Avastin versus Lucentis to Treat Age-related Macular Degeneration (AMD)

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Cost Effectiveness Research

There has been much interest in the $1.1 billion allocated within the $787 billion economic stimulus bill approved by the United States (US) Congress in the first-quarter of 2009 (1Q09; bostonglobe.com, 2/14/09) to reportedly, for the first time, provide substantial amounts of money for the federal government to compare the effectiveness of different treatments for the same illness (nytimes.com/Pear, 2/16/09). Under the legislation, researchers will conduct comparative efficacy studies of drugs, medical devices, surgical procedures, and other specific treatments. While such interventions are intended to reduce healthcare costs and reward “true” innovation, others believe that innovation and public health will suffer, in turn (Vernon & Goldberg, 2011). For example, one can point to the pressure brought upon physicians in the case of the lipid lowering statin drugs. The Bayer statin, Baycol was priced lower than market leaders, Pfizer’s Lipitor (atorvastain) and Merck’s Zocor (simvastatin; Angelmar, 2007). Baycol had begun to take market share, when the Bayer statin was removed suddenly from the market due to safety issues - a severe muscular disorder called rhabdomyolysis. Thus, while on the market, when managed care encouraged patients to shift to Baycol, based on formulary positioning, this, in retrospect, can be seen as an example of CER leading to poorer public health outcomes (heartlandinstitute.com, 5/11).

While the CER debate appears to be accelerating in rancor, it should be noted that prior to the stimulus bill legislation, the US government initiated a key comparative effectiveness study, albeit with less fanfare. This study is sponsored by the National Eye Institute (NEI), part of the National Institutes of Health (NIH), to evaluate Roche’s Avastin (bevacizumab) versus Roche’s Lucentis (ranibizumab) in the treatment of patients with wet age-related macular degeneration (AMD), the leading cause of blindness among individuals over the age of 55 years (cf. Eye Diseases Prevalence Research Group, 2004). Briefly, Lucentis is approved to treat wet AMD whereas Avastin is not. However, Lucentis costs about $2,000 per injection, whereas Avastin costs about $50 per injection, a 40-fold differential in pricing.
The NEI study is likely to determine whether more than $1 billion in US revenue continues to be allocated to treat AMD, including $500 million in Medicare payments, the governmental program for the elderly and disabled. For example, Lucentis cost Medicare $537 million in 2008, whereas Avastin cost about $20 million, according to a study by ophthalmologist Philip Rosenfeld of the University of Miami School of Medicine (therubins.com, 5/02/11). More recently within Medicare, off-label use of Avastin accounts for nearly 60% of their AMD injections, as compared with about 40% for Lucentis (online.wsj.com, 6/17/10). In terms of revenue, in contrast, Medicare paid $537 million for Lucentis in 2008 versus only $20 million for Avastin. This is due to the differential pricing: based on data from more than 200,000 Medicare patients, Medicare paid on average $42 a dose for Avastin in the eye, as compared with $1,593 a dose for Lucentis.

This review article is designed to explore the rationale for this landmark study, starting with the two drugs. Avastin is a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), whereas Lucentis is an antigen binding fragment derived from the same humanized mouse antibody (createbusiness.com, 5/10/11). Each is manufactured by the Swiss large pharmaceutical company, Roche, and was crafted by its 100%-owned US subsidiary, Genentech.

**Roche/Novartis’ Lucentis**

Lucentis (ranibizumab) was approved for wet AMD in the US in 2Q06 (fda.gov, 6/30/06), in Europe in 1Q07 (ophthalmology-timeseurope.com, 1/28/09), and in Japan in 1Q09, according to the latter source. Phase III studies of Lucentis enrolled more than 800 AMD patients treated monthly for up to two years. Patients had their vision stabilize or improve, relative to controls, including the standard-of-care, at the time, Visudyne’s photodynamic therapy. In the MARINA study, approximately 40% of patients treated with Lucentis achieved vision of 20/40 or better, at one-year versus 11% of patients in the MARINA sham control group (Rosenfeld, et al., 2006). Stronger results clinically were observed in year two: 42% of Lucentis patients versus 6% with sham control treatment, based on this criterion. In the second Phase III study, at one-year follow-up, Lucentis had over 94% of patients lose less than 15 letters, as compared with 64% with for photodynamic therapy, Visudyne (Brown, et al., 2006).

