A Prescription for Savings: Reducing Drug Costs to Medicare
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Philip J. Rosenfeld, MD PhD
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami Miller School of Medicine

Chairman Kohl, Ranking Member Corker, and other members of the Committee, thank you for inviting me today to testify on this important topic. I'm Dr. Philip Rosenfeld, Professor of Ophthalmology at the Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine. I joined the faculty 15 years ago after completing both my MD and PhD degrees at the Johns Hopkins School of Medicine in 1988. I then completed a research fellowship and ophthalmology residency program at the Massachusetts Eye and Ear Infirmary of Harvard Medical School followed by a vitreoretinal surgical fellowship at the Bascom Palmer Eye Institute where I stayed on as a faculty member. I am a molecular biologist, a geneticist, and a retinal specialist, but I am not a specialist in healthcare policy. I do bring to the discussion a real-world perspective on the forces that influence the choice between two commonly used drugs, with very different costs, for the treatment of wet age-related macular degeneration (AMD) and how changes in the way clinicians are compensated when using these drugs could significantly reduce the cost to Medicare for all physician-administered drugs. These statements are my own opinion, and not those of the University of Miami or Bascom Palmer Eye Institute

Wet Age-Related Macular Degeneration

AMD is the leading cause of irreversible blindness worldwide among the elderly. It's a disease that usually causes slow, progressive vision loss after the age of 60. Patients rarely go totally blind, but they eventually lose their central vision and become legally blind. Central vision is the vision we need for reading, driving, recognizing faces, and performing even the simplest visual tasks. The disease is always in both eyes. We know the disease runs in families, and many of the genes that cause the disease have been identified. We also know that poor nutrition and smoking accelerate the disease, while a healthy lifestyle can slow the disease. What's important for our discussion today is that this disease starts off slowly as dry AMD, and then it can convert to wet AMD. The term "wet" refers to the abnormal growth of blood vessels in the back of the eye that leak and bleed. This leakage and bleeding accelerates the onset of blindness.

Avastin and Lucentis

Based on the groundbreaking scientific research performed at Genentech and elsewhere, we now know the factor responsible for the growth of abnormal blood vessels in wet AMD. It's the same factor responsible for blood vessel growth into

cancers, allowing them to grow even larger and metastasize. Genentech developed two fabulous drugs that block this growth factor and prevent the formation of these abnormal blood vessels. These two drugs are known as Avastin and Lucentis. Both drugs are derived from the same mouse monoclonal antibody specifically developed by Genentech to block the growth factor. Avastin is a full-length form of this antibody, originally developed for colon cancer treatment, and Lucentis is a smaller piece of this antibody known as an antigen-binding fragment, which was developed to treat wet AMD. Avastin is infused through an arm vein every 2 weeks, while Lucentis can be injected every month into the eye. Avastin was FDA-approved for cancer treatment in February 2004, while Lucentis was approved for the treatment of wet AMD in June 2006.

Based on my extensive review of the scientific literature, my scientific training, and my extensive experience using Lucentis in clinical trials, I approached Genentech and asked to use Avastin to treat wet AMD due to its molecular similarity to Lucentis. This was 3 years before the FDA approved Lucentis. Genentech did not provide assistance, so in 2004, I initiated a small clinical study exploring the use of systemic Avastin for wet AMD.[1,2] Encouraged by the success of systemic Avastin, I sought additional support from Genentech for a larger study. When that support failed to materialize in May 2005, we reached out to colleagues all over the country to organize a multicenter clinical trial. While designing this larger trial, I realized an injection of Avastin into the eye should be theoretically equal to an injection of Lucentis into the eye. When injecting Avastin into the eye, I used 1/500th the amount of drug used in a systemic (arm) infusion of Avastin. As a result, an eye injection was both safer and cheaper than an arm infusion of Avastin because during an arm infusion, the entire body is exposed to the drug at high levels. When Avastin is injected into an eye, the drug is taken directly from its vial and placed into a syringe just like Lucentis.

