

*Avastin versus Lucentis: Why It Matters**

Remarkable advances in treating macular degeneration have come with a huge price tag of over \$1 billion in drug costs annually, significantly burdening our strained health care system. Fortunately, Avastin is an affordable, effective therapy for macular degeneration. Why isn't it the predominant choice for our patients?

As physicians, we have an obligation to protect the interests of society by utilizing limited health care dollars responsibly. Growing health care expenses (to which rapidly rising drug costs have contributed heavily) are unsustainable, and there are consequences for physicians as well as society in general. Because office drug use and physician fees come from the same Medicare Part B allocation, rising drug costs impact physician compensation. Indeed, Medicare has been attempting to reduce all physician fees, a move Congress blocked at the last minute in 2006. Meanwhile, in 2007 ophthalmology experienced a 3% cut for certain commonly used ophthalmology codes, and we face annual cuts of 1% for four years. Further, there are prospects of deep Medicare cuts for physicians in general and ophthalmologists in particular.

How Might Lucentis Affect Physician Compensation?

In 2007, Lucentis sales will likely exceed \$800 million.¹ To put this figure in perspective, the projected 2008 total Medicare Allowed Charges for *all* of ophthalmology is \$4.642 billion. That \$4.642 billion covers office-administered drugs (like Lucentis, Visudyne, and Macugen), physician fees, practice expenses, malpractice Relative Value Units, and imaging.

With Lucentis costing \$1950, treating a single episode of exudative age-related macular degeneration (AMD) in one eye with monthly doses of Lucentis for two years per the MARINA and ANCHOR study protocols would cost a staggering \$53,280.² Compare this figure with the median annual household income in the U.S. in 2005 – \$46,326. While alternative protocols, such as PrONTO and PIER, could reduce the number of injections by as much as 75%, Lucentis' potential public health burden is huge, given that there are 200,000 new cases of exudative AMD in the US each year.

In contrast, the cost for treating a patient with

Avastin, using a typical regimen of 4-5 doses, is about \$1000-1200.

Avastin's Benefits

In contrast to Lucentis' cost, the drug cost for Avastin is only about \$50 per dose. Further, many treating physicians 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 long-term, randomized clinical trials.
3. Lucentis might be safer than Avastin.
4. Lucentis is designed for better retinal penetration and has greater activity *in vitro*.
5. Avastin has medico-legal liability.

1. *Avastin is approved:*

While not approved by the FDA for ocular use, Avastin has been approved by Medicare for reimbursement, because it has become a standard of care in the medical community.

2. *Avastin has been studied:*

Avastin and Lucentis are structurally very similar, and ophthalmologists' collective experience with Avastin has shown results comparable to those with Lucentis.³ The planned two-year NEI/CMS head-to-head study should further clarify this issue. Indeed, the National Eye Institute's sponsorship demonstrates its confidence in Avastin's safety and efficacy.

3. *Avastin is safe:*

After thousands of applications, the ocular safety of both Lucentis⁴ and Avastin⁵ has been well demonstrated. In terms of systemic safety, thromboembolic events (such as angina, heart attacks, and strokes) have been the main concern. Preliminary long-term data indicate that Lucentis in the ocular dose of .5 mg (as currently prescribed) has a four-fold increased risk of stroke compared to a .3 mg dose, and this risk seems to involve primarily people with a history of prior stroke.⁶ There is less long-term data on ocular use of Avastin. Among patients using Avastin systemically for metastatic colon cancer, 4.4% who had Avastin in combination with other colon cancer chemotherapies had thromboembolic events, compared to 1.9% who received various colon cancer chemotherapies and no Avastin. However, this finding is of doubtful relevance to ocular use of Avastin for several reasons. Principle among them, the ocular dose (1.25 mg) is about 1/300th of the systemic dose (5 mg/kg) used to treat metastatic co-

lon cancer, and 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 approximately 1/1000th of the systemic exposure compared to intravenous use. As a smaller molecule, Lucentis has a shorter systemic half-life than Avastin, but it is unknown whether Lucentis has less systemic toxicity.⁷

4. *In vivo supersedes in vitro:*

While *in vitro* data suggest that there is possibly greater penetration of the smaller Lucentis molecule than Avastin, this feature could also increase the rate of Lucentis' diffusion out of the eye and decrease Lucentis' relative efficacy. Furthermore, *in vivo* experiences with thousands of patients has demonstrated comparable efficacy of Avastin and Lucentis, perhaps because the 1.25 mg Avastin dose effectively blocks all VEGF receptors.

5. *Avastin is a standard of care:*

Avastin has become a standard of care for most exudative AMD patients. A January 2007 Internet survey of the American Society of Retinal Specialists (ASRS) with 276 respondents found that 58.76% usually recommend Avastin for patients with subfoveal CNVM due to AMD when these patients have both Medicare and secondary insurance coverage (9.97% of these recommend Avastin plus PDT for such patients). For patients without secondary coverage, for whom the co-payment on Lucentis treatment is substantial, 79.20% of ASRS respondents usually recommend Avastin (2.77% of these recommend Avastin plus PDT).

