

# Avastin versus Lucentis: Why It Matters

Although Lucentis is a remarkably safe and effective treatment for exudative macular degeneration, it could cost our health care system over \$9 billion, which poses substantial risks to the economic viability of ophthalmology. Fortunately, it appears that Avastin is roughly equal to Lucentis in safety and efficacy, and Avastin's far lower cost makes it an attractive alternative. We encourage wider use of Avastin, which can help sustain the health care system that has benefited our patients medically and ourselves professionally.

Rising health care expenses (to which drug costs have contributed heavily) are unsustainable. In response to these rising costs, Medicare has been attempting to reduce all physicians fees, a move Congress blocked at the last minute this year. Right now, ophthalmology faces annual cuts of 1% for four years plus a 3% cut in certain commonly used ophthalmology codes due to revised work values.

## How Might Lucentis Affect Physician Compensation?

Medicare Part B pays for physician services as well as drugs delivered in offices. In ophthalmology, Visudyne and Macugen have caused sharp increases in Medicare Part B expenses, and the impact of Lucentis is likely to far exceed that of Visudyne and Macugen combined. There are more than 200,000 new cases of exudative age-related macular degeneration (AMD) in the U.S. each year,<sup>1</sup> and we estimate that about 85% are treatable. The cost of Lucentis is about \$2227 per injection,<sup>2</sup> and the MARINA study<sup>3</sup> showed benefit from monthly Lucentis injections for two years. Therefore, after one year, Lucentis costs in the U.S. could exceed \$9 billion.<sup>4</sup>

The fact that some physicians use less than 24 treatments tempers this figure. For example, some use the PIER or PrONTO protocols.<sup>5</sup> Also, many providers currently treat exudative AMD primarily with Avastin. On the other hand, exudative AMD appears to be a recurrent condition, so many successfully treated patients may need additional rounds of therapy, just as

many of our PDT patients have developed recurrences after initial closure of the choroidal neovascular membrane (CNVM).

To put this \$9 billion figure in perspective, in 2006 the *total* Medicare Allowed Charges for *all* of ophthalmology is \$4.77 billion. That total covers physician fees, practice expenses, malpractice Relative Value Units, and imaging. In 2004, total spending for all Medicare Part B drugs for *all* medical fields was about \$12 billion. Compare the approximate \$53,448 cost of treating one eye with Lucentis monthly for two years to the \$46,326 median annual household income in the U.S. in 2005.

## Avastin's Benefits

In contrast to Lucentis' cost, the drug cost for Avastin is only about \$50 per dose. Further, many clinicians have noted that Avastin seems to be longer-acting than Lucentis, perhaps because Avastin's larger size impedes clearance from the eye. Consequently, many clinicians use a less frequent dosing regimen with Avastin than Lucentis.

## Why Would Ophthalmologists Use Lucentis?

Although Avastin is a safe, effective, inexpensive treatment of exudative AMD, some ophthalmologists have offered the following reasons to use Lucentis:

1. Lucentis is FDA-approved for this indication.
2. Unlike Avastin, Lucentis has been studied with a randomized clinical trial, and the data for Lucentis are more long-term data than those of Avastin.
3. Lucentis may be safer than Avastin.
4. Lucentis has greater activity *in vitro* and Lucentis is a smaller molecule designed for better retinal penetration.

We'll address each of these reasons in turn. First, most U.S. prescriptions are for off-label use. There is compelling evidence of Avastin's safety and efficacy for CNVM in AMD based on published reports<sup>6</sup> and widespread clinical use. Consequently, the federal Medicare program offers coverage for intraocular Avastin for this indication.

Second, Avastin and Lucentis are structurally very similar, and ophthalmologists' short-term experience with Avastin has shown results comparable to those with Lucentis. The planned National Eye Institute head-to-head study should clarify this issue.

Third, after thousands of applications, the ocular safety of both Lucentis and Avastin has been well demonstrated. In terms of systemic safety, thromboembolic events (such as angina, heart attacks, and strokes) have been the main concern. The systemic safety of Lucentis' has been well-documented. Among patients using Avastin systemically for metastatic colon cancer, 4.4% who had Avastin in combination with 5-

fluorouracil had thromboembolic events, compared to 1.9% who received chemotherapy alone. However, this finding is of doubtful relevance to ocular use of Avastin. The ocular dose (1.25 mg) is about 1/300th of the systemic dose (5 mg/kg) used to treat metastatic colon cancer. Colon cancer patients receive treatment every two weeks, while intraocular injections of Avastin are generally at least 6 weeks apart. Therefore, ocular Avastin results in roughly 1/1000th of the systemic exposure. The increased risk of thromboembolic events occurred only in colon cancer patients who concurrently used intravenous 5-fluorouracil, so the increased risk may reflect drug interactions. Finally, colon cancer often leads to hypercoagulable state, which predisposes the patient to thromboembolic events. As a smaller molecule, Lucentis has a shorter systemic half-life than Avastin, but it is unknown whether Lucentis has less systemic toxicity.<sup>7</sup>

Fourth, in practice Lucentis does not appear to be more effective than Avastin. It may be that the 1.25 mg Avastin dose effectively blocks all VEGF receptors, and any additional potency of Lucentis does not confer additional effect. Lucentis' smaller size may turn out to be a drawback, because Lucentis may clear the eye too quickly to work as well as, or as long as, Avastin.

