

# Intravitreal Bevacizumab for the Treatment of Subfoveal CNV Secondary to AMD

Data continue to support further evaluation of intravitreal bevacizumab with large controlled prospective trials.

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**S**ubfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) is associated with intraretinal and/or subretinal edema, distortion of the retinal architecture and eventual loss of central vision.

Overexpression of vascular endothelial growth factor (VEGF) has been demonstrated in eyes with both CNV and retinal neovascularization.<sup>1</sup> Inhibition of VEGF-related angiogenesis has been evaluated to treat CNV.<sup>2,3</sup>

Molecular therapy targeted to block VEGF activity has been the focus of recent therapies for CNV in AMD. Pegaptanib (Macugen; OSI/Eyetech, New York, NY and Pfizer, New York, NY) was the first agent approved by the Food and Drug Administration (FDA) for intravitreal modulation of VEGF. In most cases, pegaptanib therapy only slows the rate of loss of acuity when compared with the natural history of subfoveal CNV in AMD.<sup>3</sup> Forty-one percent of patients treated with intravitreal pegaptanib given every 6 weeks lost  $\geq 15$  letters of acuity by 2 years.

## BEVACIZUMAB IS AN FDA-APPROVED VEGF INHIBITOR

Bevacizumab (Avastin; Genetech, San Francisco) is another VEGF inhibitor. It has been FDA approved for colon cancer therapy. Two independent studies by Rosenfeld and Avery demonstrated visual benefits with-

Two independent studies have demonstrated visual benefits without serious adverse effects using intravitreal bevacizumab therapy of CNV in AMD.

out serious adverse effects using intravitreal bevacizumab therapy of CNV in AMD.<sup>4,5</sup> Unpublished data from Lowenstein and colleagues did not show any electroretinographic or visual-evoked potential abnormalities from intravitreal bevacizumab in rabbit eyes.

Systemic bevacizumab was also investigated as potential AMD therapy, however, systolic hypertension was noted in the majority of the study patients.<sup>6</sup>

A retrospective consecutive case series was undertaken at two vitreoretinal departments in Boston to evaluate intravitreal bevacizumab treatment of active CNV in AMD.<sup>7</sup> There were 71 eyes primarily treated with intravitreal bevacizumab and 100 eyes with recurrent CNV treated with intravitreal bevacizumab rescue therapy after failure of treatment with verteporfin photodynamic therapy (PDT), intravitreal pegaptanib or thermal laser photocoagulation. All patients were followed for a minimum of 30 days between August 2005 and March 2006 at the New England Eye Center, Tufts University or

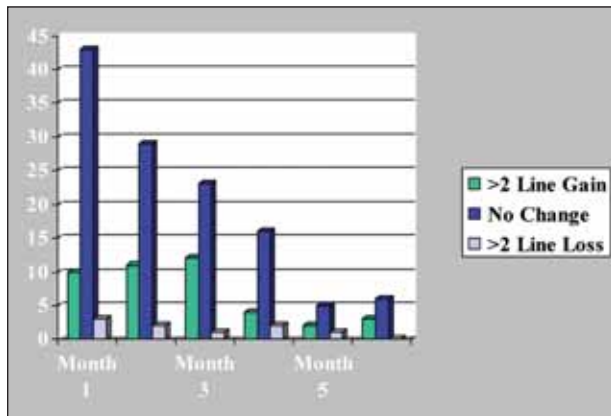


Figure 1. Patients receiving bevacizumab as primary therapy for neovascular AMD showed stability of vision throughout the study, with a significant number gaining more than two lines of Snellen acuity.