Financial Incentives to Use Lucentis

Lucentis costs ophthalmologists \$1950 and Medicare reimburses approximately \$2030, for a profit of about \$80 per dose given. In contrast, there is little profit generated by the \$50 Medicare reimbursement for Avastin. Those treating large numbers of patients with macular degen-

eration can generate large profits simply by using Lucentis rather than Avastin, while the cost to Medicare can run into the millions.

What Other Factors Might 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. While many academicians do speak their minds and report research findings in an unbiased manner, reviews of industry-sponsored research have shown biases in favor of the sponsoring company’s products.⁸

What about Patients Who Demand Lucentis?

Lucentis is not to be denied to anyone. Indeed, many people request Lucentis. After reviewing the options with patients, it would be reasonable to propose Avastin first, for it appears the two are roughly equivalent in safety and efficacy. Avastin might require less frequent injections, which could help reduce the disruption to patients’ lives, the risks of treatment, and the costs of diagnostic testing. If Avastin fails, which is uncommon, then Lucentis is a reasonable alternative.

What about Visudyne and Macugen?

With the availability of Avastin and Lucentis, few people use Visudyne as a first-line approach to exudative AMD. Visudyne with intravitreal triamcinolone is effective, but there are significant risks associated with steroid use. In addition, Visudyne carries risks, which combined anti-VEGF therapy might augment, in-

cluding loss of vision from choriocapillaris shut-down, damage to RPE from free-radicals, and a tendency of CNVM treated with Visudyne to undergo fibrotic involution. While the ongoing DENALI study might show a role for Visudyne, we currently do not encourage its routine use.

Regarding Macugen, we think that Avastin and Lucentis are both clearly superior for first-line therapy. Macugen representatives have encouraged its use for “maintenance” treatment. However, neither the need for maintenance treatment nor Macugen’s superior safety in humans has been proven. Given that Macugen costs at least 20 times more than Avastin, we do not recommend routine Macugen use.

Conclusion

Society-at-large expects physicians – as professionals with high levels of education – to make rational decisions that benefit the public good. How we manage macular degeneration will have significant implications for society in general as well as for our own professional well-being.

*As this article goes to press, Genentech just announced plans to prohibit distributors from selling Avastin to pharmacies that compound Avastin for ocular use. This move threatens to severely restrict ophthalmologists’ access to Avastin, which would have tragic consequences. The cost to patients and our health care system for the management of macular degeneration could skyrocket, with the annual Lucentis tab reaching \$3 billion/year (\$10,000/practicing US ophthalmologist/month) or more. This would be a major burden to Medicare, reducing its ability to support essential healthcare services. In addition, it might be difficult to obtain Avastin for patients who need affordable anti-VEGF treatment for non-covered indications, including anterior segment neovascularization, retinal neovascularization, and retinal edema. Finally, it would almost cer-

tainly impact ophthalmologists' efforts to prevent further major cuts in Medicare reimbursement for ophthalmic services.

1. Genentech reports \$618 million in sales through the first three quarters of 2007.
2. [\$1950 (wholesale cost) + \$80 (typical Average Sale Price mark-up as of 9/07) + \$190 (approximate injection fee)] X 24 injections/ 2 years = \$53,280.
3. Avery RL, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmol* 2006;113:363-72; Bashshur ZF, et al. Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006;142:1-9; *Retina* 2006;26:383-90; Yoganathan P, et al. Visual improvement following intravitreal bevacizumab (Avastin) in exudative age-related macular degeneration. Spaide RF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;26:994-998; Emerson MV, et al. Intravitreal bevacizumab (Avastin) treatment of neovascular age-related macular degeneration. *Retina* 2007;27:439-444; Giansanti F, et al. Intravitreal bevacizumab therapy for choroidal neovascularization secondary to age-related macular degeneration: 6-month results of an open-label uncontrolled clinical study. *Eur J Ophthalmol* 2007;17:230-237.
4. Rosenfeld PJ, et al. Ranibizumab for neovascular age-related macular degeneration. *N Eng J Med* 2006;355:1419-31.
5. Wu et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin®): results of the Pan-American Collaborative Retina Group (PACORES). *Graefes Arch Clin Exp Ophthalmol* 2007, in press, e-pub. 8/3/07.
6. Genentech. "Dear Health Care Provider" [physician advisory], 1/24/07.
7. Steinbrook R. The price of sight – ranibizumab, bevacizumab, and the treatment of macular degeneration *N Eng J Med* 2006;355: 1409-12.

8. DeAngelis CD. The influence of money on medical science. *JAMA* 2006;296:996-8; Jørgensen AW, et al. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systemic review. *Br Med J* 2006;333:782-6; Lexchin J. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Br Med J* 2003;326:1167-70.

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