Comparing Outcomes in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration Treated with Two Different Doses of Primary Intravitreal Bevacizumab: Results of the Pan-American Collaborative Retina Study Group (PACORES) at the 12-Month Follow-up

Lihteh Wu1, J. Fernando Arevalo2, Mauricio Maia3, Maria H. Berrocal4, Juan Sanchez2, and Teodoro Evans1, for the Pan-American Collaborative Retina Study Group (PACORES)

1Instituto de Cirugía Ocular, San Jose, Costa Rica; 2Retina and Vitreous Service, Clinica Oftalmológica Centro Caracas, Caracas, Venezuela; 3Universidade Federal de São Paulo, Departamento de Oftalmologia, Instituto da Visão, São Paulo, Brazil; 4University of Puerto Rico, San Juan, Puerto Rico

Abstract

Purpose: To compare the total number of injections and the anatomic and best-corrected visual acuity (VA) response after injecting 1.25 or 2.5 mg of bevacizumab as needed in patients with primary choroidal neovascularization secondary to age-related macular degeneration (AMD) at 12 months.

Methods: This was a retrospective, interventional, comparative multicenter study of 60 eyes treated with intravitreal bevacizumab (35 eyes, 1.25 mg; 25 eyes, 2.5 mg).

Results: The mean number of injections per eye was 3.8 in the 1.25-mg group and 3.2 in the 2.5-mg group ($P = 0.2752$). At 12 months, in the 1.25-mg group, 16 (46%) eyes gained $\geq 3$ lines of Early Treatment Diabetic Retinopathy Study (ETDRS) VA and seven (20%) lost $\geq 3$ lines of ETDRS VA. In the 2.5-mg group, 11 (44%) eyes improved by $\geq 3$ lines, and four (16%) lost $\geq 3$ lines ($P = 1.000$). At 12 months, in the 1.25-mg group, the mean central macular thickness decreased from 419 ± 201 μm at baseline to 268 ± 96 μm, compared with a decrease from 388 ± 162 to 296 ± 114 μm in the 2.5-mg group ($P = 0.7896$).

Conclusion: There were no statistically significant differences between the two dose groups with regard to the number of injections, anatomic and VA outcomes.

Key Words: age-related macular degeneration, bevacizumab, choroidal neovascularization, VEGF
neovascular membranes secondary to AMD. In an animal model, overexpression of VEGF in the retinal pigment epithelium is sufficient to produce CNV.

Inhibition of VEGF can be an effective treatment for CNV secondary to AMD. Bevacizumab (Avastin, Genentech, San Francisco, CA, USA) is a humanized antibody that binds to all VEGF isoforms that has been successfully used in tumor therapy as a systemic drug. Recent studies have demonstrated the promise of intravitreal injections of bevacizumab in the treatment of CNV secondary to AMD. All clinical experience to date has indicated that multiple injections of bevacizumab are required to maintain the benefits of therapy. However, the optimum dose and dosing sequence for intravitreal bevacizumab are still undefined. It is unclear if a higher dose can provide a longer disease-free interval and reduce the burden of more frequent injections. The purpose of this retrospective study was to compare the total number of injections, central macular thickness, and best-corrected visual acuity (VA) response after injecting 1.25 or 2.5 mg of bevacizumab as needed in patients with primary CNV secondary to AMD at 12 months.

Patients and Methods

A retrospective study was conducted on 60 eyes of 60 patients with CNV secondary to AMD, which were treated with off-label intravitreal bevacizumab between September 2005 and July 2007 at six institutions in Venezuela, Brazil, Puerto Rico, Costa Rica, and Argentina. Institutional review board/ethics committee approval and patients’ signed informed consent were obtained for this study at all six institutions. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. The study and data accumulation were carried out in adherence to the tenets of the Declaration of Helsinki. At onset, surgeons at three of the centers injected 1.25 mg of bevacizumab in all their AMD patients, and surgeons at the other three centers injected 2.5 mg in their AMD patients. All patients received the same dose throughout the study. Eyes with subfoveal CNV secondary to AMD, regardless of size, composition (classic or occult), or visual acuity, were included. Patients were included in this consecutive series only if they had been followed for at least 12 months. Exclusion criteria included patients with CNV secondary to AMD previously treated in any way whatsoever, and patients with a history of glaucoma, diabetic retinopathy, or macular disorders other than AMD. Occasionally, at the discretion of the treating physician, patients with a history of uncontrolled hypertension and recent thromboembolic events were also injected with bevacizumab.

Each patient underwent best-corrected visual acuity (BCVA) measurement with Early Treatment Diabetic Retinopathy Study (ETDRS) charts and an ophthalmic examination including slit-lamp biomicroscopy. Baseline central retinal characteristics were measured by optical coherence tomography (OCT) (Stratus III OCT, Carl Zeiss, Dublin, CA, USA) utilizing six diagonal slow 6-mm radial line scans, with software versions 3.0 and 4.0, through a dilated pupil. The retinal thickness of the 1-mm central retina was obtained and we used the macular thickness map for our calculations.

A 0.18-ml aliquot of commercially available bevacizumab was prepared for each patient and placed in a tuberculosis syringe by using aseptic techniques. After the eye had been prepared in a standard fashion using 5% povidone/iodine, a speculum was used to stabilize the eyelid, and either 1.25 mg (0.05 ml) or 2.5 mg (0.1 ml) of bevacizumab was injected 3.5–4 mm posterior to the limbus, through the inferotemporal pars plana with a 30-gauge needle under either topical anesthesia or subconjunctival lidocaine. After the injection, retinal artery perfusion was checked and patients were instructed to administer topical antibiotics for 3 days.

All patients were given detailed postinjection instructions and asked to call promptly if they experienced any pain or significant changes in vision. In addition, patients were examined at 2 weeks and 1 month after the first injection, and monthly thereafter. Ophthalmic examinations at 1, 3, 6, and 12 months after the initial injection included OCT and fluorescein angiography (FA). FA was conducted at the discretion of the examiner, usually every 6 weeks and not at every examination. Patients received more injections whenever there was a recurrence. Recurrence was defined as a decrease of ≥2 lines of BCVA associated with a ≥50-μm increase in central macular thickness on OCT or the presence of leakage on FA, after complete or partial resolution on previous follow-up visits. Since the optimal treatment dose or interval of intravitreal bevacizumab is unknown, treatment intervals and doses were also left to the discretion of the treating physician.

Statistical analysis was performed using GraphPad Instat (version 3.0 for Macintosh OS X, GraphPad Software, San Diego, CA, USA). The patients’ ETDRS BCVA data were transferred from their records and converted to the logarithm of the minimal angle of resolution (logMAR) scale for analysis. Categorical variables were compared with Fisher’s exact test. Nonparametric repeated-measures analysis of variance with the Mann-Whitney test was used to compare mean logMAR visual acuity values and mean central macular thickness obtained by OCT. An increase or decrease in BCVA was considered to have occurred if there was a change of ≥3 ETDRS lines. Main outcome measures included changes in BCVA and central macular thickness (CMT) on OCT. Interval data was analyzed at the 1-, 3-, 6-, and 12-month follow-ups. A P value < 0.05 was considered to be significant.

Results

The patients had a mean age of 73.6 ± 7.7 years (range, 54–88 years), and 67% were women (20 men and 40 women). Patients had a mean follow-up of 58.4 ± 6.8 weeks (range, 52–78 weeks). All eyes were followed for at least 12 months.