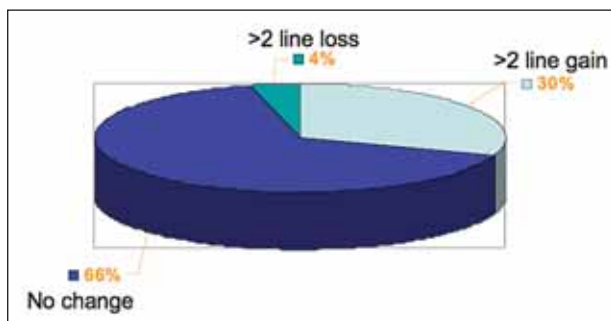


Figure 2. Almost one-third of patients primarily treated with intravitreal bevacizumab showed an increase of more than two lines of Snellen acuity at their last follow-up.

Ophthalmic Consultants of Boston (range, 1 to 6 months; median, 3 months). Individuals were followed every 4 to 6 weeks and received repeated intravitreal bevacizumab injections for intraretinal or subretinal fluid at the discretion of the treating retina specialist. Primary outcomes included Snellen visual acuity and optical coherence tomography (OCT) findings.

**PRIMARY OR RESCUE TREATMENT**

The dose of intravitreal bevacizumab injection was 1.25 mg in 0.05 mL. Patients treated with primary bevacizumab therapy were followed for a median of 3 months (range, 1 to 6 months), and patients treated with bevacizumab rescue therapy were followed for a median of 3 months (range, 1 to 6 months). There are no injection or drug-related complications noted in any eye included in this series to date.

Eyes treated primarily with bevacizumab were the most likely to gain two or more lines of vision, with 30%

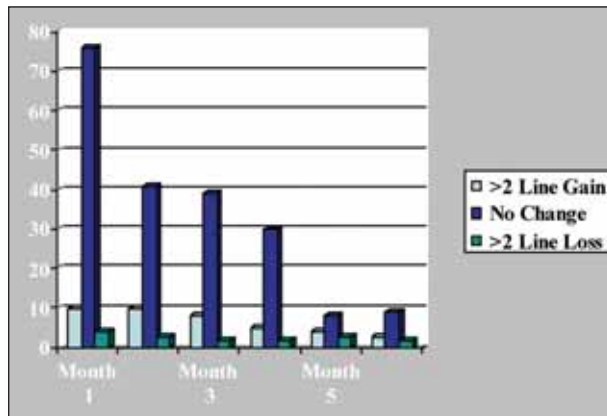


Figure 3. Patients receiving bevacizumab as rescue therapy for neovascular AMD showed stability of vision throughout the study, with few eyes losing more than two lines of Snellen acuity at any point.

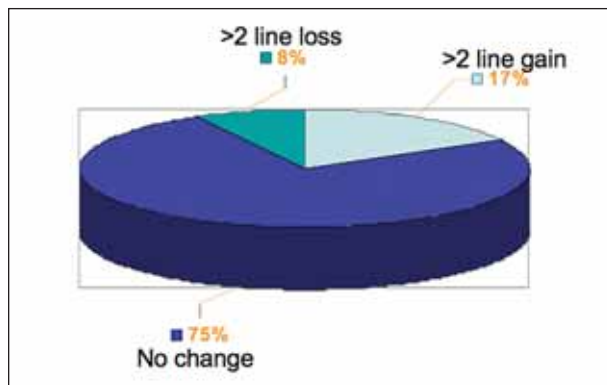


Figure 4. Three-fourths of patients rescued with intravitreal bevacizumab showed stability of visual acuity at their last follow-up.

of these eyes having visual improvement at their most recent follow-up visit. Visual stability, defined as vision remaining less than two lines different from baseline, of eyes in this group was preserved throughout the study, with 66% of these primarily treated eyes remaining stable by their last study visit (Figures 1 and 2).

Patients with rescue bevacizumab therapy were less likely to demonstrate visual improvement, but the majority of these eyes retained stable vision throughout the study period. Although only 17% of these patients gained more than two lines of vision, 75% remained within two lines of their initial acuity by their last study visit (Figures 3 and 4).

