Intravitreal Bevacizumab vs Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration

Ziad F. Bashshur, MD; Alexandre Schakal, MD; Rola N. Hamam, MD; Christelle P. El Haibi, MS; Rola F. Jaafar, MS; Baha’ N. Noureddin, MD

Objective: To compare verteporfin photodynamic therapy (PDT) with intravitreal bevacizumab for management of choroidal neovascularization (CNV) associated with age-related macular degeneration.

Methods: Patients with predominantly classic CNV were prospectively randomized to receive standard PDT or intravitreal bevacizumab injections (2.5 mg). Best-corrected visual acuity (BCVA) measured by Snellen charts, central retinal thickness by optical coherence tomography, and greatest linear dimension of the CNV by fluorescein angiography were compared between the groups at baseline and at 3 and 6 months. Main outcome measures were stability or improvement in BCVA, decrease in central retinal thickness, and stability in greatest linear dimension.

Results: Mean baseline BCVA, central retinal thickness, and greatest linear dimension were not statistically different between the bevacizumab (n=32) and PDT (n=30) groups. Mean central retinal thickness was significantly better at 3 and 6 months in the bevacizumab group vs the PDT group (P=.04 and P=.002, respectively). At 3 months, mean BCVA and greatest linear dimension were not significantly different between the 2 groups. At 6 months, mean BCVA and greatest linear dimension were significantly better in the bevacizumab group (P<.001 and P=.02, respectively).

Conclusion: During 6 months, intravitreal bevacizumab was superior to PDT in controlling predominantly classic CNV in age-related macular degeneration. Additional randomized clinical trials are necessary to determine if this benefit will remain with longer follow-up.

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The study was approved by the institutional review board at the American University of Beirut Medical Center and was in adherence to the tenets of the Declaration of Helsinki. Starting September 2005, eyes with predominantly classic CNV that met adherence to the tenets of the Declaration of Helsinki. Starting the American University of Beirut Medical Center and was in the management of neovascular AMD. This study is a randomized, prospective, interventional case series comparing, during a period of 6 months, intravitreal bevacizumab with PDT for the management of predominantly classic CNV in AMD.

METHODS

The study was approved by the institutional review board at the American University of Beirut Medical Center and was in adherence to the tenets of the Declaration of Helsinki. Starting September 2005, eyes with predominantly classic CNV that met the eligibility criteria summarized in Table 1 were enrolled in our study. Patients were randomized into the PDT or bevacizumab groups (1:1 ratio). Power calculation indicated that a sample size of 30 in each group was necessary to obtain statistical significance with 80% power and within a 95% confidence interval ($\alpha = 0.05$). The procedure and treatment options were explained thoroughly to patients who then signed a study consent form. Patients receiving intravitreal bevacizumab were informed of the off-label use of the medication.

Baseline workup included best-corrected visual acuity (BCVA) using Snellen acuity charts, slitlamp examination of the anterior segment, dilated fundus examination, fluorescein angiography, and optical coherence tomography (OCT). The greatest linear dimension of the CNV was determined using fluorescein angiography and the incorporated measuring software (Imagine Net 2000; Topcon, Tokyo, Japan). One millimeter central retinal thickness was measured using OCT (Stratus OCT, Carl Zeiss Meditec, Dublin, California). Macular retinal mapping was created from 6 consecutive slow diagonal 6-mm scans that intersected at the fovea. Retinal thickness, the distance between the vitreoretinal interface and the anterior surface of the retinal pigment epithelium, was measured automatically by the OCT software. Central retinal thickness and greatest linear dimension measurements were interpreted and recorded by an independent observer who was masked to the type of treatment.

