

# Monotherapy vs Combination Therapy for Wet AMD: *Is Ranibizumab the Insulin of AMD?*

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**T**reatments for choroidal neovascular membranes in wet age-related macular degeneration (AMD) have made dramatic improvements over the past 10 years. Before 2000, the only treatment available was Macular Photocoagulation Study laser photocoagulation.<sup>1</sup> This caused irreversible loss of central visual acuity in patients with subfoveal choroidal neovascularization (CNV).

Photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis, East Hanover, NJ) was a significant advance in the treatment of wet AMD when it became available in 2000. For the first time, up to 6% of patients with subfoveal CNV gained  $\geq 15$  letters on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart with PDT treatment.<sup>2,3</sup> Unfortunately, 30% to 40% of patients treated with PDT lost  $\geq 15$  ETDRS letters, and only patients with predominantly classic lesions appeared to benefit from treatment.

The VISION trials using pegaptanib (Macugen; OSI/Eyetech, New York, NY and Pfizer, New York, NY) demonstrated equal efficacy for all lesion types in wet AMD, and appeared to have a relatively comparable number of treated patients with 15-letter improvements (4% to 6%).<sup>4</sup> Pegaptanib is an aptamer-based therapy targeting vascular endothelial growth factor (VEGF)-165. The percentage of patients who lost  $\geq 15$  ETDRS letters was still about 40% despite intravitreal injections every 6 weeks for 2 years.

Because of reports of a 4% to 6% severe immediate vision loss associated with verteporfin therapy with standard fluency, pegaptanib approval in December 2004 was embraced by many retina specialists — particularly for patients who presented with relatively good visual acuity. Although these treatments appeared to be well tolerated, retina specialist and patients became progressively disenchanted with this regimen as average-treated patients continued to lose visual acuity even with ongoing treatment.

## PAN-VEGF INHIBITION AS MONOTHERAPY

In 2005, preliminary reports from the MARINA and ANCHOR trials with ranibizumab (Lucentis; Genentech, San Francisco) demonstrated 30% to 40% 15-letter improvements with treatment and only 4% to 8% 15-ETDRS-letter losers (Table 1).<sup>5,6</sup> Ranibizumab, a pan-isoform modified anti-VEGF antibody fragment administered by intravitreal injection, is a biologically active fragment of bevacizumab (Avastin; Genentech, San Francisco) that is secondarily modified to have a higher affinity for all isoforms of VEGF-A. Its smaller molecular weight theoretically allows it to have better retinal penetration than the full-length antibody bevacizumab.

In 1995, Rosenfeld presented initial cases of wet AMD treated with intravitreal bevacizumab (an off-label use of the systemic anti-VEGF antibody treatment Food and Drug Administration approved for the treatment of colon cancer).<sup>7</sup>

Rosenfeld's preliminary series demonstrating at least short-term safety and efficacy were supplemented by an additional larger series of AMD patients treated with bevacizumab presented and published by Spaide and colleagues and Avery and his partners.<sup>8-11</sup> These reports, coupled with the clinical unavailability of ranibizumab, caused widespread adoption by retina specialists of intravitreal bevacizumab over pegaptanib and verteporfin.

Monotherapy, with either ranibizumab or bevacizumab, reveals that rapid anatomic improvements in intraretinal, subretinal and subretinal pigment epithelium fluid can be accomplished with one to several intravitreal injections. Recently Rosenfeld and colleagues<sup>12</sup> showed 1-year visual acuity improvements of approximately two lines in the standardized but nonrandomized PRONTO trial. In this study, which sought to limit intravitreal injections, 40 patients received three monthly ranibizumab injections followed by intermittent treatments guided by optical coherence tomograph (OCT). There was resolution of all intraretinal cysts or subretinal fluid in 72% of patients at month 1, 92% at month 2 and 95% at month 3. Seven of 40 patients required no subsequent reinjection. The average patient required five or six injections in the first year of treatment.

Avery and colleagues published anatomic improvement and visual acuity results with intravitreal bevacizumab.<sup>10,11</sup> Avery et al demonstrated resolution of intraretinal, subretinal, and sub-RPE fluid in 38% of patients and 49% of patients with 2 injections. A cross-study comparison cannot be made because Avery's bevacizumab patients were often *rescue* therapy, and PRONTO enrolled only new lesions. These reports, however, show that monotherapy with a pan-isoform anti-VEGF treatment is often quite efficient at anatomically restoring retinal anatomy. Analogous to the anatomic repair of a macula-off rhegmatogenous retinal detachments, this *anatomic* restoration of macular anatomy is thought to be a prerequisite to improved visual acuity.

