Combination Therapies for Wet AMD: Latest Developments

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Age-related macular degeneration (AMD) is the most common cause of vision loss in adult white Americans. The prevalence of AMD, based on data from population-based epidemiological studies, is assumed to be increasing in many countries worldwide, in part due to the increasing longevity of the population. In recent times our understanding of the wet form of AMD — which is now considered a complex multifactorial disease with both vascular and extravascular components — has evolved markedly, as have respective therapeutic options. The current therapeutic mainstays are intravitreal corticosteroids, verteporfin photodynamic therapy (PDT; Visudyne, Novartis/QLT), and intravitreal anti–vascular endothelial growth factor (VEGF) agents. Sealing ocular blood vessels by using laser photocoagulation is another option, with only a small minority of patients eligible for this treatment.

In brief, corticosteroids treat and prevent inflammation, block the upregulation of VEGF, narrow the gaps between endothelial cells in the capillary walls, and limit fibrosis, which in turn minimizes retina scarring. PDT, a two-stage process involving the administration of verteporfin for injection and nonthermal red light, targets the vascular component of wet AMD by producing local damage to neovascular endothelium, resulting in vessel occlusion. Anti-VEGF drugs target angiogenesis, an important contributor to neovascular and exudative eye diseases.

The current therapeutic standard is consecutive monthly injections of ranibizumab (Lucentis, Genentech). The licensed indication recommends monthly injections of ranibizumab on a continuing, indefinite basis. In most cases however, these monotherapies cannot fully address the multifactorial pathogenesis of wet AMD (Figure 1). Thus, dual- and triple-combination therapies with a steroid, PDT or laser photocoagulation, and an anti-VEGF agent are now being intensely investigated. The intent is to provide different and complementary mechanisms of action to decrease inflammation, destroy existing choroidal neovascularization (CNV), prevent the formation of new CNV, and inhibit further VEGF production.

Furthermore, the additional potential benefit is an increase in visual acuity (VA) compared to the outcome produced with ranibizumab monotherapy, but with reduced need for retreatment at the same time.

This contribution will summarize highlights of combination therapy for patients with wet AMD reported in 2009. Although the main emphasis will be triple therapies, we will begin with a brief summary of available findings from two major clinical trials of dual therapies.

Figure 1. Left, the multifactorial causes of CNV: a, VEGF; b, VEGF bound to VEGF receptor; c, formation of neovascularature; d, extravasation of inflammatory cells. Right, triple combination therapy with verteporfin PDT, a steroid, and an anti-VEGF agent provides different mechanisms of action to treat several pathogenic factors: a, PDT eradicates neovascularature; b, PDT causes an inflammatory reaction that affects adjoining tissues; c, inflammation triggers new additional expression of VEGF; d, steroid therapy reduces the inflammation; e, anti-VEGF competitively inhibits the binding of VEGF, thus preventing formation of new vasculature.

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MONT BLANC AND DENALI

In these two large, prospective trials, PDT is being combined with intravitreal injections of ranibizumab. MONT BLANC, a two-year, randomized, double-masked, European multicenter trial, is comparing PDT and ranibizumab with ranibizumab alone in 255 patients. Standard-fluence PDT (or sham) was administered at baseline and then at intervals of at least three months, as required based on predefined retreatment criteria. Ranibizumab is being administered as three so-called loading doses — a term that lacks a scientific basis — followed by monthly treatment as needed, again based on predefined retreatment criteria.7

In a preliminary analysis of one-year results, mean VA improvement from baseline was limited in both groups; the combination therapy group (2.5 letters) was shown to be noninferior to that in the ranibizumab monotherapy group (4.4 letters). The percentage of patients with a three-month treatment-free interval after the last loading dose was similar, with 96% and 92% in the combination and monotherapy groups, respectively. More patients treated with dual therapy than with monotherapy had a treatment-free interval of at least four months (85% vs 72%). Median time to first retreatment was extended by approximately one month in the combination group (month 6) compared with the monotherapy group (month 5). There were no unexpected safety findings, and the adverse event incidence was similar between groups.7 Final analysis will need to be made available in order to draw firm conclusions.

The DENALI trial is a two-year, multicenter controlled study in which approximately 300 patients have been randomly assigned to receive either same-day ranibizumab plus standard-fluence PDT or same-day ranibizumab plus reduced-fluence PDT or ranibizumab monotherapy.6 Reduced-fluence PDT may be less detrimental to the choroidal vasculature while retaining an efficacy equivalent to standard-fluence therapy.6

In the first two DENALI treatment groups, ranibizumab is given at baseline, at months 1 and 2, and then as needed;

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in the third group, ranibizumab is administered monthly for the first year and as needed for the second year. PDT is being administered at baseline and then every three months as needed. Monthly follow-up will consist of VA and optical coherence tomography (OCT) assessments, and retreatment will be based on OCT findings. One-year results are expected in 2010.8

PROGRESS IN TRIPLE THERAPY IN 2009

Retrospective Studies
Sayegh and colleagues reported outcomes in 375 eyes of 251 elderly patients (mean age of 82 years) with occult CNV lesions treated sequentially with dexamethasone, bevacizumab (Avastin, Genentech), and large-spot diode laser photocoagulation. Criteria for retreatment included presence of subretinal blood or fluid on clinical exam, significant macular thickening on OCT, VA decrease, late leakage on fluorescein angiogram (FA), or occult plaque on indocyanine green (ICG).

