

# New Combination Approaches Explored for AMD Management

There is a pharmacologic hypothesis for treatments addressing both biochemical and physical aspects of neovascular AMD.

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**T**here are many challenges in the treatment of patients with age-related macular degeneration (AMD).<sup>1</sup> The average age of patients at time of diagnosis of AMD is 75 years, with a life expectancy of 11.8 years. A big concern among these patients and their physicians is maintenance dosing. Because of the frequency of treatments and elevated safety issues with intravitreal injections, a longer dosing interval is preferred.

AMD patients have a heavy treatment burden. For example, patients receiving continuous dosing with ranibizumab (Lucentis; Genentech, San Francisco) injections—following clinical trial protocols—will typically have 12 injections a year; pegaptanib (Macugen; OSI/Eyetech and Pfizer, New York, NY) patients will receive about nine injections a year. With regard to as needed dosing, the rate of reinjection is variable. For example, in the Prospective Optical Coherence Tomography (OCT) Imaging of Patients With Neovascular Age-Related Macular Degeneration Treated With Intra-Ocular Lucentis (PRONTO) study, the range was anywhere from three to 12 injections. These patients also require monthly monitoring, optical coherence tomography (OCT), and fluorescein angiography (FA) studies.

## RATIONALE FOR COMBINATION THERAPY

One rationale for studying combination therapy for the treatment of AMD is that it offers the potential for a reduced course of treatments. These agents target different pathways, and together may provide a synergistic effect. Using a combination approach may even improve upon the outcomes seen with monotherapy,

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offering patients better visual acuity and/or a better angiographic result. Accompanying the reduction in number of treatments is a reduced risk of adverse events, both systemic and ocular. Potential systemic risks of long-term pan-vascular endothelial growth factor (VEGF) blockade include thromboembolic events,<sup>2-4</sup> bleeding events, and possible blockade of neuroprotection, with possible implications for stroke recovery,<sup>5</sup> Alzheimer's disease,<sup>6</sup> and Parkinson's disease.<sup>7</sup>

Hypothetical ocular risks include damage to the retinal pigment epithelium (RPE) and choriocapillaris with exacerbation of RPE geographic atrophy, and risk of neuronal damage with progressive retinal thinning.

While several hypotheses have been proposed for the pathogenesis of AMD, none has been proven. Factors that may contribute to the development of AMD include RPE dysfunction, alterations in Bruch's membrane, oxidative stress, inflammatory processes, and ischemia.<sup>8,9</sup> Choroidal neovascularization (CNV) is a complex process that includes and involves neovascularization, RPE cells, macrophages, and other inflammatory cells and myofibroblasts.<sup>10,11</sup> Combination therapy allows for more than one factor to be addressed.

**TABLE 1. ONGOING STUDIES OF COMBINATION THERAPY**

**VERITAS:**

PDT plus triamcinolone (1 mg and 4 mg) and PDT plus pegaptanib

**LEVEL:**

pan-VEGF induction plus pegaptanib

**DENALI:**

ranibizumab plus PDT versus monthly ranibizumab

**MONT BLANC**

**(European companion study to DENALI):**

ranibizumab plus PDT versus monthly ranibizumab

### RESPONSE TO PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is the only vaso-occlusive treatment option for CNV. PDT occludes abnormal vessels and upregulates pigment epithelium derived factor (PEDF), VEGF,<sup>12</sup> and inflammatory mediators.<sup>13-16</sup> In a study of eyes that were surgically removed due to untreatable malignancy, closure of choroidal vessels was followed by the expression of VEGF in the endothelium of choriocapillaries and focally within larger choroidal vessels in treated areas.<sup>15</sup> The production of VEGF may be a consequence of tissue hypoxia resulting from localized non-perfusion.<sup>17</sup>

Hypoxia induces production of hypoxia-inducible factor (HIF)-1 alpha, which stimulates production of a variety of proteins that increase oxygen delivery (eg, erythropoietin, glucose transporters, glycolytic enzymes, and VEGF).<sup>18</sup>