### MONOTHERAPY EFFICACY

The efficacy in visual acuity results in 2-year MARINA results and 1-year ANCHOR results are unprecedented in the history of AMD therapies. These trials have demonstrated continued benefit of monotherapy with ranibizumab. Jeffrey Heier and colleagues,<sup>13</sup> presented 2-year phase 3 efficacy data on ranibizumab compared with sham injections in the treatment of occult and minimally classic CNV. Miller et al presented the safety data from the 2-year MARINA.<sup>14</sup> Results of the 2-year data extended and confirmed the results seen previously at 1 year.<sup>5</sup> Of the patients treated with ranibizumab, 90% lost <15 letters from baseline at 2 years versus 53% of the sham group. Of particular note, 26% of the 0.3-mg and 33% of the 0.5-mg ranibizumab-treated group gained three ETDRS lines of vision versus 4% of the sham-treated group. On average, ranibizumab patients in

**TABLE 1. 1-YEAR RESULTS OF PUBLISHED PREDOMINANTLY CLASSIC AMD STUDIES WITH 2-METER ETDRS REFRACTED VISUAL ACUITIES\***

	15 Letter Losers	15 Letter Gainers
Natural History (TAP control arm) <sup>2</sup>	60% to 69%	2%
Visudyne (TAP Study) <sup>2</sup>	33%	6%
Pegaptanib (VISION Study) <sup>3</sup>	30% to 40%	6%
Ranibizumab (ANCHOR) <sup>6</sup>	8%	40%

\*Direct cross study comparisons cannot be made because of the differences in inclusion criteria, etc. However, the trend for improvements in outcomes with verteporfin and pegaptanib over the natural history, and then ranibizumab over the other agents is obvious.

MARINA gained 6.6 ETDRS letters from baseline, while the control arm lost an average of 14.9 ETDRS letters.

The PIER study 1-year efficacy and safety results were recently presented. PIER was a phase 3b, randomized, double-masked study comparing sham therapy to a rationed injection protocol with ranibizumab. Patients in the treatment arms received three monthly injections of ranibizumab followed by mandatory quarterly dosing with the agent. The safety data was similar to MARINA and ANCHOR, as was the initial efficacy. Patients had improved vision analogous to MARINA by month 3, but then returned (on average) to baseline visual acuities with mandatory quarterly injections. These results imply that many patients may require more than six injections per year to achieve the improvements in visual acuity seen in ANCHOR and MARINA. It was hoped that PIER would confirm the assumption that ranibizumab could be used less frequently.

PRONTO data seem to imply that decreased injections with good efficacy can be achieved if patients are treated based on OCT guidance of disease activity. PRONTO still required an average of five to six injections in the first year of therapy.

While the anatomic results seen with bevacizumab are better than that of many previous agents, no long-term visual acuity results have been presented in a standardized fashion (ETDRS refractions and masked observer examinations). It is yet to be determined if bevacizumab is as efficacious as ranibizumab. Despite this, the widespread use of intravitreal bevacizumab by retina surgeons should provide

(Continued on page 49)

(Continued from page 24)

at least anecdotal evidence of how this agent compares to ranibizumab (once available) when used as monotherapy.

### ARGUMENT FOR COMBINATION THERAPY— NEED FOR REPEAT INJECTIONS

Prior to the availability of ranibizumab and bevacizumab, numerous cocktails of verteporfin, pegaptanib and intravitreal steroid therapy have been tried in an attempt to improve results. No combination therapy to date has demonstrated the 30% to 40% three-line improvements of refracted visual acuity at 1 year comparable to MARINA and ANCHOR monotherapy trials. Both MARINA and ANCHOR protocols, however, consisted of monthly intravitreal injections. Each intravitreal injection carries with it a definite risk of endophthalmitis and sight-threatening retinal detachment. PIER and PRONTO show that six injections per year are probably the minimum average number of required injections in the first year of treatment. The rationale for combination therapy in a postranibizumab approval era would be to devise a treatment regimen that could duplicate the visual acuity gains seen in the ranibizumab trials and decrease the total number of intravitreal injections necessary to accomplish these gains.

An ideal treatment for CNV in AMD would address oxidative stress reduction, block the neovascular stimulus, inhibit growth of abnormal blood vessels, cause maturation of the abnormal vessels in the CNV, eliminate edema and repair or decrease retinal scarring.<sup>15</sup> Effective monotherapy anti-VEGF agents are thought to block the neovascular stimulus, inhibit the growth of abnormal blood vessels and eliminate edema. It is primarily the antipermeability effects of ranibizumab in eliminating retinal and subretinal edema that led to the unprecedented improvements in visual acuity seen in ANCHOR and MARINA. Combinations of other agents with such an anti-VEGF agent may decrease the number of treatments by addressing the components that are not effected by the anti-VEGF agent alone.

### DOUBLE ANTI-VEGF COMBINATION THERAPIES

Double anti-VEGF therapies fail to address any of the deficiencies of anti-VEGF monotherapy. They only make sense if they decrease the overall number of injections necessary with monotherapy or augment deficiencies in any particular anti-VEGF agent to try to equal the efficacy of ranibizumab alone. It is quite possible that the smaller molecule pegaptanib may indeed have better retinal penetration than bevacizumab. Hence this combination may allow VEGF inhibition at a subretinal and intraretinal level over bevacizumab alone.