## Are Medicolegal Concerns with Avastin Reasonable?

We see no reason to believe that ocular use of Avastin poses significant risk of systemic toxicity or more such risk than other anti-VEGF ocular drugs. While some providers avoid Avastin in patients with a recent thromboembolic event,<sup>8</sup> ocular Avastin has become a standard of care for most exudative AMD patients. An Internet survey of the American Society of Retinal Specialists (ASRS) with 278 respondents found

that 59.79% usually recommend Avastin for patients with subfoveal CNVM due to AMD when these patients have both Medicare and secondary insurance coverage (17.6% of these recommend Avastin plus PDT for such patients). For patients without secondary coverage, for whom the co-payment on Lucentis treatment is substantial, 79.63% of ARSR respondents usually recommend Avastin (14.2% of these recommend Avastin plus PDT).

### ***What Other Factors Influence Pharmaceutical Use?***

Pharmaceutical companies have always been eager to court “opinion-shapers,” academic clinicians whom their colleagues trust to offer informed recommendations. The companies readily sponsor research by these academicians, hire them as consultants, and pay them for speaking engagements. These people deny that their objectivity has been compromised, but a general review of industry-sponsored research showed a bias in favor of the sponsoring company’s products.<sup>9</sup> Of course, many academicians do speak their minds, regardless of corporate relationships.

### ***Who Is Paying for Lucentis?***

For many years, growth in government expenditures for health care has exceeded the rate of inflation. Such growth is not sustainable. In an attempt to control rising costs, there are federally mandated restrictions on Medicare cost increases, effectively putting health care providers in direct competition with drug companies for limited Medicare Part B dollars. If we cannot control pharmaceutical costs, our patients will suffer, and we ophthalmologists will likely

suffer as well. While it may be more politically expedient in the short term for Medicare to cut reimbursement to physicians than to reduce benefits, rising health care costs will eventually result in larger patient premiums, increased co-payments, or reduced access to care. Ultimately, our patients will suffer to the degree that the health care system is financially crippled.

### ***What about Patients Who Demand Lucentis?***

Genentech’s media blitz has encouraged many people to request Lucentis. We tell patients that Avastin appears roughly equal in safety and effectiveness. One reason we prefer Avastin is that it may require less frequent injections, which would help reduce the risks of anti-VEGF treatment. We also note that, for people without secondary insurance, the out-of-pocket cost of Lucentis is much higher. Then we leave the choice to our patients. When using Lucentis, we generally follow the PrONTO study guidelines. That protocol often results in far fewer than 24 treatments for each CNVM episode.

### ***What Should We Do?***

Until the NEI completes its recently announced study of Avastin versus Lucentis, we need to carefully monitor outcomes. As professionals, we have obligations to society-at-large as well as our patients. We ophthalmologists, alone, cannot fix the growing health-care crisis. However, particularly in this new era of extremely (we think outrageously) expensive drugs for macular degeneration, we should be mindful of the public-health consequences of our practices.

1. Postgrad Med 1998;103(5):153-164.
2. \$1950 (wholesale cost) + \$97.50 (Average Wholesale Cost mark-up) + \$180 (approximate injection fee).
3. New Eng J Med 2006;355:1419-1431.
4. After one year, there could be 170,000 eyes receiving monthly treatments and another 170,000 added in the second year. Each eye would receive 12 treatments per year at \$2227 per treatment.
5. Ophthalmol Clin North Am 2006;19(3):361-372.
6. Ophthalmol 2006;113:363-372; Am J Ophthalmol 2006;142:1-9; Retina 2006;26:383-390.
7. New Eng J Med 2006;355:1409-1412.
8. Ophthalmol 2006;113:363-372
9. Br Med J 2003;326:1167-1170.

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STEPHEN R. KAUFMAN, M.D., CLEVELAND, OH  
LEON A. BYNOE, M.D., FORT LAUDERDALE, FL  
JAMES G. RANDALL, M.D., MISSOULA, MT  
J. GREGORY ROSENTHAL, M.D., TOLEDO, OH

*All authors are retinal specialists.*

Those without ties to pharmaceutical industries interested in joining a grassroots effort to disseminate unbiased assessments about the risks and benefits of therapies for AMD should e-mail [pharmeal@yahoo.com](mailto:pharmeal@yahoo.com).

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Medical Research Modernization Committee  
P.O. Box 201791  
Cleveland, Ohio 44120