Patients randomized into the PDT group were treated with PDT using verteporfin (Visudyne; Novartis Ophthalmics, Basel, Switzerland). A 30-mL solution containing 6 mg of verteporfin per square meter of body surface area was infused for 10 minutes followed by activation with a 689-nm diode laser at an irradiance of 600 mW/cm² 5 minutes later for 83 seconds producing a fluence of 50 J/m². Treatment was applied to a spot size 1000 µm greater than the greatest linear dimension. Best-corrected visual acuity, slitlamp examination of the anterior segment, dilated fundus examination, fluorescein angiography, and OCT were performed at 3- and 6-month follow-up visits. Photodynamic therapy was repeated if leakage from CNV was present on fluorescein angiography.

Bevacizumab (Avastin, Genentech, San Francisco, California) was prepared by the hospital pharmacy into 1-mL tuberculin syringes and stored at 2°C to 8°C based on protocols described in previous studies. Eyes randomized to receive intravitreal bevacizumab were prepared with povidone iodine, 5%, solution and anesthetized with subconjunctival lidocaine, 2%. Using a 30-gauge needle, 2.5 mg of bevacizumab was injected intravitreally through the pars plana 3.5 mm from the limbus. Paracentesis was performed 20 minutes after the injection if intraocular pressure was greater than 25 mm Hg or if the optic nerve head was not adequately perfused. Patients unpatched the eye the next day and applied topical ciprofloxacin (Ciloxan; Alcon, Puurs, Belgium) 3 times a day for 3 days. Patients were examined at 1 week after an injection and then every month for 6 months. At each visit, BCVA was measured and slitlamp examination of the anterior segment and dilated fundus examination were performed. Optical coherence tomography and fluorescein angiography were repeated every month and every 3 months, respectively.

All patients in the bevacizumab group had blood pressure measurements at every visit. Complete blood count and urinalysis were taken at baseline and 1 week after any injection. Patients were observed for any systemic thromboembolic events or ocular complications.

The induction phase of bevacizumab treatment started with the first injection and spanned 1 to 2 months depending on the number of injections the patient required. The need for retreatment after the first injection was based on the presence of subretinal fluid or cystic maculopathy as determined by OCT. As such, if there was total resolution of subretinal fluid and cystic maculopathy on OCT (ie, dry lesion) 1 month after the first injection, then the patient was followed up monthly. If there was persistent subretinal fluid or cystic maculopathy, then a second injection was given, and if needed, a third injection was given 1 month after the second. No more than 3 consecutive injections were given in the induction phase even if the lesion was not totally dry.

After the induction phase, patients were observed with monthly OCT. We assumed that determining worsening subretinal fluid and especially cystic maculopathy on OCT images could be somewhat subjective in a lesion that was not previously dry. We considered that an increase in central retinal thickness measured by OCT would more objectively reflect an increase in subretinal fluid and cystic maculopathy in such lesions. Therefore, reinjection during follow-up was based on the following criteria: (1) recurrence of subretinal fluid or cystic maculopathy on OCT in a previously dry lesion; (2) increase in central retinal thickness by more than 100 µm, especially for lesions that were not totally dry; (3) a new area of classic CNV; (4) new hemorrhages; or (5) decrease of 2 or more lines in highest recorded BCVA associated with increased leakage on fluorescein angiography or OCT. Photodynamic therapy was considered if the treating ophthalmologist judged that bevacizumab treatment was not working of the patient.

Main outcome measures were stability or improvement in BCVA, decrease in central retinal thickness, and stability in greatest linear dimension. Snellen acuities were converted to logarithm of the minimum angle of resolution units to facilitate sta-

Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>Subfoveal predominantly classic CNV in AMD</td>
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<tr>
<td>Presence of subretinal fluid, cystic maculopathy, or central retinal thickness</td>
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<tr>
<td>250 µm on OCT</td>
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<tr>
<td>Best-corrected visual acuity between 20/50 and 20/200</td>
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<tr>
<td>Submacular hemorrhage not involving the fovea</td>
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<tr>
<td>Submacular scarring not involving the fovea</td>
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<tr>
<td>Choroidal neovascular membrane &lt;5400 µm in greatest linear dimension</td>
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<td>Ability to understand and sign consent form</td>
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<table>
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<tr>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Prior treatment for CNV</td>
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<tr>
<td>Corneal, lenticular, or vitreous opacification that prevents good quality angiograms</td>
</tr>
<tr>
<td>or OCT</td>
</tr>
<tr>
<td>History of uveitis</td>
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<tr>
<td>Diabetic retinopathy</td>
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<td>Other ocular conditions that affect vision</td>
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Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; OCT, optical coherence tomography.
A total of 64 patients, equally divided between the 2 groups, were recruited for this study. Two patients in the PDT group were lost to follow-up shortly after the first treatment and were not included. By the end of the study, 32 patients in the bevacizumab group and 30 patients in the PDT group completed 6 months of follow-up. The mean age was 75.4 and 74.6 years in the bevacizumab and PDT groups, respectively (P = .67). There were 18 women and 14 men in the bevacizumab group, while there were 13 women and 17 men in the PDT group.

Patients in both groups had no systemic or ocular complications. There was no remarkable change in blood pressure in the bevacizumab group at any follow-up visit. Similarly, there was no change in the urinary analysis or complete blood count after any bevacizumab injection.

The PDT group received a mean 2.3 treatments during 6 months vs a mean 2.4 injections in the bevacizumab group (P = .4). In the PDT group, 18 eyes (60.0%) required 3 treatments, 10 eyes (33.3%) required 2 treatments, and 2 eyes (6.7%) received 1 treatment during the 6 months. Patients in the bevacizumab group received a mean 1.6 injections in the induction phase and a mean 0.8 injections during follow-up. In the induction phase, 6 eyes (18.75%) received 3 consecutive injections, 6 eyes (18.75%) received 2 consecutive injections, and 20 eyes (62.5%) received 1 injection. The mean time between the last injection in the induction phase and the need for retreatment was 3.2 months. During follow-up, 4 eyes (12.5%) received 2 injections, 20 eyes (62.5%) received 1 injection, and 8 eyes (25.0%) did not require any injections. During 6 months, 18 of 32 (56.3%) eyes required fewer than 3 bevacizumab injections.

Mean baseline BCVA was 20/119 in the bevacizumab group and 20/108 in the PDT group (P = .50). At 3 months, mean BCVA was 20/89 in the bevacizumab group and 20/118 in the PDT group (P = .09). At 6 months, mean BCVA had improved to 20/68 in the bevacizumab group, while mean BCVA was 20/143 in the PDT group (P < .001). By 6 months, 6 of 32 (18.8%) eyes in the bevacizumab group had 20/40 or better BCVA, while no PDT eyes achieved this visual acuity (P = .02). Five of 30 (16.7%) eyes in the PDT group ended with a BCVA worse than 20/200, while no eyes in the bevacizumab group did (P = .02). Table 2 summarizes the change in mean BCVA over time and Table 3 presents the distribution of visual acuity at baseline and 6 months for both groups. At the conclusion of the study, 32 of 32 eyes in the bevacizumab group and 22 of 30 (73.3%) eyes in the PDT group avoided losing more than 3 lines of BCVA (P = .002), while 16 eyes (50.0%) in the bevacizumab group had improvement in BCVA vs 5 (16.7%) in the PDT group (P = .007).

Baseline central retinal thickness was 352 µm and 354 µm in the bevacizumab and PDT groups, respectively (P = .92). At 3 months, central retinal thickness decreased to 262 µm in the bevacizumab group and 300 µm in the PDT group (P = .04). At 6 months, central retinal thickness decreased further to 241 µm in the bevacizumab group and 292 µm in the PDT group (P = .002). Table 4 presents the change in mean central retinal thickness of both groups at baseline and at 3 and 6 months. At 3 months, 22 of 32 (68.8%) eyes in the bevacizumab group had a dry lesion vs 8 of 30 (26.7%) eyes in the PDT group (P = .001). At 6 months, 23 eyes (71.9%) in the bevacizumab group and 15 eyes (50.0%) in the PDT groups had dry lesions (P = .12).

