The RADICAL Trial: Exploring Combination Therapies

This ongoing trial will evaluate results with double and triple therapies and reduced fluences for PDT.

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The RADICAL (Reduced Fluence Visudyne–anti-VEGF–Dexamethasone in Combination for AMD Lesions) trial is one of a handful of ongoing, prospective, randomized clinical trials investigating combination therapy for the treatment of patients with age-related macular degeneration (AMD). The trial, sponsored by QLT Inc. (Fort Collins, Colorado), includes four treatment arms (Table 1) and has several unique features: it incorporates triple-therapy and double-therapy arms, as well as two reduced-fluence light doses with verteporfin (Visudyne; Novartis, Basel, Switzerland) photodynamic therapy (PDT).

The purpose of RADICAL is similar to that of other prospective trials evaluating verteporfin PDT followed by ranibizumab (Lucentis; Genentech, South San Francisco, California) in combination therapy (namely the SUMMIT program, sponsored by Novartis, which includes two clinical trials, DENALI and MONT BLANC). The objective of RADICAL is to determine whether combination therapy reduces retreatment rates compared with ranibizumab monotherapy while maintaining similar visual acuity outcomes and an acceptable safety profile. RADICAL will follow patients for 24 months.

Other prospective trials evaluating verteporfin PDT followed by ranibizumab in combination therapy include the SUMMIT program (DENALI and MONT BLANC).

RATIONALE FOR COMBINATION THERAPY

The rationale for combination therapy in choroidal neovascularization (CNV) due to AMD has been described[1-3] and is fundamentally the same as the combination therapy rationale in oncology. In combination therapy, each treatment component has a different mechanism of action, so combining treatment components attacks the diseased area in different ways (Table 2).

The development of CNV due to AMD is complex and poorly understood, but we know that it involves inflammation, angiogenesis, and neovascularization. In the combination therapy used in the RADICAL trial, verteporfin PDT occludes existing neovascularization; ranibizumab, an inhibitor of vascular endothelial growth factor (VEGF), stops angiogenesis and reduces leakage; dexamethasone

TABLE 1. RADICAL TREATMENT ARMS			
Treatment(s)	**PDT Light Dose**	**Regimen**	**Number of Patients**
Monotherapy: ranibizumab	N/A	Three monthly treatments, then as needed	40
Double therapy: verteporfin PDT, followed by ranibizumab	Reduced fluence: 25 J/cm^2 (300 mW/cm^2 given for 83 seconds)	Once, then as needed	40
Triple therapy: verteporfin PDT, followed by ranibizumab and dexamethasone	Reduced fluence: 25 J/cm^2 (same as above)	Once, then as needed	40
Triple therapy: same as above	Very low fluence: 15 J/cm^2 (180 mW/cm^2 given for 83 seconds)	Once, then as needed	40
			TOTAL: 160

fights inflammation. It is hypothesized that such a multicomponent, multitarget approach to therapy should result in good visual outcomes that last longer than outcomes associated with ranibizumab monotherapy, which must be administered monthly to maintain the best vision benefit.[4-6]

A longer-lasting effect means fewer retreatments, which would lessen the burden of frequent clinic visits for patients, free retinal specialists to treat more patients, and lower the costs of treatment for patients and health care payers.

EVIDENCE FOR COMBINATION THERAPY

Evidence supporting combination therapy with verteporfin PDT and an anti-VEGF component is available from early prospective trials of pegaptanib[7] (Macugen; OSI/Eyetech, New York, New York) and ranibizumab,[8] from case series using bevacizumab[9,10] (Avastin; Genentech) and from one prospective study with bevacizumab.[11] These studies were either short-term, open-label, retrospective, or early trials not designed specifically to assess combination therapy. As such, they do not conclusively establish a benefit for combination therapy. Long-term, prospective, controlled trials are needed to confirm beneficial visual outcomes and lower retreatment rates with combination therapy.

Dexamethasone was chosen as the antiinflammatory component for RADICAL combination therapy based on supporting case series evidence in triple therapy[10] and the fact that the frequently used alternative, triamcinolone acetonide, is associated with cataract formation and increases in intraocular pressure (IOP).[1]

REDUCED FLUENCE

The light dose (fluence) associated with standard verteporfin PDT is 50 J/cm^2, administered at an intensity (fluence rate) of 600 mW/cm^2 for 83 seconds. This fluence, which was used in the pivotal trials of verteporfin PDT to establish its efficacy and safety in CNV due to AMD,[12-15] is the only one described in the approved labeling for verteporfin.

Reduction of fluence can be achieved by reducing the fluence rate or by reducing the time of light administration (see *Fluence Equation*, below).

