

Evidence for Combination Therapies in AMD Continues to Grow

No randomized prospective trial results have been published, but prospective case series suggest the efficacy of these approaches.

BY MARK S. HUGHES, MD, FACS; AND DELIA N. SANG, MD, FACS

Vision loss from age-related macular degeneration (AMD) places an increasing burden on patients, physicians, and the health care delivery system in the United States. Patients are on average 75 years of age at the time of diagnosis of AMD with an additional life expectancy of almost 12 years.¹ With current treatments for choroidal neovascularization (CNV) in AMD labeled for monthly or 6-weekly administration,^{2,3} patients theoretically may face a decade or more of nine to 12 yearly visits for monitoring and treatment of their disease.

Variable dosing schedules for vascular endothelial growth factor (VEGF) inhibitors show promise for reducing the treatment burden,⁴ but these strategies have not yet been evaluated in prospective randomized clinical trials.

A number of combination therapies are under investigation in small case series. The goal of these combination treatments is to take advantage of possible synergy or complementary modes of action of different agents to provide similar efficacy to already approved therapies while reducing the frequency of treatment required.

This article reviews the rationale for combination therapy and presents results of a prospective case series in which we evaluated the effectiveness of one particular combination of therapies—reduced-duration photodynamic therapy (PDT) plus intravitreal injection of dexamethasone and ranibizumab (Lucentis; Genentech, South San Francisco, California)—in treatment-naïve patients with CNV due to AMD.

RATIONALE: SAFETY

The underlying rationale for combination therapy is to reduce risk. Reducing the frequency of dosing of VEGF inhibitors decreases hypothetical systemic risk.

Chronic use of a nonselective VEGF-blocker theoretically

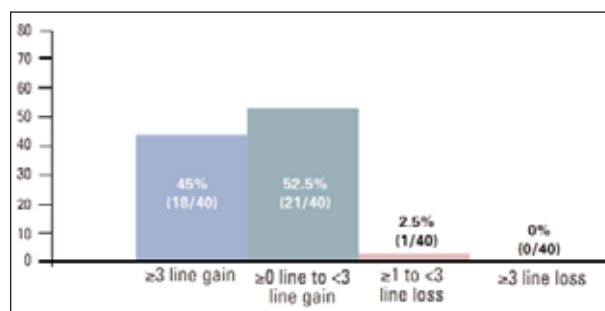


Figure 1. Visual acuity changes, baseline to month 12 (N = 40). Mean visual acuity (Snellen) improved from approximately 20/200 to 20/80 by month 2 and to almost 20/70 by month 12.

may increase the risk of thromboembolic events^{5,6} and bleeding events and may affect neuroprotection, with possible implications for stroke recovery,⁷ Alzheimer's disease,⁸ and Parkinson's disease.⁹

An interim data analysis in the SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) clinical trial showed a higher incidence of stroke with a higher dose of ranibizumab (1.2% in the group treated with 0.5 mg vs. 0.3% in the group treated with 0.3 mg).¹⁰ This information was announced by Genentech in a letter to health care providers in January 2007, when average follow-up time in the trial was 230 days. The 1-year data from the trial have not yet been published.

In addition to the theoretical systemic risk, there are also potential intraocular risks with use of VEGF inhibitors. Potential 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 with the use of anti-VEGF monotherapy. There are also risks associated with intravitreal injection,

including infection and retinal detachment, and these are multiplied with schedules that call for multiple injections.

RATIONALE: EFFICACY

The pathophysiology of CNV in AMD is multifactorial, and anti-VEGF monotherapy does not address all aspects of the condition. VEGF inhibition targets angiogenesis, but CNV also includes an inflammatory component and a vascular component—larger vessels with established structural elements.

Combinations of different modes of treatment for CNV may help to address these other disease components. For instance, intravitreal corticosteroids, which are angiostatic and help to reinforce the blood-retinal barrier,^{11,12} may quiet the inflammatory component of CNV. And PDT may be used to occlude the more mature blood vessels not susceptible to anti-VEGF agents.^{13,14} On the other hand, PDT also upregulates the production of VEGF and other inflammatory mediators,¹⁵ but steroids may help to limit the VEGF upregulation and other inflammatory activity.^{16,17} Some of these characteristics may offer complementary or synergistic effects in combination treatment of CNV.

Also, it must be remembered that not all patients respond to anti-VEGF monotherapy. Up to 20% of patients respond slowly to ranibizumab^{5,6} so this must be considered in our treatment approach.