Initially, this off-label use of Avastin was offered to patients as salvage therapy in patients who had failed standard-of-care treatment at the time and there was no hope of avoiding blindness.[3-5] This was before Lucentis was available. The treatment was successful, and one patient led to many more patients. Our success in treating patients with intraocular Avastin for wet AMD spread nationally and then globally leading to the use of Avastin eye injections in a wide-range of retinal diseases. This rapid spread of Avastin in 2005 was fueled by the availability of Avastin worldwide, its apparent efficacy, its low cost, and the fact that Lucentis was not yet approved, though the preliminary results with Lucentis had been promising. When a pharmacy follows strict sterile guidelines, as mandated by the United States Pharmacopeia, a syringe of Avastin should cost between $20 and $40. In contrast, a syringe of Lucentis now costs about $2000. As a result, even after the approval of Lucentis in June 2006[6-8], Avastin continued to be the preferred drug for the treatment of eye diseases and is viewed worldwide as the affordable, low-cost alternative to Lucentis. In the U.S., the Medicare allowable payment per dose is about $2000 for Lucentis and $50 for Avastin.

Comparison of Age-Related Macular Degeneration Treatment Trial (CATT)
Over the past 6 years, controversy has swirled around the off-label use of Avastin for eye diseases, and this controversy escalated once Lucentis was approved in 2006. Since 2005, over 1500 scientific papers have been published in peer-reviewed journals exploring the safety and efficacy of Avastin in the eye. Despite all this published information and the clinical perception that Avastin and Lucentis were similar with respect to safety and efficacy, we did not have definitive data comparing Avastin and Lucentis in a large clinical trial. Survey after survey showed that the majority of patients in the U.S. were being treated with Avastin even in the absence of this definitive data. All that changed when the results of the Comparison of Age-Related Macular Degeneration Treatment Trial (CATT) were published in May 2011 in the New England Journal of Medicine.[9, 10] Dr. Daniel Martin, chairman at the Cole Eye Institute of the Cleveland Clinic, chaired this National Eye Institute-sponsored multicenter clinical trial. This study compared injections of Avastin and Lucentis in 1200 patients with wet AMD. After one year, monthly injections with Avastin were shown to be equivalent to monthly injections with Lucentis, and "as-needed" injections with Avastin were shown to be equivalent to "as-needed" injections with Lucentis. The study now continues for a second year. Contrary to popular expectations, I do not think these results will change the use of Avastin and Lucentis in the U.S. My opinion is based on research performed in collaboration with Dr. Ross Brechner, a lead medical officer and ophthalmologist at the Centers for Medicare and Medicaid Services (CMS). I believe most clinicians have decided to use one drug versus the other based on existing financial incentives and disincentives.

Avastin and Lucentis in the United States
In 2009, Dr. Brechner and I initiated a study to identify the use of Avastin and Lucentis among Medicare fee-for-service beneficiaries with wet AMD.[11] We reviewed the 100% Medicare Part B claims file from 2008 and found that approximately 60% of Medicare beneficiaries received Avastin while 40% received Lucentis. These numbers were virtually identical to the annual surveys previously performed by the American Society of Retina Specialists (ASRS). During 2008, we found a total of 841,782 eye injections were performed. CMS paid $20,290,952 for the 60% given Avastin and $536,642,692 for the 40% given Lucentis. While Avastin accounted for 60% of the injection volume, it was responsible for only 3.6% of the drug payments associated with treatment. The use of Avastin saved CMS over $800 million in 2008 alone. This research has been published, and we have continued our investigation by examining the 2009 database. In 2009, the total number of injections increased to about 1 million, with Avastin maintaining its 60% share of the market.

Dr. Brechner and I also explored the use of each drug throughout the country, and we found enormous variability on a state-by-state basis. In the western U.S., Avastin was used more frequently while in four central plains states (Nebraska,

Kansas, North Dakota, and Iowa) Lucentis was used more frequently. In the South, only Florida and Tennessee used mostly Lucentis, while in the Northeast, the states of Pennsylvania, New Jersey, Vermont, Connecticut, and Maine used mostly Lucentis. Overall, 11 states use Lucentis more than Avastin, while the remaining 39 states used Avastin more often. Given the fact that CMS reimbursed for both Avastin and Lucentis in wet AMD, how can we explain the variability seen throughout the U.S.?

