Parallel with the introduction of new, potent monotherapies for choroidal neovascularisation (CNV), we are facing a clear trend toward individualized medicine. With CNV, this may mean combination therapy. Various US populations confirm that the prevalence of age-related macular degeneration (AMD) increases with age.1-4 The prevalence of AMD in the US population ≥40 years old is estimated at 1.47% (1.75 million cases), and the number of cases is expected to increase by 50% to 2.95 million by 2020.1 Western Europe is estimated to have 3.35 million cases of AMD, and Australia has 130,000 cases.1

**DRAWBACKS OF COMBINATION THERAPY**

All relevant available therapies for CNV have drawbacks as monotherapies. These therapies include photodynamic therapy (PDT) with verteporfin (Visudyne, QLT/Novartis) and anti-vascular endothelial growth factor (VEGF) therapies (ranibizumab [Lucentis, Genentech], bevacizumab [Avastin, Genentech], and pegaptanib sodium [Macugen, OSI/Pfizer]), which have primarily been evaluated in patients with CNV due to AMD (ie, patients age 50 years or older).

While several monotherapies are available for CNV, none is perfect. The benefit is either limited (PDT) or monthly intravitreal injections seem to be required (anti-VEGF drugs). PDT, pegaptanib, and anecortave acetate (Retaane, Alcon) do not improve vision in most patients. Ranibizumab improves vision, but continuous monthly intravitreal injections are required to maintain improved vision. Bevacizumab is believed to improve vision based on its similarity to ranibizumab, but it also appears to require monthly or 6-week injections. A practical need for combination therapy exists to address these shortcomings of monotherapy.

Combination therapy for CNV is derived from the combination therapy concept in oncology. In both therapeutic areas (oncology and ophthalmology), the goal of combination therapy is to disrupt the multiple stimuli that lead to pathologic cellular proliferation. In cancer, tumors and the neovasculature that feeds the tumors are targets, while in CNV, the neovasculature itself is the target.

Numerous factors have been identified as being important in the pathogenesis of CNV due to AMD. Most notably, the role of inflammation and genetic predisposition to inflammation is being elucidated. Complement factor H polymorphism appears to be associated with AMD pathogenesis.5-8

The 3 main therapeutic targets of CNV development and proliferation are therefore the established neovascularisation, angiogenesis, and inflammation. A current therapy that addresses these targets is the combination of verteporfin plus PDT to eradicate established CNV, an anti-VEGF therapy to block angiogenesis, and an anti-inflammatory approach to stop inflammation. The rationale for combination therapy with 2 or all 3 of these agents has been described in detail.9-12

Evidence for combination comes from several trials. First, verteporfin plus PDT was combined with intravitreal triaminolone acetonide (TA). Available data for this combination were reviewed in 200513 and 2006.14 The major drawback of this approach was the relatively high risk of increases in intraocular pressure, which may even occur as late as 9 months after therapy. With the introduction of intravitreal anti-VEGF therapies for CNV, the opportunity arose for combination therapy that would provide better vision outcomes and safety profile than the PDT plus TA combination.

**PATIENTS AND METHODS IN OUR CASE SERIES**

A prospective case series evaluated 104 patients with CNV due to AMD who were treated with a combination of PDT plus intravitreal bevacizumab (1.5 mg) and dexamethasone (0.8 mg).11 Reduced-fluence PDT (42 J/cm² given at the standard fluence rate of 600 mW/cm² for a reduced time of 70 seconds) was administered 16 hours before beva-
cizumab and dexamethasone injections.

RESULTS

Patients attended follow-up visits every 6 weeks. After an average follow-up of 62 weeks, the mean increase in visual acuity (VA) was 1.78 lines (8.9 letters; \( P < 0.01 \)). Thirty-nine percent of patients had VA improved by at least 3 lines. Mean decrease in central retinal thickness was 171 µm (\( P < 0.01 \)). No serious adverse events were observed. The Figure shows a clinical example from this series.

In addition to these published studies, results from several other studies have been presented at scientific meetings. These preliminary results have revealed good vision outcomes and/or lower retreatment rates, good safety profiles, and/or favorable morphological effects for double therapies\(^{15-17} \) and triple therapies\(^{18,19} \) with anti-VEGF, PDT, and (for triple therapy) steroid combinations. The ideal AMD therapy would improve vision safely and conveniently (1 treatment). Based on the current data available, combination therapy, and triple therapy in particular, as described above comes the closest to meeting this goal.

The number of available and emerging therapies for the treatment of patients with CNV is increasing. With different therapies, doses, timing, and treatment sequences possible, conducting definitive large randomized trials to determine the best therapy or combination therapy becomes cumbersome if not impossible. The multiplicity of therapies for CNV is both a blessing and a challenge: we have many options to offer patients, but we do not know which option offers the greatest risk/benefit/feasibility profile.

Patient variability and disease manifestation further complicate treatment choices. Disease characteristics such as CNV predominance and morphology, a high variability of VEGF values, and varied inflammatory drivers may ultimately have important implications for treatment choice.

No therapy can claim a cure for CNV. Ultimately, the underlying cause of the disease remains unknown. As current options allow chronic control of the disease’s manifestations, how will the disease now manifest in this setting?

Nevertheless, combination therapy with PDT and ranibizumab or bevacizumab anti-VEGF therapy appears be effective in eradicating CNV, such that vision improvement is comparable to that with ranibizumab monotherapy with fewer retreatments. The addition of a steroid component to target inflammation may provide better longevity of vision improvement so that even fewer retreatments are needed. This is our experience with triple therapy using PDT, bevacizumab, and dexamethasone; in most cases, only 1 treatment was required to maintain vision improvement of nearly 2 lines over a 10-month period.\(^{11} \)

CONCLUSION

Definitive studies are still necessary, but multiple options for therapy remain, and combination therapy is our
COMBINATION THERAPY FOR CHOROIDAL NEOVASCULARISATION

best hope for durable outcome and satisfied patients. RP

REFERENCES

15. Schmidt-Erfurth U, Gabel P, Hehn T; Protect Study Group. Preliminary results from an open-label, multicenter, phase II study assessing the effects of same-day administration of ranibizumab (Lucentis™) and verteporfin PDT (PROTECT Study). Paper presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology; April 30-May 4, 2006; Fort Lauderdale, FL.

Figure 1. Small classic lesion with a large RPE detachment. Left: early and late phase angiography and OCT before therapy; right: early and late phase angiography and OCT >12 months after therapy. Circle indicates the PDT-treated area. VA increased from 20/160 to 20/80. Follow-up is more than 12 months in this case. Only 1 treatment was necessary to achieve a complete regression.