Over two years of follow-up, the mean number of treatments was 2.1. VA was stable or improved in nearly 90% of patients.10 Nelson retrospectively analyzed outcomes with ICG-directed triple therapy, consisting of half-fluence PDT, ranibizumab, and triamcinolone acetonide, in 40 patients with persistent leakage following three initial monthly ranibizumab injections. Group 1 consisted of 30 patients who did not have subretinal retinal pigment epithelium (RPE) exudation. Group 2 consisted of 10 patients with RPE detachments. Ranibizumab was given on day 1 and PDT and triamcinolone were given seven days later. Triple therapy was repeated if leakage and neovascularization recurred.

Patients in group 1 had a sustained OCT reduction (mean 82 μm), and all required retreatment (mean 7.6 months). Mean VA improvement was three letters, with 12% having three lines of visual improvement. Nine patients in group 2 had a complete collapse of the RPE detachment, and mean VA improvement was five letters. ICG was also useful in identifying patients with non-VEGF–driven pathophysiologic processes not completely responsive to standard anti-VEGF therapy.11

Bakri et al. administered same-day reduced-fluence PDT, dexamethasone, and bevacizumab to both previously treated, as well as treatment-naïve, patients.12 Triple therapy maintained visual acuity and decreased macular thickness in all 31 patients over a mean follow-up of 13.7 months. Both treatment-naïve and previously treated patients (all treated with an anti-VEGF agent) benefited and had the same mean number of repeat triple therapy treatments (0.3). No adverse effects were noted at one year of follow-up.

Prospective Case Series
A triple therapy consisting of PDT, bevacizumab, and dexamethasone was administered to 146 patients (Figure 2). Over a mean follow-up of 74 weeks, 11 patients (8%) required one more course of triple therapy and 46 (32%) required one additional bevacizumab injection (Figure 3). Results compared to baseline included a considerable mean VA increase of 9.35 letters and a mean decrease in retinal thickness of 167 μm (P < .01) for both treatment options, while no serious adverse events occurred.13

Veritti et al. applied PDT plus ranibizumab plus juxtascleral triamcinolone to 30 patients. PDT was given as standard fluence (50 J/cm²) or reduced fluence (25 J/cm²), with either standard (600 mW/cm²) or reduced irradiance (300 mW/cm²). Over six months of follow-up, no angiographic leakage occurred and mean best corrected VA was improved in all three groups (0.29±0.39 in group 1, -0.13±0.34 in group 2, and -0.15±0.22 logMAR in group 3, respectively). Choroidal ischemia was noted in two eyes treated with standard fluence/standard irradiance PDT.14

Randomized Controlled Clinical Trials
Results of controlled clinical trials were also reported in 2009. RADICAL, a multicenter, randomized, single-masked trial is currently comparing PDT plus ranibizumab plus dexamethasone with ranibizumab monotherapy. A total of 162 patients/eyes were randomly assigned to one of four treatment groups: quarter-fluence PDT (15 J/cm²) followed within two hours by ranibizumab and then dexamethasone; half-fluence PDT (25 J/cm²) followed within two hours by ranibizumab and then dexamethasone; half-fluence PDT followed within two hours by ranibizumab; or ranibizumab alone.15

Entry criteria included age ≥50 years, no previous treatment for AMD, VA letter score 73 to 25 (approximately equivalent to Snellen scores of 20/40 to 20/320), and <9 disc area lesion size.

Patients randomly assigned to combination treatment groups received one initial treatment and those randomly
Figure 3. Early- and late-phase angiography and OCT of a case who received a triple therapy (PDT, bevacizumab, dexamethasone) and four months later a second bevacizumab injection due to remaining edema and some metamorphopsia. Visual acuity increased from 20/100 to 20/50. After the bevacizumab administration a further increase in visual acuity to 20/32 could be achieved and both metamorphopsia and edema disappeared. This case has been stable for more than 10 months now.

assigned to ranibizumab monotherapy received three initial treatments (baseline and months 1 and 2). Patients were assessed for retreatment on a monthly basis via OCT and FA. Best corrected VA and safety were assessed throughout.

One-year results show that VA gain appears similar in all treatment groups (3.6 to 6.5 letters), although wide confidence intervals were noted. There was less need for retreatment with combination therapy (three to four times) compared to monotherapy (five times), while no additional safety concerns occurred. As noted, these are one-year results of a one-year trial and, as with the MONT BLANC and DENALI trials, final results are awaited.15

In the multicenter CAVE Study, reduced-fluence PDT plus bevacizumab plus triamcinolone therapy was compared with bevacizumab monotherapy, as well as with PDT plus bevacizumab dual therapy. Data from 103 patients were evaluated at one year.16 All patients were treated at baseline and returned for follow-up every six weeks, with retreatment as needed based on FA and OCT criteria.