The use of one drug versus the other didn't seem to depend on the state's financial prosperity, its political party affiliation, nor the urban versus rural distribution of its population. If it was solely a question of ethics behind the use of on-label versus off-label drugs, then why would there be such variability throughout the U.S.? By exploring the differences in the use patterns of these drugs, we wanted to take this unique opportunity to better understand the forces influencing clinicians to choose between similar treatments with very different costs.

How do clinicians choose between Avastin and Lucentis?

Among the fee-for-service Medicare population, the choice between Avastin and Lucentis should be between the physician and the patient. If we assume that all clinicians and patients are informed about these drugs, in particular the differences between on-label and off-label treatment, and if we assume that the clinician has equal access to both drugs, then we wanted to identify the forces influencing the decision. The most obvious influence is cost, and cost becomes a very important issue when the patient does not have secondary or Medigap insurance coverage to pay the 20% balance not covered by Medicare. Not surprisingly, when we examined the CMS database, we found a correlation between the use of Avastin and the absence of this Medigap coverage. After all, the co-pay for Lucentis would be about $400 while the co-pay for Avastin would be $10, and these injections are performed as often as every month. However, this group of patients represented only a minority of patients receiving Avastin. The majority of patients had secondary insurance, so the cost should not have mattered to the patient, yet they still received Avastin. While the cost didn't matter to the patient, perhaps the cost mattered to the physician. In some practices, the cost of offering Lucentis was a financial hardship, while in other practices, the use of Lucentis turned out to be a financial windfall. As a result, we became increasingly interested in the forces that incentivized clinicians to choose Lucentis.

CMS Incentivizes Clinicians to Choose the Most Costly Alternative

Medicare Part B reimburses for physician-administered drugs such as Avastin and Lucentis. This is different than prescription drugs, which are reimbursed by Medicare Part D. In Medicare Part B, physicians receive a payment from Medicare that covers the cost of the drug when they administer the drug. In addition, Medicare supplements the payment by adding an additional payment equal to 6% of the average sales price (ASP) of the drug. For Lucentis, the

average sales price is about $1950, so Medicare pays the clinician an additional $115. Does it make sense to base the physician's payment on their choice of drugs, with a higher priced drug resulting in a higher payment? The current 6% payment of $115 is a tempting incentive, almost like a sales commission, and almost equals the entire $125 reimbursement for performing the injection. If Medicare considers this 6% payment as an interest payment to the clinician for the up-front purchase of Lucentis, then this $115 would translate into an annual uncompounded interest rate return of at least 70%, given the fact that most clinicians are paid by CMS and the secondary insurance within one month of injecting the Lucentis and that initial $2000 investment keeps getting a 6% return every month when the Lucentis is purchased for retreatment. Given this kind of return on an investment, I'm sure many of our patients would be willing to purchase the drug monthly if they were guaranteed at least a 70% annual return.

CMS also incentivized the use of Lucentis by dramatically decreasing the reimbursement for Avastin in hospital-based practices from $50 to $7. In the summer of 2009, CMS announced that they were planning to reduce the allowable payment for Avastin from $50 to $7. This decision was met with outrage within the ophthalmologic community. A concerted effort by our lawmakers, other government officials, and our professional societies successfully reversed this policy decision. However, this decision to reverse the payment decrease only applied to private practices. For hospital-based practices, such as our own practice in Miami, the reimbursement for Avastin remains at $7. As a result, this decision by CMS had unintended consequences even though the decrease in reimbursement was no longer in effect for private practices. Our evaluation of the 2009 CMS database suggested that the threat of decreasing the Avastin reimbursement to all practices resulted in the increased use of Lucentis nationally.

Another policy that could increase the use of Lucentis in a hospital-based practice is the Disproportionate Share Hospital (DSH) status of the hospital and the 340B drug discount program. Hospitals are granted this designation based on a disproportionate amount of indigent care provided at their facility. The drug discount program allows for the purchase of drugs at a discount of up to 20%. Consequently, if the hospital purchases Lucentis with a 20% discount for about $1600, then it would get reimbursed $2000 by CMS and the secondary insurance. As a result, the hospital would get $400 every time a clinician injects Lucentis. This payment could be another attractive incentive to use Lucentis, and raises the question why the cost savings aren't passed through to CMS?