Inflammation, hypoperfusion, and VEGF overexpression following PDT treatment with verteporfin (Visudyne; Novartis, Basel, Switzerland) may be associated with both undesirable and desirable effects.<sup>19</sup> The undesirable effects include recurrent growth of CNV, with subsequent increases in permeability and leakage from the new vessels. Desirable effects include prevention of retinal damage due to hypoxia. In addition, increased VEGF expression may allow recovery of surrounding choroidal vessels and encourage maturation of CNV that is less permeable and less susceptible to the reinitiation of neovascularization.

### ADJUNCTIVE TREATMENT WITH PDT

The rationale for using angiostatic or steroidal agents as adjuncts to verteporfin is that although the initial PDT will occlude CNV, there is subsequent

upregulation in the expression of biochemical signals in the retina, such as VEGF, PEDF, and intercellular adhesion molecule-1. Administration of anti-VEGF and antiinflammatory agents would then be expected to block upregulation of VEGF and inflammatory responses that may lead to posttreatment angiogenesis and leakage.

The currently available anti-VEGF agents decrease vessel permeability, are thought to inhibit the initiation of new vessel growth, and apparently do not destroy mature, abnormal vessels.<sup>20,21</sup> Intravitreal steroids inhibit inflammatory mediators, are angiostatic, and contribute to the stabilization of the blood-retinal barrier.<sup>22,23</sup>

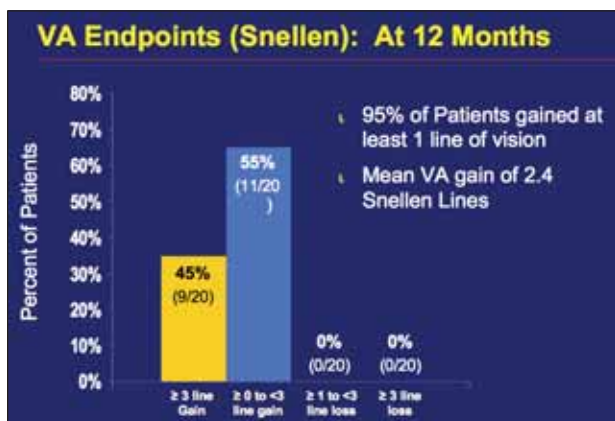
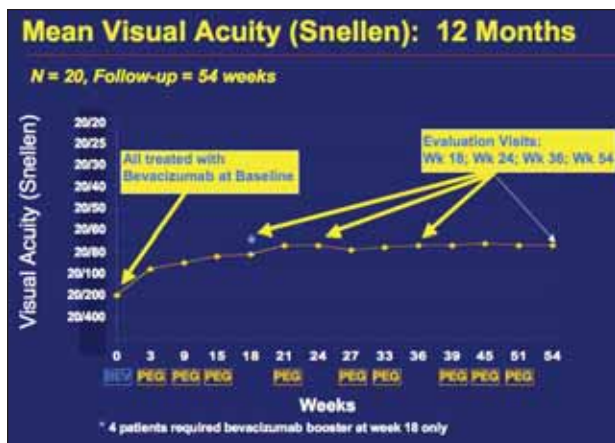
Several compounds have been shown to reduce vascular permeability, including steroids and anti-VEGF agents. For example, the anti-VEGF agent ranibizumab targets all of the VEGF isoforms and may have more pronounced antipermeability effects than other compounds that target a single VEGF isoform.<sup>24-26</sup> The optimal dosing of PDT and order of interventions in combining PDT with anti-VEGF drugs has not yet been determined.

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### COMBINATION STUDIES

Previous combination studies have studied ranibizumab plus PDT (RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety [FOCUS]), ranibizumab plus same day PDT (PROTECT), and pegaptanib plus PDT (Vascular Endothelial Growth Factor Inhibition Study in Ocular Neovascularization [VISION]). Ongoing combination therapy studies include VERITAS (Verteporfin Intravitreal Triamcinolone Acetonide Study), LEVEL (Evaluation of Efficacy and Safety in Maintaining Visual Acuity with Sequential Treatment of Neovascular AMD), DENALI and its European companion study, MONT BLANC (Table 1).

