Trials That Matter: Two Faces of Progress in the Treatment of Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a common ocular condition that may destroy central vision and have a devastating effect on the quality of life of people over the age of 55. Since the population of the United States is now living longer, more people are at risk for developing the disease as the population ages. By age 70, nearly 1 of 3 people shows signs of at least mild AMD on ophthalmologic examination.

The earliest recognizable manifestation of AMD is the presence of drusen—white deposits that can be observed in the macula during an ophthalmoscopic examination. Patients with drusen are classified as having early (dry) AMD. These patients may have no visual symptoms or may require additional light to read small print. Most patients with dry AMD will never develop severe vision loss or progress to late (wet) AMD.

Some patients with drusen, however, develop leaky blood vessels, a form of wet AMD known as choroidal neovascularization. Leakage of fluid or blood from choroidal neovascularization can cause a precipitous loss of central vision. Fluorescein angiography, a diagnostic technique used frequently by retina specialists, facilitates the categorization of patients with choroidal neovascularization into 3 groups: predominantly classic, minimally classic, and occult. These angiographic categories have been useful in predicting the outcome of the disease and in developing guidelines for photodynamic therapy of AMD.

Until recently, the only pharmacologically based therapies for treatment of patients with wet macular degeneration have been photodynamic therapy with verteporfin and intravitreous injections of pegaptanib sodium. Although the pathophysiology of AMD is still poorly understood, it is increasingly clear that vascular endothelial growth factor A plays an important role in the promotion of neovascularization and the vessel leakage that leads to loss of central vision. While vascular endothelial growth factor A occurs in several biologically active forms, a recombinant, humanized monoclonal antibody Fab, ranibizumab (marketed as Lucentis [Genentech, Inc., Vacaville, California]), neutralizes all forms of this growth factor. Two recently published phase 3 trials give hope for better control of neovascular AMD but also raise major issues about appropriate management strategies that use this expensive new drug.

What Did These Landmark Trials Show?

The first trial, a 2-year, prospective, randomized, double-blind, sham-controlled, multicenter study of monthly intravitreous injections of ranibizumab, enrolled 716 patients with minimally classic or occult choroidal neovascularization (1). The goal was to evaluate the efficacy of ranibizumab in slowing visual loss over the course of the trial. After randomization of the patients into 3 groups, investigators administered intravitreous injections at 2 different dose levels (0.3 mg or 0.5 mg) of ranibizumab or sham injections every 4 weeks. Ninety-five percent of patients who received either dose of ranibizumab maintained stable vision (defined as fewer than 3 lines of vision loss) at 12 months, compared with 62% in the sham group. In addition, one quarter of the patients treated with the lower dose of ranibizumab and one third of those treated with the higher dose actually gained significant visual acuity during the course of the study, compared with 5% of those in the sham injection group. Improvement in visual acuity scores was evident in the ranibizumab-treated patients within 7 days after the first injection. Serious ocular adverse events included presumed endophthalmitis in 1.0% of patients, which was attributed to the injection procedure, and uveitis in 1% to 2% of patients, which was attributed to ranibizumab. Nonocular adverse events of the type that have been associated with intravenous administration of the drug, such as vascular and thromboembolic events, are common in an elderly population. However, these events occurred in fewer than 4% of participants and did not differ significantly in frequency or severity between those receiving intravitreous ranibizumab and those receiving sham injections. The results were similar at 24 months.

The second trial, published simultaneously with the first, compared ranibizumab with a well-established modification of laser therapy that depends on concentration of intravenously administered photosensitizing pigment in abnormal subfoveal vessels followed by application of low-intensity laser therapy. This trial reports the results of the first year of a 2-year, phase 3 comparison of the efficacy and safety of repeated intravitreous ranibizumab injections versus photodynamic therapy with verteporfin in patients with predominantly classic neovascular lesions (2). Patients in this trial received either 0.3 or 0.5 mg of ranibizumab plus sham verteporfin therapy (140 patients in each group) or sham injections plus active verteporfin photodynamic therapy (143 patients). The primary efficacy end point consisted of a measure of loss of visual acuity identical to that used in the first trial and showed that significantly more patients retained a prespecified level of visual acuity in the ranibizumab groups (94.3% of patients who received 0.3 mg and 96.4% of those who received 0.5 mg ranibizumab) than those who received verteporfin (64.3%). As in the first trial, significant improvement in visual acuity occurred more frequently in the ranibizumab groups (35.7% in patients treated with 0.3 mg and 40.3% in patients treated with 0.5 mg) than in those treated with verteporfin (5.6%). Serious ocular adverse events were un-

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common: 1 patient had endophthalmitis and 2 patients had uveitis in the higher-dose ranibizumab group. One episode of rhegmatogenous retinal detachment (detachment resulting from a hole or tear in the retina) and 1 episode of vitreous hemorrhage occurred in patients receiving the lower dose of ranibizumab.