FLUENCE EQUATION

Fluence (J/cm^2) = fluence rate (mW/cm^2) X time of light administration (seconds)

Reducing the fluence may be a way to optimize verteporfin PDT within a combination-therapy regimen. The basis of this hypothesis lies in the mechanism of action of verteporfin PDT. Verteporfin preferentially accumulates in CNV. Localized light administration then selectively occludes CNV without damaging the overlying retina. CNV occlusion occurs through a free-radical–driven PDT mechanism that depends on three factors within the CNV, any of which could be rate-limiting: the concentrations of the verteporfin photosensitizer and oxygen in the target CNV tissue and the light dose and intensity.

With standard-fluence PDT, oxygen could become rate-limiting, and the selectivity of the PDT effect on CNV could be significantly reduced, despite verteporfin's selective accumulation in the CNV,[16,17] because of the high fluence and fluence rate. That is, large amounts of both light and photosensitizer could deplete oxygen in the target CNV tissue. If this is the case, according to the hypothesis, reducing the fluence may decrease oxygen consumption, allowing verteporfin concentration to be the rate-limiting factor rather than oxygen concentration. This would thus improve the selectivity of the PDT reaction in the CNV because verteporfin concentration is higher in the target

TABLE 2. TARGETS OF COMBINATION THERAPY		
Disease Target	**Disease Effect**	**RADICAL Treatment Component**
Neovascularization (new blood vessels)	Leaks fluid and causes scarring, impairing vision	Verteporfin PDT
Angiogenesis	Promotes growth of new blood vessels	Ranibizumab
Inflammation	Initiates angiogenesis	Dexamethasone

CNV tissue than in the nontarget choriocapillaris.

Preliminary clinical evidence with reduced-fluence verteporfin PDT from two monotherapy studies[18,19] suggests the clinical potential of reduced-fluence PDT in combination therapy.

The VIM (Visudyne in Minimally Classic CNV) trial[18] included 38 patients treated with half-fluence PDT (25 J/cm^2: 300 mW/cm^2 for 83 seconds), 39 patients treated with standard-fluence PDT (50 J/cm^2), and 40 patients who received placebo. A trend toward better visual acuity outcomes was observed in the half-fluence group compared with the standard-fluence group at the 12- and 24-month time points. Furthermore, visual disturbance adverse effects (vision decrease, visual field defects, and abnormal vision) were less common in the half-fluence group (5% of patients) than in either the standard-fluence group (13%) or the placebo group (10%).

Michels and colleagues[19] used sensitive angiographic techniques to evaluate the effects of verteporfin PDT on the CNV and the choroidal vasculature in six patients who received standard-fluence PDT and 13 patients who received half-fluence PDT (25 J/cm^2) either through reducing treatment time (600 mW/cm^2 for 42 seconds; six patients) or fluence rate (300 mW/cm^2 for 83 seconds; seven patients). PDT's effect on CNV closure was the same in both groups, but less effect on the choroidal vasculature was observed in the half-fluence groups.

In RADICAL, verteporfin PDT is administered with reduced fluence in all three combination therapy arms of the study (Table 1). The reduced light dose is achieved by reducing the fluence rate.

RETREATMENT

After their initial randomized study treatment in RADICAL, patients in the combination therapy groups return to the clinic monthly for evaluation. We do not expect monthly retreatment to be necessary, but it is important to verify this expectation by evaluating retreatment criteria monthly.

RADICAL retreatment criteria are based on optical coherence tomography (OCT) and fluorescein angiography (FA). If OCT central retinal thickness is 250 µm or greater or is increased more than 50 µm compared with the lowest previous central retinal thickness measurement, the patient is re-treated. If neither OCT criterion applies, the patient may still be re-treated if FA shows evidence of lesion growth or leakage from CNV.

Combination retreatment may not be administered more frequently than every 2 months. If retreatment is needed in an intervening month, the patient will receive ranibizumab injection only.

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Allowing combination therapy retreatment that includes verteporfin PDT at a 2-month interval is unusual, as the standard treatment interval for PDT is 3 months. The safety of a 2-month interval is supported by evidence from two studies. The first, the VER (Visudyne Early Retreatment) trial,[20] included 323 patients randomly assigned (1:1) to verteporfin PDT as needed, at either 6-week or 3-month intervals. This trial showed that the efficacy results and safety profile in the two treatment arms were similar. The second study[21] showed that retreatment at 2- to 4-week intervals was well-tolerated, even with double the standard light dose.