We conducted a study of bevacizumab (Avastin; Genentech, San Francisco) induction therapy followed by pegaptanib in 20 treatment-naïve eyes.<sup>27</sup> At baseline, patients received 1.25 mg of bevacizumab followed by pegaptanib injection 3 weeks later. Patients



Figures 1 and 2. The mean visual acuity at 12 months (top) and 12-month visual acuity endpoints.

then received pegaptanib injections every 6 weeks, and were reevaluated at 18 weeks after the third pegaptanib injection. Patients received repeat bevacizumab 1.25 mg if the greatest linear diameter increased by >15% on FA. Patients were followed for 12 months and Snellen measurements were recorded. Mean visual acuity at 12 months is shown in Figure 1, and the 12-month visual acuity endpoints are shown in Figure 2.

A retrospective review by Guarav Shah from the Barnes Retina Institute looked at combined verteporfin PDT and pan-VEGF blockade with bevacizumab (Avastin; Genetech, San Francisco). Patients had subfoveal and juxtafoveal lesions and received bevacizumab followed by PDT with a 1- to 2-week interval between the two treatments. All patients were treatment-naïve, patients with <6 months follow-up were excluded, and retreatment in this study was based on OCT or FA. In this group, 20 eyes (83%) had stabilization of visual acuity at 7 months follow-up, 16 eyes had an improvement in visual acuity, 38% of these

patients gained three lines and 22% ended up at  $\geq 20/40$ . Additionally, 15 eyes required only a single initial treatment of combination therapy and eight eyes required a single retreatment within the 7-month follow-up interval.

### REDUCED-DURATION PDT COMBINATION

Our group also investigated combined reduced duration PDT and pan-VEGF blockade with ranibizumab.<sup>28</sup> In this prospective analysis of 20 eyes, patients had a mean baseline vision of 20/200 and a mean baseline OCT of 378  $\mu\text{m}$ . Forty percent of these patients had occult lesions, 25% were minimally occult, and 35% were classic. Included patients had CNV secondary to AMD.

Patients in this study received reduced-duration PDT for 60 seconds and intravitreal ranibizumab 0.5 mg within 1 to 2 days. Patients then received ranibizumab injections every 4 weeks if OCT revealed an eye that was not dry. At 12 weeks, patients were reevaluated using OCT and FA, and the initial combination was repeated if FA showed leakage. Follow-up in this study was 4 months.

The visual acuity endpoints on Snellen at 4 months showed that 90% of patients gained at least one line of vision, with a mean visual acuity gain of 2.2 Snellen lines (Figure 3).

We also investigated a regimen of triple therapy, using full- or reduced-duration PDT with verteporfin, intravitreal dexamethasone (400  $\mu\text{g}$  or 800  $\mu\text{g}$ ), and an anti-VEGF agent. We treated a 72-year old woman with metamorphopsia in her left eye. Her visual acuity was 20/30 OD and 20/400 OS (Figures 4 and 5). She was treated with low-duration PDT (42 seconds) on