Mean retreatment rates were highest with bevacizumab monotherapy (4.57) and lowest with triple therapy (3.18). There were no significant between-group differences in mean VA gains (0.4 to 3.9 letters). Interestingly, the greatest extent in treatment–free interval was with dual therapy, leading the investigators to conclude that addition of triamcinolone did not produce additional benefit.16

In treatment-naïve patients, Hughes and Sang gave reduced-duration PDT plus dexamethasone plus ranibizumab and compared outcomes with monthly ranibizumab monotherapy (n=30 in each group). A single “booster” ranibizumab injection was given one month after triple therapy and patients were followed monthly.

At one year, 19 (63%) of triple therapy patients had received only one retreatment. No patient received more than two cycles of triple therapy or two additional ranibizumab injections. Compared with monotherapy, triple therapy produced a greater mean reduction in center point thickness (196 µm vs 186 µm) and greater improvement in mean VA (11.9 letters vs 8.8 letters).17

Sang and Hughes have also studied triple therapy as rescue treatment. They administered reduced-duration PDT (42 seconds, 66 mW/cm²), dexamethasone, and bevacizumab to 40 patients who did not respond to previous therapy. After initial triple therapy, if central thickness increased by >75 µm, subretinal fluid was seen on OCT, or hemorrhage occurred, retreatment with bevacizumab was given within one to two months or with triple therapy at three months.

At one year, 31 (77%) patients required additional treatment, with mean time to retreatment measured at 4.8 months. Mean VA improved by a considerable eight letters, center point thickness decreased by 126 µm, and no adverse events were noted.18 Busquets et al. retrospectively analyzed 24 eyes treated with ranibizumab plus PDT plus dexamethasone after failure to respond to monthly ranibizumab. In these elderly patients (median age of 80 years) followed for one year, frequency of ranibizumab injections decreased after triple therapy; however, VA did not improve, which the investigators attribute, at least in part, to subretinal fibrosis and atrophy.19

Other Findings
Biochemical findings also support the use of triple therapy. Augustin et al. measured myeloperoxidase (MPO) activity, an inflammatory marker, and VEGF values and showed that intravitreal tissue damage, MPO, and VEGF levels were significantly elevated (P<0.01) in eyes with wet AMD vs control eyes. Eyes with larger lesions and with fibrosis had a more pronounced inflammatory response than those with smaller lesions or no fibrosis.20

Data on real world practice patterns regarding dual and triple therapies are also beginning to accrue. The Visudyne registry database compiled data on treatment outcomes of over 1,600 patients, including VA assessments, results of ocular exams, serious adverse event reporting, and any additional treatments. Results show that PDT plus an anti-VEGF agent plus a corticosteroid can improve VA (means of 5.7 to 6 letters) with infrequent retreatments. The safety profiles for dual and triple therapy were also acceptable, with 11 serious ocular events reported in both databases.20

FUTURE DIRECTIONS: NEW INVESTIGATIONAL DRUGS
Several novel agents are now being evaluated for possible use. Furthest along in development is VEGF Trap-Eye
Review of recent clinical evidence suggests that a combination approach may reduce retreatment rates and result in larger treatment-free intervals.

(Regeneron/Bayer), a receptor decoy that targets VEGF with higher affinity than ranibizumab and other currently available anti-VEGF agents. In a double-masked, multicenter phase 2 trial (CLEAR-IT 2), 157 patients with neovascular AMD were randomized to monthly intravitreal injections of VEGF Trap-Eye 0.5 mg or 2.0 mg or quarterly injections of 0.5, 2.0, or 4.0 mg for an initial three-month fixed dose period, after which they received the same doses on an as needed basis at monthly visits up to one year.

At year 1 there was a significant improvement in best corrected VA in all treated groups combined (5.3 letters; P<.0001). The best results were found in patients receiving three monthly doses of the 2-mg strength (9.0 letters; P<.0001 vs baseline).

Another potential therapeutic strategy involves blockade of VEGF effects by inhibiting the tyrosine kinase cascade downstream from the VEGF receptor; vatalanib and pazopanib are drugs in this class currently under exploration. Small interfering RNA (siRNA) technology–based therapies may be able to downregulate the production of VEGF or VEGF receptors by degrading specific messenger RNA. RPE–derived factor–based therapies, nicotinic acetylcholine receptor antagonists, and integrin antagonists are other new drugs under investigation for use in treating wet AMD. The immunosuppressant sirolimus may also be of use in wet AMD.

SUMMARY
Combination therapy is likely to play an increasing role in treating wet AMD. Review of recent clinical evidence suggests that a combination approach may improve VA outcomes, reduce retreatment rates, and consequently result in larger treatment-free intervals. This may lead to a lesser treatment burden for many patients and potentially a reduction of overall treatment costs. Numerous new drugs under investigation suggest that new combinations will follow.

REFERENCES