COMBINATION THERAPY TRIALS

To take advantage of these potential synergies, a number of investigators have evaluated combinations of two or more of these treatment modalities. Published reports of combinations used to treat CNV in AMD have included anti-VEGF agents plus PDT,^{18,19} steroids plus PDT,^{20,21} and all three modalities together.²²⁻²⁴

Ongoing trials of combination therapies include VERITAS (Verteporfin Intravitreal Triamcinolone Acetonide Study), combining PDT and steroid; LEVEL (Evaluation of Efficacy and Safety in Maintaining Visual Acuity with Sequential Treatment of Neovascular AMD), evaluating induction with

ranibizumab and maintenance with pegaptanib (Macugen, OSI/Eyetech, New York, New York); and a pair of trials evaluating monthly ranibizumab versus ranibizumab plus PDT, called the SUMMIT series—the US study DENALI and its European counterpart, MONT BLANC. Also ongoing is the RADICAL trial (Reduced Fluence Visudyne—anti-VEGF—Dexamethasone in Combination for AMD Lesions), which includes double- and triple-therapy arms with reduced-fluence PDT. A number of single-center, investigator-sponsored trials or case series have also reported results.

TRIPLE-THERAPY TRIAL

We performed a prospective 1-year study to examine the efficacy and safety of a triple combination of ranibizumab, reduced-duration PDT, and the corticosteroid dexamethasone over a 12-month period.²⁵

We chose the steroid dexamethasone because it has five times the potency of triamcinolone²⁶ and it is short-acting, with faster clearance from the vitreous. Because it is short-acting, and it is administered in pulse form, it is less likely to result in glaucoma or cataract progression than use of sustained-delivery triamcinolone or dexamethasone.^{23,27}

The study included 40 eyes of 40 patients with CNV secondary to AMD. Eyes with any of the following were excluded: intraocular surgery between treatments; previous PDT; previous anti-VEGF treatment; myocardial infarction within 2 months of baseline; stroke within 6 months of baseline; incomplete follow-up.

For initial treatment, all eyes received triple-therapy:

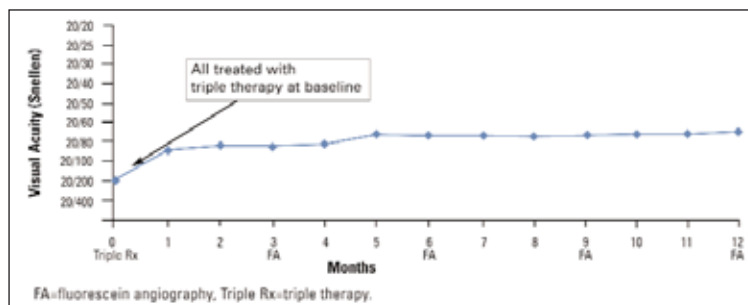


Figure 2. Mean visual acuity, baseline to month 12 (N = 40).

TABLE 1. VISUAL ACUITY AND NUMBER OF TREATMENTS BY LESION SUBTYPE (N=40)*

	Mean Improvement	Visual Acuity Improved	Single Triple Treatment	Second Triple Treatment	Ranibizumab Booster
Classic (n=14)	3.00 lines	100%	79%	21%	36%
Occult (n=16)	2.00 lines	88%	75%	25%	38%
Minimally classic (n=10)	2.40 lines	80%	80%	20%	20%
Overall (n=40)	2.45 lines	90%	78%	22%	33%

*No patient received more than two cycles of triple therapy and one ranibizumab booster.

reduced-duration PDT, intravitreal dexamethasone 0.8 mg within 1 to 2 days after PDT, and intravitreal ranibizumab 0.5 mg within 3 to 5 days after administration of dexamethasone. Reduced-duration PDT in this trial was administered for 42 seconds, at 600 mW/cm², for a light dose of 25 J/cm².

Patients were followed for 12 months. Visual acuity testing and optical coherence tomography (OCT) were performed monthly, and fluorescein angiography (FA) was taken at months 3, 6, 9, and 12. Injections of ranibizumab were administered every 4 weeks if any of the following were observed: increase of central retinal thickness by >75 µm on OCT; decrease of visual acuity with any evidence of fluid on OCT; evidence of new blood. The triple therapy was repeated if leakage was noted on FA.

Mean age of the patients was 80.2 years, and 58% were female. Lesions were occult in 40% of eyes, minimally classic in 25%, and classic in 35%. Mean baseline visual acuity was 20/200, and mean center point retinal thickness was 378 µm.

RESULTS

No subjects discontinued the study, and compliance was excellent. Nine of the 40 patients received a second round of triple therapy between 3 and 12 months. Thirteen subjects received a "booster" of ranibizumab, based on the study criteria, at 1 to 2 months after triple therapy. Five of these patients had also received the triple-therapy cycle a second time. At 12 months, 90% of study eyes improved by at least one line of vision from baseline. Mean gain in visual acuity was 2.45 lines (Figure 1). Mean Snellen visual acuity improved from approximately 20/200 to 20/80 by month 2 and to nearly 20/70 by month 12 (Figure 2).

Visual acuity in eyes with all lesion subtypes is shown in Table 1. At least 75% of eyes in each subtype required only a single treatment. Overall, 78% of eyes received only one treatment, and 22% received one additional triple treatment. Mean center point retinal thickness decreased 190 µm from baseline to month 12 ($P < .0001$).