The mean baseline greatest linear dimension was 2801 µm in the bevacizumab group and 2366 µm in the PDT group (P = .79). By 3 months, the mean greatest linear dimension was 2665 and 2871 µm in the bevacizumab and PDT groups, respectively (P = .46). At 6 months, mean greatest linear dimension had improved to 2593 µm in the bevacizumab group, while mean greatest linear dimension in the PDT group was 3377 µm (P = .02).

The first evidence of recurrence in the bevacizumab group was subretinal fluid or intraretinal cystic changes on OCT but this was considerably less than baseline. Despite this recurrence on OCT, late leakage on fluorescein angiography was generally absent or sometimes much milder than baseline.

Table 2. Mean Visual Acuity for the Bevacizumab and Photodynamic Therapy (PDT) Groups at Baseline and at 3 and 6 Months

<table>
<thead>
<tr>
<th>Time of Measurement</th>
<th>Bevacizumab Group</th>
<th>PDT Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20/119</td>
<td>20/108</td>
<td>.50</td>
</tr>
<tr>
<td>3 mo</td>
<td>20/89</td>
<td>20/118</td>
<td>.09</td>
</tr>
<tr>
<td>6 mo</td>
<td>20/68</td>
<td>20/143</td>
<td>&lt;.001</td>
</tr>
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</table>

Table 3. Distribution of Visual Acuity for the Bevacizumab and Photodynamic Therapy (PDT) Groups at Baseline and 6 Months

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Bevacizumab Group, No. (%) (n = 32)</th>
<th>PDT Group, No. (%) (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20/40 or better</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20/50 to 20/100</td>
<td>17 (53.1)</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td>20/200</td>
<td>15 (46.9)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>&lt;20/200</td>
<td>0</td>
<td>0</td>
</tr>
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The main aim of this study was to compare intravitreal bevacizumab with PDT for management of predominantly classic CNV in neovascular AMD. Predominantly classic CNV cases were selected in this study because it was more meaningful to compare intravitreal bevacizumab to PDT in the management of the lesion subtype that is most responsive to PDT. Best-corrected visual acuity, central retinal thickness, and greatest linear dimension were used to gauge disease control. During 6 months, intravitreal bevacizumab was superior to PDT in controlling the CNV. Generally, the difference was more significant after 6 months than 3 months. It seems that anti-VEGF therapy causes rapid resolution of edema and subretinal fluid but does not completely eradicate the CNV lesion, which probably lays dormant as long as VEGF is inhibited. Once well established, CNV may not be eliminated with suppression of VEGF alone.19 This may explain why we did not observe a rapid reduction in greatest linear dimension with bevacizumab vs PDT.

Photodynamic therapy can cause temporary occlusion of the choriocapillaris in the area of treatment, increased release of VEGF, early increase in subretinal fluid, and possible damage to the retinal pigment epithelium.20-22 Although PDT induces closure of the CNV soon after treatment, it does not address the state of increased VEGF in neovascular AMD, which allows reproliferation of the CNV.25-27 Therefore, repeated treatments may lead to cumulative damage to the retina and choriocapillaris, which eventually may affect visual acuity. Recent studies have shown that intravitreal bevacizumab does not seem to be toxic to the retina or retinal pigment epithelium.28,31 Bevacizumab may deprive the CNV of VEGF, which causes decreased vascular permeability and inhibits progression of immature vessels without having a direct effect on surrounding tissue in the short term.22,23 It is not possible from this study to predict if prolonged VEGF inhibition will eventually cause damage to the retina or the normal retinal and choroidal vessels.