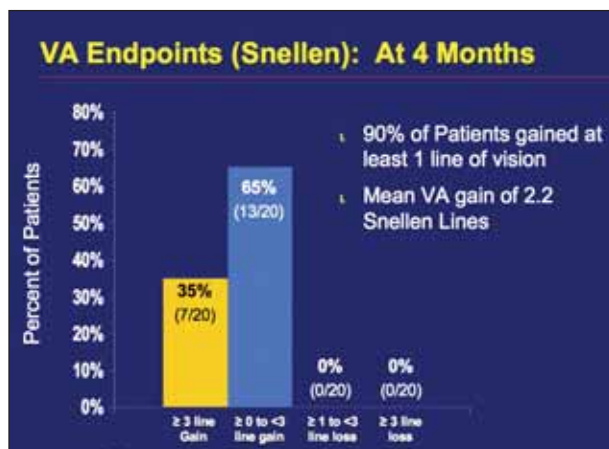
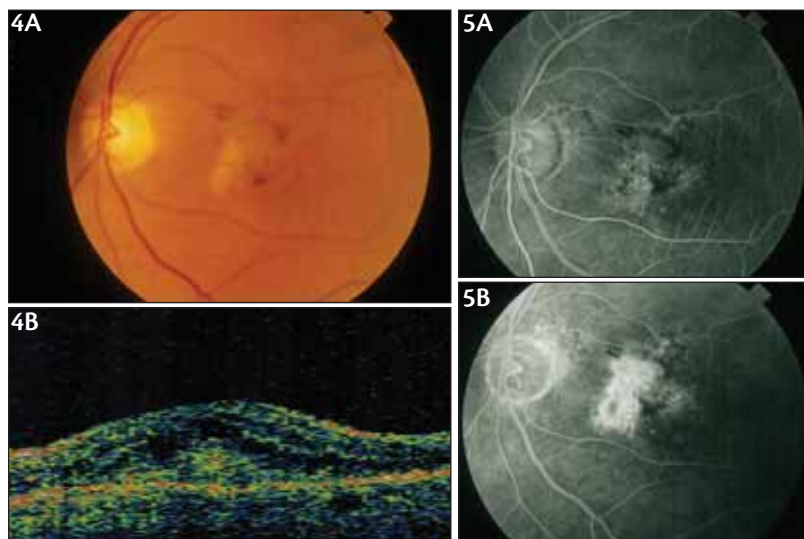


Figure 3. The visual acuity endpoints on Snellen at 4 months showed that 90% of patients gained at least one line of vision with a mean visual acuity gain of 2.2 Snellen lines.



Figures 4 through 5. Pretreatment and FA of a 72-year old woman with metamorphopsia in her left eye. Her visual acuity was 20/30 OD and 20/400 OS. FA and OCT upon presentation showed occult CNV with leakage. Treatment consisted of reduced-duration PDT (42 seconds) on day 1, 1,800 µg intravitreal dexamethasone on day 2, and 0.3 mg intravitreal pegaptanib on day 7.

day 1, 1,800 µg intravitreal dexamethasone on day 2, and 0.3 mg intravitreal pegaptanib on day 7. At 6 weeks posttreatment with pegaptanib, the patient's vision was 20/80 OS (Figure 6) and 20/50 (OS) at 15 weeks post-PDT (Figure 7).

### VEGF BLOCKADE

There may be a potential or theoretical risk of pan-VEGF blockade among AMD patients with agents such as bevacizumab or ranibizumab. We know that these patients live an average of 12 years after diagnosis and we cannot predict the cumulative effect of a pan-VEGF blockade for an extended time. The potential risk forms part of the rationale for pan-VEGF induction therapy, followed by selective VEGF inhibition, combined with PDT treatment.

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The published randomized clinical trials have not been powered with a sufficient number of patients to answer the question of increased systemic risks. There may be an increased risk of thromboembolic events

with ranibizumab<sup>2,3</sup> but the number was not considered statistically significant. A recent advisory letter from Genentech<sup>4</sup> announced that Cohort 1 of the Safety Assessment of Intravitreal Lucentis for AMD (SAILOR) trial had found a statistically significant 1.2% risk of cerebral vascular accident in the 0.5-mg treated group versus 0.3% in the 0.3-mg group. The announcement stated that the risk was greater in the population that had suffered a previous stroke, but no further data was given. In order to determine if there is a stroke risk associated with pan-VEGF blockade, a clinical trial must enroll a large enough number of patients to have a meaningful result. Hopefully, the future results from the phase 3b SAILOR will provide this information.