How Do These Trials Advance Knowledge?

Inhibitors of vascular endothelial growth factor A have held tempting possibilities for the treatment of choroidal neovascularization since the first of this class of drugs, bevacizumab (marketed as Avastin [Genentech, Inc.]), was approved by the U.S. Food and Drug Administration in 2004. Bevacizumab was initially approved for treatment of metastatic colorectal cancer, in which it functioned as an inhibitor of tumor-vessel growth. Shortly after its approval for that indication, ophthalmologists began off-label use of the intravenous preparation to treat the vascular lesions of AMD (3). The idea of using a much lower dose of bevacizumab by intravitreous injection for AMD was conceived because the cost of treatment could be dramatically decreased by using much smaller doses administered locally to the eye, and the smaller doses could reduce the risk for systemic exposure. Use of intravitreous bevacizumab for treatment of AMD quickly gained traction among ophthalmologists despite the absence of data from any randomized clinical trial to support its use. The factors that drove this phenomenon included both the reasonable cost and the fact that a therapeutic effect was obvious within 24 hours of the first treatment. Bevacizumab was quickly and widely adopted as a first-line therapy for neovascular AMD by many retina specialists in the United States because ranibizumab had not been approved by the U.S. Food and Drug Administration. Subsequent uncontrolled, consecutive case series supported the contention that bevacizumab is effective for treatment of neovascular AMD (4, 5).

Ranibizumab, the subject of the 2 trials described above, is biologically related to bevacizumab but is specifically formulated for use in the eye. Whereas bevacizumab is a complete monoclonal antibody with a relatively large molecular size (150 kd), ranibizumab is a much smaller fragment (49 kd) of a monoclonal antibody that may be able to penetrate the retina more easily, thereby making it a more effective therapeutic agent. The 2 randomized, controlled trials described here reliably demonstrate that ranibizumab is highly effective and has an acceptable safety profile.

Should Clinicians Adopt Ranibizumab as the Standard Therapy for AMD?

Although these trials suggest that ranibizumab is a significant step forward in the treatment of neovascular age-related macular degeneration, no evidence suggests that it is better than bevacizumab. The question of relative efficacy is one of great medical, social, and financial importance. Ranibizumab—at a cost of $1950 per injection—is 50 times more expensive than bevacizumab, and current regimens call for an injection every 28 days for 2 years. With up to 200 000 new cases of neovascular AMD annually in the United States, the annual drug cost alone would exceed $10 billion. Bevacizumab costs $50 per injection and its treatment frequency—usually much less than once per month—is based on clinical response. The calculation of cost is further complicated by the fact that the optimum duration of therapy with these drugs is not known, owing to the lack of long-term studies. Ranibizumab must not only be proven effective to be accepted as standard therapy, it must be proven substantially more effective than its much less expensive alternative. Since no study comparing these drugs has been performed, such proof does not exist. However, the National Eye Institute, part of the National Institutes of Health, has recently funded investigators at Emory University, University of Pennsylvania, and Duke University to conduct a head-to-head comparison of bevacizumab and ranibizumab. The researchers plan to enroll 1200 patients at 40 clinical centers across the United States in this multicenter, randomized clinical trial, which will compare these 2 drugs directly, evaluate different dosing strategies, and determine other variables that might predict a favorable outcome with less frequent injections.

Age-related macular degeneration is a disease that seriously degrades the quality of life of many patients under the care of general internists. The prospect of developing and testing effective treatments for this disease should galvanize the internal medicine community, increasing its vigilance for early signs of AMD in patients and encouraging an active interest in the evidence basis for treatments that hold promise for its control. Now that the scientific possibilities for control of AMD are expanding, proceeding with a direct head-to-head comparison of the 2 drugs is the only socially responsible way to provide answers. The financial cost of such a study will be high, but the cost of failing to provide a reliable answer may be even higher.

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