabolism and Pharmaco-Kinetic Profile

Ranibizumab (Lucentis, Genentech) is a 48 kDa Fab fragment of a recombinant humanized IgG1 kappa monoclonal antibody that binds to VEGF-A—specifically, $VEGF_{110}$. The binding of ranibizumab with VEGF-A prevents VEGF-A from interaction with VEGF-A receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells reducing endothelial cell proliferation, leakage and new blood vessel formation. It was approved by the FDA for use in treating patients with Age-related Macular Degeneration in June, 2006.

Cynomolgus monkey studies[7] showed a half-life ($t½$) for ranibizumab in the vitreous, aqueous humor and retina equal to 2.6 days. The peak serum concentration was 6 hours after intravitreal injection, and the overall serum ranibizumab concentration after intravitreal administration was >1500-fold lower than the corresponding vitreous concentration. The serum $t½$ was approximately 3.5 days, which was comparable to the half life in the ocular compartments. Similar results for the vitreous $t½$ (2.88 days) were seen in Dutch-belted rabbit eyes.[8] In the rabbit eyes an intravitreal concentration of >0.1 µg/ml was still measurable at 29 days. No ranibizumab was detected in the serum or the fellow eye in this study.

Bevacizumab (Avastin, Genentech) is similar to ranibizumab in being a recombinant humanized IgG1 monoclonal antibody that binds to the active forms of VEGF-A. It differs from ranibizumab in being the complete IgG molecule, and not the Fab fragment only, with a molecular weight equal to 149 kDa and binds all isoforms of VEGF. It was the first antiangiogenic drug commercially available. Bevacizumab was approved by the Food and Drug Administration (FDA) in February 2004 for use in metastatic colorectal cancer when used with standard chemotherapy treatment. It subsequently was approved for use in combination with other chemotherapeutic agents in treating lung cancer (2006) and breast cancer (2008).

Assessment of bevacizumab metabolism in rabbits following a single systemic dose of ^{125}I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. Cynomogulus monkey[9] studies show that ^{125}I-bevacizumab is found in the inner retinal layers within 1 day of administration, and subsequently, is found in the outer retinal layers. Bevacizumab was also found in the choroid on day 1. The systemic metabolism and elimination of bevacizumab is similar to endogenous IgG, primarily via proteolytic catabolism throughout the body, and does not rely primarily on elimination through the kidneys and liver. The $t½$ is consistent with the terminal elimination half-life for human endogenous IgG, which is 18 to 23 days. Dutch-belted rabbit studies[10] following intravitreal bevacizumab injection showed a $t½$ of 4.32 days with a vitreous concentration >10 µg/ml at 30 days. In contrast to ranibizumab, bezacizumab was detected in the serum with a peak concentration of 3.3 µg/ml, at 8 days, and a serum $t½$ of 6.86 days. Small concentrations of bezacizumab were also found in the fellow eye.

In vitro studies[11] utilizing porcine retina and RPE showed both ranibizumab and bevacizmab being

equally effective in neutralizing VEGF at clinical doses. Of note, the study found ranibizumab to be more efficient at neutralizing VEGF at lower doses.

Clinical Studies/Efficacy

Ranibizumab completed phase III FDA clinical trials for the treatment of CNV in exudative AMD, with the MARINA and ANCHOR studies leading to FDA approval. However, several other trials (e.g. the FOCUS, Pier, and PrONTO) investigated the efficacy of the drug for this indication using different treatment criteria.

The MARINA study[12] was a multicenter, randomized, double-masked, sham-controlled trial comparing ranibizumab (0.3 mg or 0.5 mg) to sham injections in patients with minimally classic or occult CNV secondary to AMD. 716 patients were enrolled in the study. The study had very limited inclusion criteria. The patient's visual acuity ranged from 20/40 to 20/320, and the fluorescein angiogram had to demonstrate a subfoveal neovascular complex. The primary end point was loss of <15 letters (3 lines) of visual acuity on an ETDRS visual acuity chart. At 24 months, 92% of the patients given 0.3 mg of ranibizumab and 90% of patients given 0.5 mg lost fewer than 15 letters, as compared with 52.9% of patients receiving sham injections ($P < 0.001$). Visual acuity actually improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the sham-injection group ($P < 0.001$). Mean increases in visual acuity were 5.4 letters in the 0.3-mg group and 6.6 letters in the 0.5-mg group, as compared with a decrease of 14.9 letters in the sham-injection group ($P < 0.001$). The benefit in visual acuity was maintained throughout 24 months.