Regarding safety, no cases of stroke, myocardial infarction, endophthalmitis, or intraocular pressure elevation >25 mm Hg were seen. No cataract progression was observed. Retinal pigment epithelial tear occurred in two patients. These encouraging results reflect safety and the maintenance or increase of visual acuity outcomes over a 1-year period with reduced frequency of intravitreal treatment in comparison with available monotherapies. It is not our recommendation to replace anti-VEGF monotherapy with combination therapy. Rather, with multiple approaches available for the treatment of CNV in AMD, therapy can be tailored to the individual patient. The majority of patients may do well with anti-VEGF monotherapy, while others may benefit from

some combination of therapies. The evaluation of these treatments in prospective randomized clinical trials remains to be addressed. ■

Mark S. Hughes, MD, FACS, and Delia N. Sang, MD, FACS, are with Ophthalmic Consultants of Boston and Schepens Eye Research Institute, Harvard Medical School. Dr. Hughes states that he has no financial interest in the companies or products mentioned; he may be reached at MSHughes@eyeboston.com; phone: +1 617 367 4800. Dr. Sang may be reached at DNSang@eyeboston.com; phone: +1 617 367 4800.



- 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.
- Lucentis prescribing information; Genentech Inc. Available at: <http://www.gene.com/gene/products/information/tgr/lucentis/insert.jsp>. Accessed Jan. 17, 2007.
- Macugen prescribing information; OSI/Eyeteach. Available at: <http://www.macugen.com/macugenUSPI.pdf>. Accessed Jan. 17, 2007.
- Lalwani GA, Fung AE, Michels S, et al. An OCT-guided variable-dosing regimen with ranibizumab (Lucentis) in neovascular AMD: two year results of the PRONTO study. Poster presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology; May 7, 2007; Fort Lauderdale, Florida.
- 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.
- Rosenfeld PJ, Brown DM, Heier JS, et al, for the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
- 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.
- 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.
- Yasuhara T, Shingo T, Kobayashi K, et al. Neuroprotective effect of VEGF upon dopaminergic neurons in a rat model of Parkinson's disease. *Eur J Neuro*. 2004;1494-1504.
- Genentech "Dear Healthcare Provider" letter. Jan. 24, 2007. Available at: <http://www.gene.com/gene/products/information/pdf/healthcare-provider-letter.pdf>. Accessed Jan. 16, 2008.
- Kaiser PK. Verteporfin therapy in combination with triamcinolone: published studies investigating a potential synergistic effect. *Curr Med Res Opin*. 2005;21:705-713.
- Jonas JB. Intravitreal triamcinolone acetonide for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol Scand*. 2005;83:645-663.
- Ng EW, Adams AP. Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. *Can J Ophthalmol*. 2005;40:352-368.
- Jo N, Mailhos C, Ju M, et al. Inhibition of platelet-derived growth factor B signaling enhances the efficacy of anti-vascular endothelial growth factor therapy in multiple models of ocular neovascularization. *Am J Pathol*. 2006;168:2036-2053.
- Tatar O, Adam A, Shinoda K, et al. Influence of verteporfin photodynamic therapy on inflammation in human choroidal neovascular membranes secondary to age-related macular degeneration. *Retina*. 2007;27:713-723.
- Saishin Y, Saishin Y, Takahashi K, et al. Inhibition of protein kinase C decreases prostaglandin-induced breakdown of the blood-retinal barrier. *J Cell Physiol*. 2003;195:210-219.
- Uckermann O, Kutzera F, Wolf A, et al. The glucocorticoid triamcinolone acetonide inhibits osmotic swelling of retinal glial cells via stimulation of endogenous adenosine signaling. *J Pharmacol Exp Ther*. 2005;315:1036-1045.
- Heier JS, Boyer DS, Ciulla TA, et al. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol*. 2006;124:1532-1542.
- Lazic R, Gabric N. Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration. *Ophthalmology*. 2007;114:1179-1185.
- Spaide RF. Fundus autofluorescence and age-related macular degeneration. *Ophthalmology*. 2003;110:1517-1525.
- Augustin AJ, Schmidt-Erfurth U. Verteporfin therapy combined with intravitreal triamcinolone in all types of choroidal neovascularization due to age-related macular degeneration. *Ophthalmology*. 2006;113:14-22.
- Liggett PE, Colina J, Chaudhry NA, et al. Triple therapy of intravitreal triamcinolone, photodynamic therapy, and pegaptanib sodium for choroidal neovascularization. *Am J Ophthalmol*. 2006;142:1072-1074.
- Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina*. 2007;27:133-40.
- Ladewig MS, Karl SE, Hamelmann V, et al. Combined intravitreal bevacizumab and photodynamic therapy for neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2008;46:17-25.
- Hughes MS, Sang DN. Reduced duration PDT combined with intravitreal dexamethasone and ranibizumab for exudative age-related macular degeneration. Poster presented at the American Society of Retina Specialists. Dec. 1-5, 2007. Indian Wells, California.
- Hardman JG, et al, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill Book Co; 2001:1657, Table 60-2.
- Sivaprasad D, McCluskey P, Lightman S. Intravitreal steroids in the management of macular oedema. *Acta Ophthalmol Scand*. 2006;84:722-733.