At ARVO 2006, two small studies<sup>16,17</sup> reported results from 26 and 20 patients respectively with combination treatments of intravitreal pegaptanib and bevacizumab or triamcinolone. Both studies found approximately 30% to 35% three-

line improvements with short follow-up comparable to some of the larger short-term studies of bevacizumab alone. The combination of pegaptanib with a pan-VEGF inhibitor is being tested in an upcoming OSI/Eyetech-sponsored trial. One-year follow-up will be necessary to determine if this regimen requires fewer than six injections per year and if efficacy will be comparable to ANCHOR and MARINA.

### PDT/ANTI-VEGF COMBINATION THERAPIES

PDT with verteporfin causes thrombosis and vessel closure of CNV (a good thing) but also causes acute VEGF production and choroidal damage. PDT is secondarily thought to promote the advantageous upregulation of pigment epithelium-derived factor levels which promote CNV vessel maturation. If damage to the choroid is minimized, the addition of PDT to an effective anti-VEGF agent might be expected to decrease the number of anti-VEGF therapy injections needed. The anti-VEGF agent might ameliorate the increased VEGF caused by the PDT treatment as well. Schmidt-Erfurth and colleagues<sup>18,19</sup> presented a nonrandomized, open-label, controlled trial of 32 patients who received concomitant PDT with verteporfin and intravitreal ranibizumab (PROTECT study). Patients on average had approximately one line visual acuity gain at 3 months to 6 months follow-up. The uveitis seen in this combination reported previously in the FOCUS trial was not seen in this nonlyophilized preparation. Augustin et al reported at the 2006 preliminary visual acuity improvements in patients treated by a combination of intravitreal dexamethasone, intravitreal bevacizumab and PDT with verteporfin.<sup>20</sup>

Current PDT treatment involves a laser light at 689 nm delivered at an intensity of 600 mW/cm<sup>2</sup> over 83 seconds to give a light dose of 50 J/cm<sup>2</sup> to a round spot size on the retina with a diameter of 1,000  $\mu$ m larger than the greatest linear dimension of the choroidal neovascular lesion. This light dose causes significant choroidal filling defects demonstrated on indocyanine green angiography. The VIM trial and subsequent work by Michels et al, demonstrate that lower light levels may produce equal closure of CNV vessels with less choroidal damage.<sup>21</sup> Future combinations of PDT and anti-VEGF therapy with a decreased fluence may allow the beneficial effects of vessel maturation without the choroidal damage associated with full fluence PDT. This may decrease the number of intravitreal injections required while still achieving visual acuity gains.

### INTRAVITREAL STEROID COMBINATIONS

Intravitreal steroids are thought to stabilize vascular endothelium, have direct anti-VEGF functions and decrease concomitant inflammation seen in CNV and retinal scarring. Previous trials combining intravitreal triamcinolone with verteporfin PDT demonstrated far fewer treatments necessary compared with PDT alone.<sup>22-24</sup>

Prior to the availability of anti-VEGF therapies, the addition

of intravitreal triamcinolone to PDT was the most common and widespread combination therapy used in the United States and Europe. Spaide<sup>22</sup> popularized this combination and demonstrated in pilot studies that this decreased the number of PDT treatments necessary in the first 2 years of treatment to 1.7 treatments from 5.6 (seen in the TAP trial). Ongoing clinical trials to document potential improved visual acuity efficacy of this regimen are continuing although recruitment has been challenging for these trials. Combining intravitreal steroids with an anti-VEGF agent and/ or with concomitant PDT may demonstrate advantages in number of required treatments as was seen with the earlier PDT trials. Only time will tell if efficacy similar to ANCHOR and MARINA can be maintained and if these cocktails will decrease the number of required intravitreal injections.

## SUMMARY

The results of the ranibizumab MARINA and ANCHOR trials have raised our expectations that AMD patients can have improved visual acuity with treatment. This expectation has come from well-controlled studies with monthly intravitreal injections. PRONTO and PIER have demonstrated that many patients may more than six injections per year.

These ranibizumab monotherapy studies set the gold standard for visual acuity improvements analogous to the the discovery of insulin in the treatment of diabetes. The rationale for combination therapy would be to influence other factors involved in wet AMD in an attempt to decrease the number of required intravitreal injections while still maintaining overall visual acuity gains.

Future studies with standardized refractions at baseline and follow-up will be required to see if this lofty goal can be attained. Additional longer-acting anti-VEGF agents will undoubtedly be developed providing additional benefits to patients. In summary, monotherapy with ranibizumab may indeed be the pig-derived insulin of our day. It is hoped that AMD treatments, however, will see continued advances analogous to longer acting insulins, the insulin pump and the development of oral antidiabetic agents that have made subcutaneous porcine insulin virtually obsolete. ■

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