Patients in the bevacizumab group had monthly follow-up with OCT to determine the need for further treatment. Recurrence was noted on OCT before any changes occurred on fluorescein angiography. There are some small, nonrandomized studies that incorporated OCT with PDT treatment.14-17 However, our purpose was to compare intravitreal bevacizumab with standard-care PDT for management of predominantly classic CNV. This is why treatment and follow-up in the PDT group were based on recommendations from major studies, most notably the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy studies.6-8

A second aim of this study was to examine the efficacy of intermittent OCT-guided bevacizumab injections. This study showed that during the induction phase, the CNV was dry in 81.3% of eyes after the first or second injection (mean 1.6 injections), and this treatment benefit seemed to last for a mean 3.2 months. Reinjectons were done when there was an early recurrence on OCT, making it unnecessary to resort to multiple consecutive injections once the lesion was dry. As a result, 87.5% of eyes required fewer than 2 injections (mean, 0.8) during follow-up. Minimizing the number of injections may reduce potential ocular or systemic adverse effects of prolonged and constant VEGF inhibition.

The ability of bevacizumab to cross the retina has been the subject of some speculation. Based on previous animal studies, it was assumed that the bevacizumab molecule was too large to cross all the retinal layers to reach the subretinal space.28 However, a recent study showed that bevacizumab crossed into the subretinal space in the rabbit retina.30 Moreover, clinical data from previous studies16-19 and this study seem to support the fact that intravitreal bevacizumab can cause regression of CNV and reduction in vascular permeability.

An intravitreal dose of 2.5 mg (0.25 g/L) of bevacizumab was well tolerated and no postinjection inflammatory response was noted. This is compared with ranibizumab, which has a maximal tolerated dose of 0.5 mg (0.1 g/L).36 One possibility is that ranibizumab can be more immunogenic than bevacizumab. As bevacizumab is a full-length antibody, the Fc fragment can interact with immune effector cells, but this may actually cause an inhibitory effect.40 Nevertheless, the dose of intravitreal bevacizumab used in this study was twice that of other studies.18,19 The purpose for such a higher dose was to allow a greater concentration of bevacizumab to penetrate the retina. It was also hoped that the longer half-life of bevacizumab41 and larger dose may allow a more prolonged inhibition of VEGF and decrease the frequency of reinjections.

There are several potential ocular and systemic complications related to intravitreal bevacizumab injections. Systemic adverse effects from intravenous use of bevacizumab include increased risk of thromboembolic events, hypertension, epistaxis, hemoptysis, proteinuria, delayed wound healing, and impaired reproductive function.42 The dose in intravitreal injections is several magnitudes smaller than the systemic dose, and direct intraocular use may reduce systemic adverse effects and allow direct targeting of the CNV. However, there is the potential for acute vision loss, ocular vascular occlusions, retinal pigment epithelial tears, subretinal hemorrhage, ocular toxicity, and inflammation.43 There are also risks that can be encountered from any kind of intravitreal injection, including endophthalmitis, retinal detachment, vitreous hemorrhage, corneal abrasions, and lens injury.43 In this study, no ocular or systemic adverse effects were noted after several injections during a period of 6 months.

In conclusion, intravitreal bevacizumab can be used to manage predominantly classic CNV in AMD. It may

### Table 4. Mean Central Retinal Thickness for the Bevacizumab and Photodynamic Therapy (PDT) Groups at Baseline and at 3 and 6 Months

<table>
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<th>Time of Measurement</th>
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<th>Bevacizumab Group</th>
<th>PDT Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>354</td>
<td>352</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>262</td>
<td>300</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>241</td>
<td>292</td>
<td>.002</td>
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even be superior to PDT in the short term. Another potential benefit for intravitreal bevacizumab for treatment of AMD is the relatively low cost. In this study, the mean cost of verteporfin for a period of 6 months was $3450 vs $160 for bevacizumab. As far as we are aware, this is the only randomized, prospective controlled case series comparing PDT with intravitreal bevacizumab for the management of neovascular AMD. However, this study has many shortcomings. Most notable are the limited follow-up, small number of patients, and nonstandard re-
fraction. Additional, larger, randomized clinical trials are necessary to determine the efficacy and safety of intravitreal bevacizumab in the long-term treatment of neovascular AMD. Issues of the most appropriate dose and treatment interval need to be addressed.

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Author Contributions: The principal investigator Dr Bashshur had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

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