The Anchor Study[13] was a multicenter, randomized, double-masked, active-treatment-controlled clinical trial comparing ranibizumab with verteporfin photodynamic therapy (PDT) in predominantly classic CNVM. 423 patients were enrolled in the study and randomized to verteporfin PDT therapy plus sham intravitreal injections, or monthly intravitreal ranibizumab (0.3 or 0.5 mg) injections plus sham PDT treatments. The primary end point was again loss of <15 letters of visual acuity. At 24 months 90% of patients treated with ranibizumab injections lost <15 letters of vision (3 lines) compared with 65.7% of veteporfin PDT patients ($P < 0.0001$). 34.0% of patients receiving the 0.3 mg dose of ranibizumab and 41.0% of patients receiving the 0.5 mg dose gained ≥15 letters (vs. 6.3% of PDT group); on average, VA was improved from baseline by 8.1 letters (0.3 mg dose) and 10.7 letters (0.5 mg dose) compared to a mean decline of 9.8 letter s in the PDT group.

The FOCUS[14,15] trial compared monthly ranibizumab injections in combination with verteporfin PDT therapy to verteporfin PDT therapy alone. 162 patients were enrolled in the study. All patients received verteporfin PDT therapy at day 1. Patients were then randomized to sham injections with continued PDT therapy or monthly ranibizumab injections and PDT therapy every 3 months as needed. 88% of ranibizumab + PDT patients had lost <15 letters from baseline versus 75% for PDT alone ($P < 0.05$). 25% of ranibizumab + PDT patients had gained ≥15 letters; only 7% of patients treated with PDT alone gained ≥15 letters ($P < 0.05$). The two treatment arms differed by 12.4 letters in mean VA change ($P < 0.05$). The ranibizumab + PDT patients exhibited less lesion growth and greater reduction of CNV leakage and subretinal fluid accumulation, and required fewer PDT retreatments than PDT-alone patients (mean = 0.4 vs. 3.0 PDT retreatments).

The PIER[16] study was a Phase IIIb, multicenter, randomized, double-masked, sham injection-controlled trial which looked at a loading dose of ranibizumab (consisting of monthly doses for the first 3 months) followed by subsequent doses every quarter. The aim of this study was to see if patients required monthly injections, or if the number of injections could be reduced. 184 patients were randomized 1:1:1 to receive sham injection, 0.3 mg ranibizumab, or 0.5 mg ranibizumab. In contrast to what was seen previously all arms of the study, on average, lost visual acuity. The sham injection group lost an average 16.3 letters; the 0.3 mg group, 1.6 letters; the 0.5 mg group, 0.2 letters. Furthermore, the treatment effect declined in the ranibizumab groups with quarterly dosing. At three months the mean changes from baseline visual acuity were gains of 2.9 and 4.3 letters for the 0.3 mg and 0.5 mg doses, but at 1 year the gains were lost.

The PrONTO study[17] was a phase I/II trial with an OCT-guided, variable dosing regimen of monthly intravitreal ranibizumab (0.5 mg) for 3 months

followed by intravitreal ranibizumab as needed based on OCT-defined retreatment criteria in 40 patients. At 1 year, 95% of treated patients had lost less than 15 letters of visual acuity; 35% (14/40) of treated patients had gained at least 15 letters of visual acuity, and the mean change in visual acuity was +9.3 letters for treated patients. The mean number of injections over the course of the year was 5.6 (range 3–13). These results demonstrated that successful visual and morphologic outcomes can be achieved by using visual acuity and OCT imaging to guide the need for retreatment.

The use of intravitreal bevacizumab was first reported in 2005 by Rosenfeld et al[18] in a patient with recurrent neovascular AMD who had previously failed veteporfin PDT with intravitreal triamcinolone acetonide and intravitreal pegaptanib therapy. The patient had resolution of visual distortion and subretinal fluid after treatment. A review of the literature reveals 3 randomized clinical trials involving intravitreal bevacizumab treatment for AMD.[19–21] These 3 trials, while being prospective and randomized, lacked masking of the treating physician and subject.