After their initial randomized study treatment, patients in the ranibizumab monotherapy group receive mandatory retreatment at months 1 and 2, and retreatment is thereafter as needed, based on the criteria described above. Although monthly therapy is the standard regimen for ranibizumab, a regimen of three doses followed by retreatment as needed with monthly assessments is supported by a recent study.[22]

In all treatment arms, monthly assessment with potential retreatment continues through 12 months. Between 12 and 24 months, patients will attend the clinic at least once every 3 months, or more frequently at the investigator's discretion.

ASSESSMENTS, OUTCOME VARIABLES

BCVA is assessed with the ETDRS (Early Treatment Diabetic Retinopathy Study) method at screening, before treatment on the day of initial treatment, at monthly visits through 6 months, and at the 12-, 18-, and 24-month visits. FA is assessed at screening, at the 3- and 12-month visits, and as required according to retreatment criteria. OCT is assessed to determine retreatment criteria at every visit. Safety, including IOP measurement, is also evaluated at every visit.

Study outcomes include visual acuity, central retinal thickness, lesion size, number of retreatments, and safety. The primary efficacy variables are mean number of retreatments and mean change from baseline in visual acuity score.

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CONCLUSION

RADICAL is currently enrolling patients with subfoveal CNV due to AMD who are aged ≥50 years, have never received treatment for CNV due to AMD in the study eye (with the exception of non-subfoveal laser treatment), have a BCVA letter score of 73 to 24, and have a CNV lesion size of less than nine disc areas.

Basic inclusion and exclusion criteria, as well as study information and study centers, are outlined at ClinicalTrials.gov (www.clinicaltrials.gov/ct2/show/NCT00492284).

As one of the few prospective, randomized trials in combination therapy for CNV in patients with AMD, the RADICAL trial will contribute important information on the benefit of such therapy. RADICAL results after 12 months of follow-up are expected in 2009. ■

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1. Augustin AJ, Offerman I. Combination therapy for choroidal neovascularisation. *Drugs Aging*. 2007;24:979-990.
2. Kaiser P. Verteporfin photodynamic therapy and anti-angiogenic drugs: potential for combination therapy in exudative age-related macular degeneration. *Curr Med Res Opin*. 2007;23:477-487.
3. Spaide RF. Rationale for combination therapies for choroidal neovascularization. *Am J Ophthalmol*. 2006;141:149-156.
4. Rosenfeld PJ, Brown DM, Heier JS, et al; The MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
5. Brown DM, Kaiser PK, Michels M, et al; The ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1444.
6. Lucentis (ranibizumab injection) prescribing information. San Francisco, California: Genentech; 2006. Available at: http://www.gene.com/gene/products/information/tgr/lucentis/index.jsp. Accessed Jan. 14, 2006.
7. 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.
8. 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.
9. Dhalla MS, Shah GK, Blinder KJ, Ryan EH Jr, Mittra RA, Tewari A. Combined photodynamic therapy with verteporfin and intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration. *Retina*. 2006;26:988-993.
10. Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina*. 2007;27:133-140.
11. 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.
12. 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: one-year results of 2 randomized clinical trials—TAP report 1. *Arch Ophthalmol*. 1999;117:1329-1345.
13. 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. Kaiser PK, Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: 5-year results of two randomized clinical trials with an open-label extension TAP report no. 8. *Graefes Arch Clin Exp Ophthalmol*. 2006;244:1132-1142.
15. Verteporfin In Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularia-tion – Verteporfin In Photodynamic Therapy report 2. *Am J Ophthalmol*. 2001;131:541-560.
16. Miller JW, Walsh AW, Kramer M, et al. Photodynamic therapy of experimental choroidal neovascularization using lipoprotein-delivered benzoporphyrin. *Arch Ophthalmol*. 1995;113:810-818.
17. Kramer M, Miller JW, Michaud N, et al. Liposomal benzoporphyrin derivative verteporfin in photodynamic therapy: selective treatment of choroidal neovascularization in monkeys. *Ophthalmology*. 1996;103:427-438.
18. Visudyne in Minimally Classic Choroidal Neovascularization Study Group. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration: 2-year results of a randomized clinical trial. *Arch Ophthalmol*. 2005;123:448-457.
19. Michels S, Hansmann F, Geitzenauer W, Schmidt-Erfurth U. Influence of treatment parameters on selectivity of verteporfin therapy. *Invest Ophthalmol Vis Sci*. 2006;47;371-376.
20. Stur M, VER Study Group. Verteporfin Early Retreatment (VER): 12-month results of a phase IIIb controlled clinical trial. Paper presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology; April 27, 2004; Fort Lauderdale, Florida.
21. Schmidt-Erfurth U, Miller J, Sickenberg M, et al. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of retreatments in a phase 1 and 2 study. *Arch Ophthalmol*. 1999;117:1177-1187.
22. Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2007;143:566-583.