The Role of Verteporfin Photodynamic Therapy in Current Therapy for Exudative Age-related Macular Degeneration

a report by
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Introduction

Exudative age-related macular degeneration (AMD) develops in approximately 10 of out 1000 people per three-year period in the US, which projects an estimated 125,000 new cases per year. Exudative AMD is the commonest cause of legal blindness in developed countries. Given the increasing size of the aging population, this condition presents a substantial threat to quality of life in this group. Fortunately, enormous advances in treatment have occurred in the last few years, and at an accelerating pace. This has resulted in a sea change in both patients' and physicians' expectations from treatment, changing from the beneficial but unsatisfying outcome in 2003 of delayed vision loss, to the current status of the typical patient regaining previously lost vision. This review will detail the advances in pharmacologic therapy of AMD responsible for these improvements in quality of life for patients with this disease.

Thermal laser was the only treatment available for choroidal neovascularization (CNV) until the introduction of verteporfin photodynamic therapy (PDT) in 2000. Several National Institutes of Health (NIH)-funded studies detailed the application of thermal laser for CNV in AMD, ocular histoplasmosis and idiopathic CNV. Unfortunately, only a minority of patients were eligible for treatment with this modality, and those who were treated had a high failure rate. The majority of patients with AMD had occult or poorly defined CNV and were not suitable candidates for a thermal laser approach since the borders of treatment could not be delineated. In addition, patients with subfoveal CNV who were treated with laser lost vision immediately as a consequence of treatment, though there was a benefit of treatment in that they tended to lose less vision over time than their untreated cohorts. It was difficult to convince patients of this benefit.

The first major pharmacological agent for exudative AMD treatment was verteporfin (Visudyne.) This is a benzoporphyrin derivative formulated in a lipid-based solution for intravenous injection. Verteporfin PDT is a two-part treatment. The drug is infused intravenously and accumulates selectively in the endothelial cells of CNV. A low-powered, non-thermal, 689-nanometer laser is then used to activate verteporfin causing release of singlet oxygen. This reactive molecule damages vascular endothelium, which results in vasoconstriction and thrombus formation. This selectively occludes CNV while sparing the overlying retinal circulation.

Verteporfin PDT was evaluated in multiple clinical studies including AMD with classic subfoveal CNV—treatment of AMD with PDT (TAP) study—myopic CNV—verteporfin in photodynamic therapy (VIP) study—and occult or minimally classic CNV—Visudyne in minimally classic (VIM) study). Verteporfin PDT treatment was shown to result in slowing of vision loss in treated patients compared with controls. This treatment was approved by the US Food and Drug Administration (FDA) for use in April 2000 and entered clinical practice. This treatment held the promise of a greater number of treatable lesions, and possible visual improvement, but in fact a minority of patients achieved visual improvement and/or reading vision. Both patients and physicians were frustrated by the typical outcome of slow visual decline as a result of an expensive treatment.

Periocular and/or systemic corticosteroids have long been known to have a suppressive effect on choroidal neovascularization. The use of intravitreal triamcinolone as a treatment for subfoveal recurrent CNV has been explored and was found to be useful in a small study. The combined use of intravitreal triamcinolone and verteporfin PDT was first reported in 2003, and this combination therapy rapidly became frequently utilized by retinal physicians.

This was the first treatment of exudative AMD in which visual improvement was more common than gradual visual deterioration. Another attractive aspect of this treatment was the long duration of closure of the CNV. One treatment often led to no need for retreatment for six or nine months or in some cases, years. Intravitreal triamcinolone has several potential complications including cataract acceleration, endophthalmitis (sterile and otherwise), and elevation

of intraocular pressure. This last complication occurs in up to 30% of patients and results in the need for surgical glaucoma intervention in 1% of patients in some studies. This combination treatment has not been subjected to randomized studies though numerous case series have reported positive results.

