Can further studies lower the cost of preserving vision?

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The results of two large, randomized clinical trials published October 5, 2006, in the *New England Journal of Medicine* demonstrate that the drug ranibizumab is an effective treatment for neovascular macular degeneration, a complication of age-related macular degeneration that leads to the vast majority of legal blindness associated with the disorder.

In an accompanying editorial, Howard Hughes Medical Institute investigator Edwin M. Stone at the University of Iowa contends that now that these trials have shown the drug's "miraculous" effects on patients' eyesight, a crucial next step is to compare ranibizumab to a related drug, bevacizumab. Although it is not FDA-approved for use in the eye, bevacizumab also appears to be effective in treating neovascular macular degeneration. Importantly, a single dose of bevacizumab costs less than $150, compared to more than $2,000 per dose for ranibizumab.

Both ranibizumab and bevacizumab work by inhibiting a protein known as vascular endothelial growth factor (VEGF), which promotes blood vessel growth. Bevacizumab was originally designed to block blood vessel growth in tumors, halting cancer cells' growth by eliminating their oxygen supply. In 2004, bevacizumab, which is marketed by Genentech under the brand name Avastin, was approved by the FDA for the treatment of metastatic colon cancer.

In neovascular macular degeneration, new blood vessels grow underneath the retina, altering the eye's structure and function. Only about 10 percent of patients with macular degeneration develop

neovascularization, but in those who do, the effects are often severe. While blocking blood vessel growth is exactly what doctors who treat neovascular macular degeneration would like to do, some scientists suspected bevacizumab might be too large a molecule to reach the part of the eye where it was needed. Ranibizumab is a smaller molecule, specifically designed to eliminate this problem.

In the two clinical trials published in the *New England Journal of Medicine*, researchers showed that monthly injections of ranibizumab on average improved eyesight in patients with neovascularization, whereas vision continued to decline on average in patients who received either placebo or photodynamic therapy. In June of 2006, based in part on the results of these trials, the FDA approved ranibizumab, which Genentech markets as Lucentis, for treatment of neovascular macular degeneration.

"The results of these two studies are extremely encouraging," Stone said. "But now some important unresolved questions need to be answered." In particular, he urges researchers to follow up on the current studies with a trial to evaluate the ideal dosing strategy for anti-VEGF drugs – suggesting that the two years of monthly injections given in the Rosenfeld, et al., study might be far more than most patients need. Equally important, Stone said, are clinical trials that directly compare the efficacy of ranibizumab to those of bevacizumab.

Prior to the completion of the ranibizumab trials, some physicians had already begun using bevacizumab as an "off-label" treatment for neovascular macular degeneration. Injecting a very small portion of the dose typically prescribed to a cancer patient directly into the eye, they found, was remarkably effective at treating neovascularization. Within months of the initial reports of the drug's efficacy, Stone said, hundreds of doses of bevacizumab had been given, and papers reporting uncontrolled, retrospective studies began to appear. "These were not randomized, double-masked trials," he pointed out, "but to those of us

who had been taking care of people with this disease for a while, it was evident that this was pretty potent stuff -- the best we'd ever had."

"Tens of thousands of doses of Avastin were given nationwide, while doctors were waiting for ranibizumab to get approved," Stone said. "And it often worked very well. But what no one knows at the moment is whether one drug is really significantly better than the other."

It's important to find out, Stone argues, because a single dose of ranibizumab often costs more than $2,000, compared to less than $150 per dose for bevacizumab. "It does matter how much it costs," Stone said – particularly for patients with an age-related disease such as macular degeneration, who often have fixed incomes and limited health insurance.

"Ranibizumab is an absolutely spectacular drug compared to treatments we had in the past," Stone said. "But what if it turns out that the $150 stuff is just as good?"

Source: Howard Hughes Medical Institute