Bashshur et al[19] randomized 64 patients with predominantly classic CNV secondary to AMD to receiving intravitreal bevacizumab (n = 32) or verteporfin PDT (n = 32). They reported 6 months of data with a baseline best corrected snellen visual acuity of 20/119 in the intravitreal bevacizumab group and 20/108 in the verteporfin PDT group ($P = 0.5$). At 6 months, the best corrected snellen visual acuity in the bevacizumab treated group improved to 20/68 and the verteporfin PDT group declined to 20/143 ($P < .001$).

Lazic et al[20] randomized 165 patients to receive either a single verteporfin PDT session (n = 55), a single injection of intravitreal bevacizumab (n = 55) or their combination (n = 55). Best-corrected VA measured at baseline showed no significant differences between the 3 groups ($P = 0.32$). At 1-month follow-up, significant improvements in best-corrected VA were observed in the 3 groups. The largest improvement was noted in the group with combined treatment (0.246 logMAR, approx 12.3 letters); this improvement was significantly better than the improvements in the intravitreal bezacizumab group (0.171 logMAR, approx 8.6 letters) and the PDT alone group (0.049 logMAR, approx 2.5 letters). All these differences were statistically significant ($P < 0.001$) At 3-months follow-up, significant improvements in comparison with baseline were still observed in the intravitreal bevacizumab and the combined groups, as opposed to a slight worsening noted in the PDT group. In the intravitreal bevacizumab group, the improvement at 3-months follow-up was less than half of the improvement observed at 1 month, whereas it remained about the same in the combined group (0.223 logMAR). The change from baseline at the 3-month follow-up in the combined group was significantly greater than that observed in the 2 other groups ($P < 0.001$).

Lastly, Weigert et al[21] randomized 28 patients to intravitreal bevacizumab 1 injection per month for 3 months, then as needed (based on OCT findings) or verteporfin PDT + intravitreal triamcinolone acetonide (one treatment at baseline, then every 3 months based on fluorescein angiography). The intravitreal bevacizumab group gained on average 11 letters over the month study, while visual acuity remained unchanged in the verteporfin PDT + intravitreal triamcinolone acetonide group. This difference was statistically significant ($P = 0.03$).

While there are only 4 short term, relatively small randomized prospective clinical trials in the literature, all of which showing a significant positive treatment effect of intravitreal bevacizumab compared to PDT, there are multiple prospective[22–31] and retrospective[32–45] studies emphasizing the beneficial effect of intravitreal bevacizumab for the treatment of exudative AMD in the literature. All of these studies demonstrated clinically significant improvement in mean visual acuity, reduction in fluorescein angiography leakage and central retinal thickness on OCT, and resolution of macular edema in patients treated with intravitreal bevacizumab. Schouten et al[46] reviewed and compiled all trials from the literature and evaluated the combined efficacy of bevacizumab (1435 patients from 26 articles) in treating neovascular AMD. They found the weighted mean gain in visual acuity was 12.8 letters (range 11–14) for patients treated with intravenous bezacizumab, and a weighted mean gain of 8.6 letters (range 2–26) of visual acuity in patients treated with intravitreal bevacizumab. Caution must be taken when evaluating the results of this meta-analysis as patient population, inclusion/exclusion criteria, and study design differed in each study.

Safety

When looking at the use of intravitreal ranibizumab and bevacizumab in the treatment of neovascular

AMD, it is important to look at both the ocular and systemic side effects of these medicines. While there have been many efficacy studies involving ranibizumab, there have been few safety trials.

The ocular side effects of both intravitreal ranibizumab and bevacizumab were similar. The incidence of serious ocular adverse events was low. The ocular side effects are more a result of the procedure, i.e. intravitreal injection, than the medicine itself. The most common ocular complaints in patients receiving ranibizumab in randomized clinical trials were transient subconjunctival hemorrhage, minor intraocular inflammation, and transient elevated intraocular pressure.[12,13,47] The more serious ocular complications, such as retinal detachment and iatrogenic cataract formation, were less than 1% with the rate of infectious endophthalmitis, 0.5%–1.6%. Similar results were seen in compilation of patients treated with intravitreal bevacizumab,[48] and mirror the results seen in other studies employing an intravitreal injection. There have been reports in the literature of a higher incidence of retinal pigment epithelial (RPE) rips in patients treated with bevacizumab.[49]