Vascular endothelial growth factor (VEGF) is a protein secreted as a response to ischemia in tissues. This growth factor is a stimulant for new blood vessel growth in the eye, as well as elsewhere in the body. A number of therapeutic approaches to suppression of VEGF have been pursued. Three of these are important to the eye to date. Pegaptanib (Macugen) was the first of the anti-VEGF therapies to be approved for treatment of exudative AMD. This is an oligonucleotide that binds to extracellular VEGF. The recommended treatment involved monthly intravitreal injections with no definite end point. The pre-approval studies of its usefulness showed a slowing of vision loss to a degree quite similar to PDT with Visudyne. Macugen offered the ability to treat a broader range of choroidal neovascular membranes than were treatable with verteporfin PDT, but the retinal specialists' experience with Macugen has been somewhat disappointing.

Bevacizumab (Avastin) is an anti-VEGF antibody that was FDA-approved for treatment of metastatic colon cancer and is administered systemically for this treatment. Philip Rosenfeld explored the use of systemic Avastin to treat exudative AMD and found that the treatment was beneficial, but the systemic risks were unacceptably high. He then initiated intravitreal treatment with Avastin in early 2005 and found strikingly good results with patients on average gaining vision. The news of the apparent significant suppression of CNV by intravitreal treatment with Avastin spread through the retina community rapidly, and this soon became the treatment of choice for exudative AMD or any cause of CNV. The intraocular dose administered is equal to 1/400 of the systemic dose of Avastin, and systemic complications were expected to be rare. An additional benefit for patients was that the cost per injection was quite low, as a single cancer dose could be divided 400 times for ocular treatment.

Ranibizumab (Lucentis) is a fragment of the anti-VEGF antibody that was still going through clinical testing for FDA approval and was not yet available. Most clinicians felt that Avastin as the parent molecule of Lucentis was quite likely to have a similar treatment benefit to Lucentis and, in fact, the clinical experience of most treating physicians was similar to what was being reported in the Lucentis trials. The theoretical advantage of Lucentis is that the small antibody fragment would penetrate the retina more readily. As of the spring of 2006, intravitreal Avastin was the most common treatment for exudative AMD. Lucentis was approved by the FDA in June 2006 and is now commercially available. This has been tested for the eye in controlled studies, and has a proven safety profile, which are advantages over Avastin. However, it must be given monthly, and is 40 times as expensive as Avastin, so it is unclear which of these drugs will be used most often. A trial comparing the two is in development.

The combination of verteporfin PDT and anti-VEGF drugs is a logical one. PDT uses photodynamically mediated thrombosis to close CNVs but when used alone often requires multiple treatments because the lesions reperfuse. Animal studies have also shown that repeated PDT can lead to increased VEGF expression, which may work against the initial lesion closure. It has certainly been observed that PDT alone requires upwards of six treatments to permanently close a CNV, generally with some loss of vision, while PDT plus intraocular steroids resulted in much earlier and more permanent closure of CNV with, on average, some increase in vision. There also is some evidence that anti-VEGF drugs induce increased VEGF expression over time, which can lead to treatment resistance. This makes a compelling argument for the combination of PDT and an anti-VEGF drug to try to get a more permanent CNV closure with fewer treatments. There is a great deal of interest in combination therapy at present. The program of the 2006 American Society of Retina Specialists/ European Vitreoretinal Society (ASRS/EVRS) meeting in Cannes, France, includes two papers addressing Lucentis and PDT, four papers addressing Avastin and PDT and four papers addressing triamcinolone and PDT. In a review of PDT combined with Avastin, Dhalla et al. found that 63% of patients treated with this combination required a single treatment over a seven-month period of follow-up and gained, on average, two lines of vision.

Given the advent of effective treatments for exudative AMD, most of which require multiple treatments in a growing population of at risk individuals, the retinal community is being inundated with new and returning patients with AMD. In addition, these treatments are expensive with projected annual costs per patient of US$12,000–20,000 per year. These two considerations place an enormous burden on the healthcare system. For these two reasons alone, the promise of good visual outcomes after fewer treatments with combination therapy is attractive. Sorting out the most effective combination treatment approaches will take some time and will likely be dependent on small, investigator-driven studies. These are exciting times, and the future of treatment of exudative AMD is increasingly bright.