### CONCLUSION

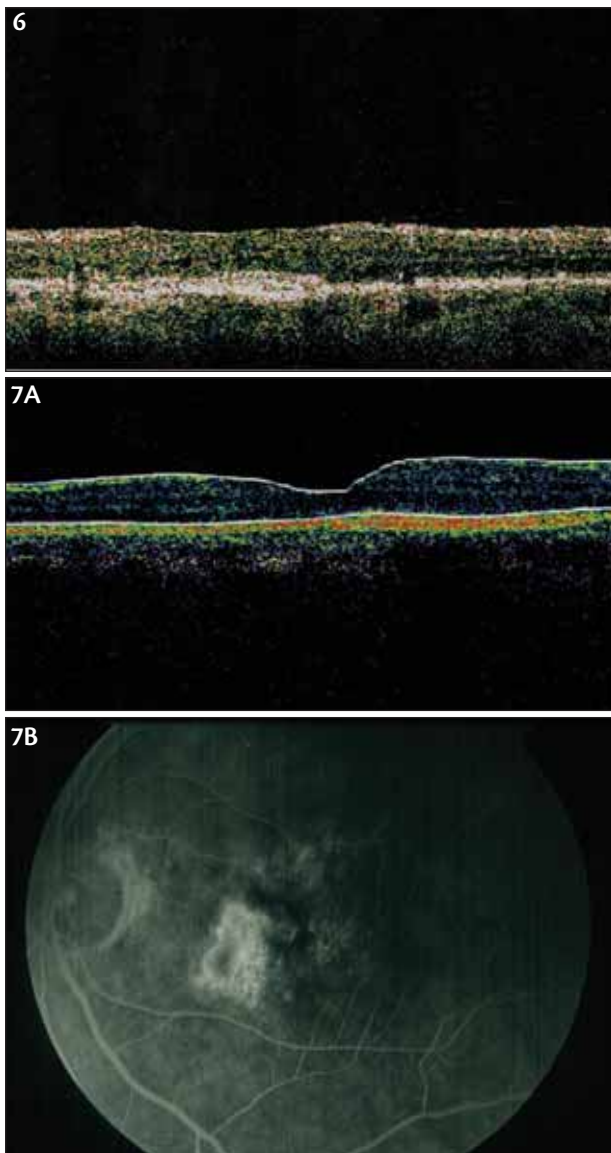
While the vision results with ranibizumab treatment for AMD from ANCHOR and MARINA are impressive, combination therapies may allow us to maintain or improve efficacy while reducing both systemic and ocular risk. Other ophthalmic specialties, such as glaucoma, as well as other disease states, such as hypertension and diabetes, have been using combination therapy for many years.

As retina specialists, we should be striving for improved outcomes with reduced risk. We may be able to not only reduce the pharmacologic burden to the patient and the financial burden that results from monotherapy, but also reduce the volume of office visits, observation and diagnostic testing, and the logistical burden on patients' families.

CNV secondary to AMD is a dynamic, multifactorial process involving vascular, nonvascular, and inflammatory components. There is a pharmacologic hypothesis for treatments addressing both biochemical and physical aspects of neovascular AMD.

Ongoing clinical trials are investigating the safety and efficacy of different combination therapies. ■

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**Figures 6 and 7. Posttreatment 6 weeks with pegaptanib the patient's vision was 20/80 OS (Figure 6) and 20/50 (OS) at 15 weeks post-PDT (Figure 7). Please note: Figure 6 is a horizontal slice and figure 7A is a vertical slice.**

1. Hughes MS. New combination approaches for the management of AMD. Presented at Retina, held in conjunction with Hawaiian Eye 2007. Jan. 14-19, 2007. Kauai, Hawaii.
2. Brown DM, Kaiser PK, Michels M, for the ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1444.
3. Rosenfeld PJ, Brown DM, Heier JS, et al, for the the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
4. Genentech informational "Dear Healthcare Provider" letter. Jan. 24, 2007.
5. Zhu W, Mao Y, Zao Y, et al. Transplantation of vascular endothelial growth factor-transfected neuronal stem cells into the rat brain provides neuroprotection after transient focal ischemia. *Neurosurgery*. 2005;57:325-333.
6. Solerte SB, Ferrari E, Cuzzoni G, et al. Decreased release of the angiogenic peptide vascular endothelial growth factor in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2005;19:1-10.

