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OP-ED

Drugs, Doctors, Profits, and Conflicts of Interest—Avastin versus Lucentis

Stephen R. Kaufman, MD

Fee-for-service private practice frequently generates conflicts of interest between the financial goals of the practice and the needs of a patient or the health care system at large. In fee-for-service-based practices, physician income is generally linked to the number of patients seen, the number of procedures performed, and, occasionally, the choice of therapeutics. Many physicians can now generate money by using more expensive medications, a situation that pharmaceutical companies can exploit by offering physicians inducements to use costlier drugs. For example, the choice ophthalmologists make when deciding between Avastin and Lucentis for the management of age-related macular degeneration (ARMD) illustrates how fee-for-service conflicts of interest might compromise patient care and burden the health care system.

Age-related macular degeneration is a leading cause of legal blindness (visual acuity 20/200 or worse in each eye) among senior citizens. The main cause of vision loss in exudative ARMD is new blood vessel growth (neovascularization) underneath the retina, which eventually results in permanent damage to the retinal photoreceptors from fluid leakage and bleeding underneath the retina and swelling of the retina itself. Scar tissue forms, leaving patients with poor central vision. Since the formation of new blood vessels leads to central vision loss and substantial visual disability in these patients, interventions have focused on impeding neovascularization in the eye through the use of vascular endothelial growth factor (VEGF) inhibitors, which induce regression of the new blood vessels and decrease retinal edema.

The development of effective VEGF inhibitors has had an effect on the management of age-related macular degeneration that is little short of miraculous. Prior to the introduction of these agents, patients with exudative ARMD generally lost vision, usually to degrees that severely compromised their reading, facial recognition, and driving abilities. The VEGF inhibitors have maintained or improved vision for a large fraction of patients, helping to preserve their quality of life. Originally used primarily to treat ARMD, VEGF inhibitors are now used in management of forms of diabetic retinal disease, glaucoma, and other eye conditions that may be related to aberrant blood vessel growth or retinal edema.

Though anti-VEGF treatment has had significant public health benefits, it has also raised some challenging ethical issues. Since their introduction in 2005, bevacizumab (Avastin) and ranibizumab (Lucentis) have been the two dominant

anti-VEGF agents on the market. Studies [1, 2] suggest the two drugs are comparable, but Medicare reimbursement for FDA-approved uses of Lucentis is over \$2,000 per treatment, while Avastin, which has been FDA approved for systemic (but not intraocular) use, costs Medicare less than \$55 per injection. This per-treatment cost difference can present a conflict of interest to treating ophthalmologists.

Looking at Benefits

In terms of efficacy, Lucentis is a smaller molecule than Avastin, and might more readily cross the retina (i.e., have greater effect), but it might also be cleared by the eye more quickly. Many ophthalmologists share my experience that Lucentis has a shorter duration of action and requires more injections over time than Avastin. Initial clinical trials with Lucentis involved monthly dosing for 2 years, and it appears that this regimen may be optimal for preservation of vision. Adding the injection procedure cost to the drug cost, the total cost of treatment for 2 years can exceed \$50,000 for one eye, and it is not uncommon for patients to need more than 2 years of treatment. To reduce these costs, many ophthalmologists increase the time between treatments for stable patients or choose to observe patients closely without treatment once they feel it is safe.

Because exudative ARMD is a leading cause of legal blindness among senior citizens, Lucentis has increased Medicare expenses for eye disease substantially, now amounting to over \$500 million per year. Were it not for Avastin's use, that figure would likely be about 150 percent higher [3]. From a health care finance standpoint, it is fortunate that Avastin also became available in 2005 and was quickly covered by Medicare. Since that time, it appears that most retinal specialists have chosen Avastin over Lucentis [4]. Still, many retinal specialists prefer to use Lucentis. Why might that be so?

Lucentis is FDA-approved for treating ARMD, having undergone thorough safety and efficacy testing for that condition. In contrast, use of Avastin in the eye is off label. Avastin was originally approved by the FDA for use in metastatic colon cancer, and there are no long-term ophthalmic studies. Nonetheless, short-term studies have documented Avastin's safety and efficacy for ARMD, and clinicians now have vast experience with the drug, with Avastin injections probably numbering in the millions.