The Genentech Rebate Program

On November 4, 2010, Andrew Pollack of the New York Times wrote about a rebate program for clinicians using Lucentis (http://www.nytimes.com/2010/11/04/business/04eye.html?_r=1&hp=&pagewanted=all). The article suggested that practices were given rebates based on their bulk use of Lucentis and the rate of increase in their use of Lucentis. While the

details of the program remained vague, Pollack reported that the volume rebates combined with the increased usage rebates could net a practice as much as $58,000 per quarter. Following the release of this information, clinicians and our professional societies engaged in discussions about the ethics of such a rebate program. However, for the purposes of this discussion, if this rebate program does exist, then why should clinicians get this rebate rather than CMS? After all, isn't CMS paying for the drug?

Credit Card Purchases of Lucentis

Retina practices can purchase Lucentis directly from Genentech using a credit card. By using one of the American Express small business credit cards, clinicians can make an additional 1-2% in cash-back incentives, or they can accumulate points using cards from one of the other companies. Given the fact that credit card companies charge transaction fees and these transaction fees are not being added to the cost of the drug, it would appear that the drug is being sold at a discount. Shouldn't CMS be the one receiving this discount?

Total Lucentis Incentives

The current system has many attractive incentives that encourage the use of Lucentis. When added up, a busy clinical practice can make 6% on the ASP, another 1-2% by using a credit card, and an unknown amount if the rebate program exists. For a private practice, these incentives amount to a healthy return on a $2000 investment every month. In a DSH designated hospital-based practice, the incentives are even greater. With these financial rewards, why aren't all clinicians using Lucentis?

Important Lessons from the Lucentis/Avastin Controversy

I'm sure many of my colleagues who use Lucentis will be annoyed with me for openly discussing the Lucentis incentives, but I believe the clinical decision to use a drug should be based on comparative efficacy, safety, and cost. The decision should not be biased by financial incentives. Many of my colleagues feel these incentives are justified based on the dramatic and inappropriate reductions in reimbursements to clinicians from CMS over the past year. CMS decreased the injection reimbursement from $200 to $125, a 38% decrease, and decreased the reimbursement for routine imaging of both eyes from $104 to $48, a 54% decrease. While I too am outraged by these reimbursement cuts, I would argue that reimbursement to physicians should be a separate issue that needs to be addressed and should not be confused with these drug incentives. However, it will be interesting to look at Lucentis use in 2011 and see once again if these Medicare cuts to physicians resulted in unintended consequences. I would not be surprised if we see an upsurge in the use of Lucentis as clinicians feel they need additional revenue to cover the significant cuts in reimbursement for injections and imaging in patients undergoing treatment.

While the historical details of the Avastin/Lucentis controversy may be unique in the annals of medicine, the financial incentives driving the use of expensive

drugs and procedures are not unique. The Avastin/Lucentis controversy demonstrates some very salient points that should not be ignored when formulating healthcare policy. First and foremost, it is not wise to pay a percentage of the drug costs on top of the cost of the drug. CMS should pay a flat fee for the clerical efforts associated with the purchase, storage, and invoicing of a drug. However, a flat fee alone will not be enough to influence practice patterns as long as other incentives are unchanged. Second, CMS should receive the 20% discount when drugs are purchased by hospitals with a DSH designation. Third, if the rebate program exists, CMS should be entitled to the rebates. Fourth, CMS should consider the purchase of a drug with a credit card as a form of a rebate to the clinician. Lastly, CMS should immediately increase the payment for Avastin from $7 back to $50 for hospital-based practices.

As a clinician, I don't want CMS telling me which drug to use, and I don't want patients worrying that the decision to inject their eye is being influenced by financial incentives. By addressing the financial incentives that currently promote the use of the most costly alternative, CMS could level the playing field and allow physicians and patients to focus on efficacy, safety, and cost when deciding between drugs. It is noteworthy to acknowledge, that despite all the financial incentives to use Lucentis, most ophthalmologists have chosen to use Avastin suggesting that most ophthalmologists are trying to control the cost of healthcare. While my suggestions alone won't halt the escalating cost of healthcare, they do represent necessary changes in the way physician-administered drugs should be reimbursed by Medicare Part B. Removal of these incentives would save CMS billions of dollars.

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