7. Yashuhara T, Singo T, Kobayashi K, et al. Neuroprotective effect of VEGF upon dopaminergic neurons in a rat model of Parkinson's disease. *Eur J Neuro*. 2004;
8. Spaide RF, Armstrong D, Browne R. Choroidal neovascularization in age-related macular degeneration - What is the cause? *Retina*. 2003;23:595-614.
9. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. *Arch Ophthalmol*. 2004;122:598-614.
10. Espinosa-Heidmann DG, Reinosa MA, Pina Y, et al. Quantitative enumeration of vascular smooth muscle cells and endothelial cells derived from bone marrow precursors in experimental choroidal neovascularization. *Exp Eye Res*. 2005;80:369-378.
11. Spaide RF. Rationale for combination therapies for choroidal neovascularization. *Am J Ophthalmol*. 2006;141:149-156.
12. Tatar O, Adam A, Shinoda K, et al. Expression of VEGF and PEDF in choroidal neovascular membranes following verteporfin photodynamic therapy. *Amer J Ophth*. 2006;42:95-104.
13. Bressler NM. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. *Arch Ophthalmol*. 2001;119:198-207.
14. Schmidt-Erfurth U, Schlötzer-Schrehard U, Cursiefen C, et al. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. *Invest Ophthalmol Vis Sci*. 2003;44:4473-4480.
15. Schmidt-Erfurth U, Laqua H, Schlotzer-Schrehard U, et al. Histopathological changes following photodynamic therapy in human eyes. *Arch Ophthalmol*. 2002;120:835-844.
16. Visudyne [package insert]. Basel, Switzerland: Novartis; 2005.
17. Michels S, Schmidt-Erfurth U. Sequence of early vascular events after photodynamic therapy. *Invest Ophthalmol Vis Sci*. 2003;44:2147-2154.
18. Semenza GL. Expression of hypoxia-inducible factor 1: mechanisms and consequences. *Biochem Pharmacol*. 2000;59:47-53.
19. Ng EW, Adamis AP. Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. *Can J Ophthalmol* 2005;40:352-368.
20. The Eyetech Study Group. Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: Phase II study results. *Ophthalmology*. 2003;110:979-986.
21. Adamis AP, Shima DT. The role of vascular endothelial growth factor in ocular health and disease. *Retina*. 2005;25:111-118.
22. Kaiser PK. Verteporfin therapy in combination with triamcinolone: published studies investigating a potential synergistic effect. *Curr Med Res Opin*. 2005;21:705-713.
23. Jonas JB. Intravitreal triamcinolone acetonide for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol Scand*. 2005;83:645-663.
24. Gaudreault J, Fei D, Rusit J, et al. Preclinical pharmacokinetics of ranibizumab (rhuFabV2) after a single intravitreal administration. *Invest Ophthalmol Vis Sci*. 2005;46:726-733.
25. Sapiid RF. In: Yanoff M, Duker JS, editors. *Ophthalmology* 2nd ed. St. Louis, MO: Mosby; 2004:919-924.
26. Matsuda S, Gomi F, Oshima Y, et al. Vascular endothelial growth factor reduced and connective tissue growth factor induced by triamcinolone in ARPE19 cells under oxidative stress. *Invest Ophthalmol Vis Sci*. 2005;46:1062-8.
27. Hughes MS, Sang DN. Safety and efficacy of intravitreal bevacizumab followed by pegaptanib maintenance as a treatment regimen for age-related macular degeneration. *Ophth Surg Laser Imag*. 2006;37:448-454.
28. Hughes MS, Sang DN. Submitted for publication.

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