There was a decrease in OCT measurement of retinal thickness at the foveal center for both the primary and rescue bevacizumab treatment groups, with a similar and marked reduction in retinal thickness between initi-

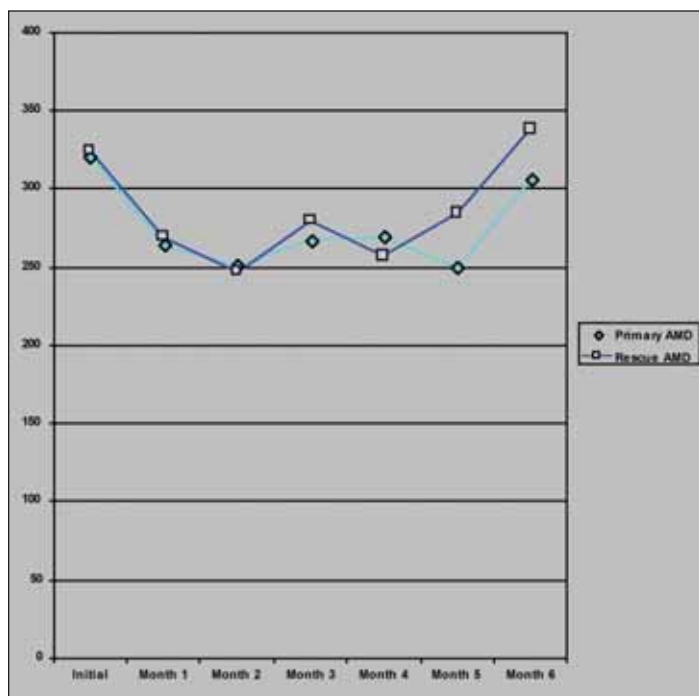


Figure 5. Average retinal thickness by OCT 3 revealed a similar decrease in thickness for both primary and rescue AMD treatments. There was a trend toward increased thickness by month 6.

ation of treatment and follow-up month 1, with a trend toward thickening by month 6 (Figure 5).

### VISUAL OUTCOMES VARIED

This open series of intravitreal bevacizumab for subfoveal CNV revealed a different visual outcome depending on whether there had been prior therapy of subfoveal CNV. While both primary and rescue groups respond to intravitreal bevacizumab with decreased macular thickening on OCT, the eyes treated with primary presentation of CNV have increased likelihood of visual improvement. The stability seen in all AMD eyes is notable and consistent with other series.

It is possible that eyes treated with primary AMD have an improved visual outcome due to a relative lack of preexisting subfoveal fibrotic scarring. Eyes secondarily treated with bevacizumab after previous verteporfin PDT or intravitreal pegaptanib may have limited visual improvement due to preexisting chronic photoreceptor damage or subfoveal fibrosis. The optimal timing to administer bevacizumab is unknown.

Consistent with Avery and Michaels (in a trial systemically administering bevacizumab for neovascular AMD),<sup>6</sup> the investigators reinjected patients when there was presence of subretinal fluid verified by OCT and

withheld treatment when the subretinal fluid had dried. This series is limited by its retrospective nature, short-term follow-up and visual acuity methodology, however, it does show a positive trend for visual improvement in eyes that previously only had delayed visual loss with other therapies. It is also notable that there were no adverse effects related to the medication or injection procedure. This safety profile is similar to that obtained by other investigators.

### RESULTS ARE ENCOURAGING

The positive results associated with intravitreal bevacizumab therapy in this study are encouraging. Avery and colleagues noted median improvement from 20/200 to 20/80 at 8 weeks postinjection.<sup>5</sup> Spaide and associates found that one-third of patients experienced visual improvement defined as halving of the visual angle between months 1 and 3.<sup>8</sup>

Reduction in retinal thickness on OCT after intravitreal bevacizumab has been described. This anatomic improvement appears to parallel maintenance or improvement in acuity. These studies support further evaluation of intravitreal bevacizumab with large controlled prospective trials. ■

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