However, of greater concern was the incidence of systemic adverse events. The phase II and III studies of ranibizumab showed a dose-dependent incidence of systemic hypertension and thromboembolic events. None of these studies showed a statistically significant difference between these rates in the treated and controlled patients, but none of these studies were powered to show this difference. Recently Ueta, et al[50] published a letter in which they combined the number of thromboembolic events from the MARINA, ANCHOR, and FOCUS studies. In meta-analysis of this larger population they found a statistically significant higher incidence of cerebrovascular accidents (CVA) in patients treated with ranibizumab than with sham injection ($-P = 0.045$; OR, 3.24; 95% CI, 0.96–10.95). There was no associated increased rate of myocardial infarction in patients treated with ranibizumab ($-P = 0.193$).

As noted previously, bevacizumab has undergone FDA approval as an adjuvant therapy for systemic use in metastatic cancer. Arterial thromboembolism (both myocardial infarction and stroke), hypertension, gastrointestinal perforation, poor wound healing, and bleeding have been associated with intravenously administered bevacizumab in patients with colorectal and lung cancer.[51,52] It should be noted though that the systemic dose of bevacizumab ranges from 5–15 mg/kg, while the intraocular dose is 1–2.5 mg. Wu et al[45] reported a low systemic complications rate after intravitreal bevacizumab. The rate of myocardial infarction, CVA, systemic hypertension and death ranged from 0.4%–0.59%. A large registry of patients (5228) receiving multiple injections (7113) of bevacizumab showed a very low rate of ocular complications, as well as systemic adverse events.[53] This may be misleading, as patients with a history of myocardial infarction and stroke are not included in these series and none of these studies were prospective or powered to reveal such serious systemic complications. Concern over the potential systemic adverse effects of these anti-VEGF drugs has been expressed by Tezel and Kaplan.[54]

Patient Preference/Place in Therapy

Generally patients do not have a significant preference of one drug over the other although most patients express a preference for fewer intraocular injections, as long as the final visual results are the same.

It is important before starting treatment that all patients understand that one treatment (bevacizumab) is off-label use, and that ranibizumab is the FDA approved therapy. It is also important that patients are aware of the potential adverse events associated with both drugs. Another important factor in patient decision is cost. Medicare will reimburse for both ranibizumab and bevacizumab in the treatment of neovascular AMD, but without supplemental insurance, the co-pay for ranibizumab can be costly to the patient. Genentech has programs to assist patients with payment for ranibizumab called Lucentis Access Solutions.

Another factor in deciding which treatment to use is the duration of effect. Bakri, et al[8,10] showed that bevacizumab's half life in the vitreous cavity is 150% greater than that of ranibizumab in rabbits. Clinical experience in humans suggests a similar difference, and most retina specialists inject ranibizumab every 4 weeks and bevacizumab every 6 weeks, at least at the onset of treatment. In a prospective study Bashur et al[31] reported that patients needed an average of 3.4 injections over 12 months on an OCT/visual acuity driven re-injection protocol using bevacizumab. With a similar re-injection protocol Fung, et al[17] reported

patients needed 5.6 injections over 12 months with ranibizumab. This is a significant difference because of the potential increase in adverse events with increased intraocular injections, as well as the burden on elderly patients caused by multiple repeat doctors' visits.

Conclusions

Anti-VEGF therapy, specifically ranibizumab and bevacizumab, has significantly changed the approach to treatment and expected outcomes of neovascular AMD. Patients can now reasonably expect to gain visual acuity and quality of life with these treatments. Ranibizumab remains the FDA approved medicine of treatment, backed by strong phase III clinical data, but a growing body of literature and experience suggests that bevacizumab is equally effective and safe in treating neovascular AMD. The NEI is currently funding the Comparison of Age-related macular degeneration Treatment Trial (CATT) to study whether ranibizumab or bevacizumab is more effective in treating neovascular AMD. The CATT study will also look at whether patients need to be on a fixed monthly dose, or whether treatment directed by OCT/visual acuity is as effective. This study will further shape the treatment of neovascular AMD in the United States.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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