Clinical experience has provided substantial evidence for Avastin's ocular safety, but some clinicians have raised concerns about the possibility of thromboembolic events. When Avastin was given systemically to colon cancer patients at a dose approximately 300 times greater than the ocular dose and given every two weeks (rather than every 4-6 or more weeks in the eye) the colon cancer patients (who have significant comorbidity and are on other anti-neoplastic agents) had a rate of thromboembolic events of 4.4 percent (the rate in the control population was 1.9 percent) [5]. If there is any increased risk of systemic thromboembolic events among patients receiving ocular Avastin treatment, it is likely very low.

The National Eye Institute's ongoing Comparison of AMD Treatment Trials (CATT) compares the safety and efficacy of Avastin to Lucentis. Initial results of the CATT will not be available until 2011. While the CATT will provide more definitive data, two nonrandomized trials comparing Avastin and Lucentis have indicated that the drugs have similar safety and efficacy. [1, 2].

Examining Costs

Deciding whether to recommend Avastin or Lucentis raises ethical issues that have significant implications for public health and health care financing. If a physician considered Lucentis marginally superior to Avastin, should the public health consequences of using a far more expensive drug trump what the doctor thinks is best for an individual patient he or she is treating at the moment?

I think society at large must decide how to allocate limited public health resources, and we as physicians are obliged to be advocates for our patients. However, it can sometimes be difficult to discern what is truly best for them. Physicians and practices stand to generate substantially greater income from Lucentis, a fact that could influence the choice between Avastin and Lucentis and generate conflicts between the financial goals of the practice and the needs of patients. For medications delivered in the office, Medicare reimburses drug cost plus 6 percent above average wholesale cost, which is a significant figure for a frequently used drug that costs clinicians \$1,995 per treatment. Further, if Lucentis requires more frequent injections than Avastin, using it increases the number of injection procedures that can be billed.

In addition to existing financial incentives to use Lucentis, the *New York Times* has revealed a secret rebate program in which Lucentis's manufacturer, Roche, has recently started to offer physicians financial inducements (about \$60 per dose) for prescribing large quantities of the drug and for increasing quarterly use. Many retinal specialists perform 1,000 injections per year, and some perform far more. Therefore, choosing Lucentis can generate substantial income without increasing physicians' work. Evidently, Roche is betting that increased revenue more than offsets the cost of the program. To the degree that Roche is correct that the rebate program influences physician choice, physicians are compromising what they regard as best patient care for the sake of financial gain.

Given the demand for anti-VEGF treatment, the physician's potential gain from using Lucentis is substantial. I would hope that this does not influence treatment decisions, and it may be that those who prefer Lucentis are genuinely convinced that it is more effective. However, our minds are very adept at rationalizing self-serving conclusions, and we humans often struggle to ascertain our true motives. Indeed, it appears that Roche expects physicians to be more influenced by financial considerations than they will admit in public, and perhaps than they will admit to themselves.

There is no easy resolution of this problem, particularly in a health care system that grants physicians considerable autonomy and, for the most part, still rewards them

on a per-treatment basis. Given that steadily rising health care costs are not sustainable, society might need to restrict physician autonomy. For example, Medicare might place limits on expensive treatments, such as Lucentis for ARMD. Medicare could require that certain criteria must be met—for example, proof that Avastin has not improved the patient's condition—before it will reimburse for Lucentis. Physicians greatly value their autonomy, yet our society might reasonably wish to curtail it if there are good reasons to believe that physician decisions are influenced by self-interest to the detriment of public health.

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Stephen R. Kaufman, MD, is an assistant professor in the Department of Ophthalmology and Visual Sciences at Case Western Reserve University School of Medicine in Cleveland, Ohio, a member of a private practice specializing in retinal diseases, and a participant in the Diabetic Retinopathy Clinical Research Network.

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