The standard dose of photodynamic therapy was 15-mg (visudyne.com, accessed 9/12/10), which has an average wholesale price (AWP) in the 2010 Red Book of $1,703 per injection. Given the impressive efficacy of Lucentis, it was not surprising that Genentech/Roche priced it at a premium to photodynamic therapy, at about $2,000 per injection for the monoclonal antibody (Raftery, et al., 2007). Current AWP, according to the 2010 Red Book is $2,438.
Lucentis is a truncated, derivative version of Avastin developed specifically for intravitreal application in the eye. Avastin contains full-length antibodies, whereas the antibody fragments in Lucentis are 1/3 the size of the Avastin antibodies (medicine.ox.ac.uk.com, 5/07). Relative to Avastin, though, Lucentis binds more strongly to the VEGF protein, which is a key to preventing blood vessel growth in the retina (i.e., neovascularization). Another parameter in which the drugs differ is that Avastin is metabolized 100-times slower than Lucentis. This is a good property for Avastin in the treatment of solid tumors, but remaining in the retina may prove harmful to patients with AMD.

In the US, incentives exist for physicians to prescribe Lucentis rather than Avastin. That is, Medicare offers physicians a profit of about $80 per prescribed dose (clinicalresponsibility.org, 10/15/07). In contrast, there is little profit generated by the $50 Medicare reimbursement for Avastin.

Roche’s Avastin

Roche/Genentech’s Avastin is a successful treatment of several oncology indications, including advanced colorectal cancer, non-squamous non-small cell lung cancer, advanced breast cancer (which may be reversed due to the absence of an overall survival benefit with Avastin, based on the recent recommendation of an FDA advisory committee, fiercebiotech.com, 7/21/10), renal cell carcinoma, and glioblastoma, a form of brain cancer that has progressed following prior therapy (Chamberlain, 2010).

The cost of Avastin was $4,400 per month to treat advanced colorectal cancer at the time of launch in the United States in 1Q04 (medicalnewstoday.com, 6/15/05). Avastin has no labeling as a treatment for AMD, though, and no attempt has been made to seek approval for this indication by Roche/Genentech or Novartis. Indeed, the companies have never sponsored a study testing Avastin in to treat AMD or any other eye disorder. Note that in the attempt to differentiate the two VEGF biologica agents, Roche/Genentech were able to secure different generic names for Avastin and Lucentis (bevacizumab and ranibizumab, respectively).
Off-label use of Avastin

This is a rather anomalous circumstance, as companies are often accused of promoting drugs for indications in which they do not have regulatory approval. Such promotion is illegal, even to members of the medical profession. The irony is that although companies are prohibited from promoting drug use off-label, licensed physicians have a legal right to prescribe drugs to patients for indications beyond those specified on the drug label. This is not the case with Avastin, however, as Roche/Genentech have a financial incentive not to promote this biologic as an off-label treatment of AMD. That is, the amount of Avastin used in the eye to treat AMD patients is miniscule, and costs about $50 per injection (Raftery, et al., 2007). This is about 1/40th the corresponding price of Lucentis to treat AMD.

Genentech/Roche attempted a more proactive attempt to inhibit use of Avastin to treat AMD. That is, Genentech announced plans in 4Q07 to prohibit distributors from selling Avastin to pharmacies that compound Avastin for ocular use (clinicalresponsibility.org, 10/15/07). This move threatened to severely restrict ophthalmologists’ access to Avastin. Facing opposition from pharmacists, and poor public relations, Genentech never enacted this threatened action, but not before Congressional inquiries into the conflict (pharmalot.com, 12/19/08).

In 2Q10, a small clinical study suggested that intravitreous Avastin was superior to standard care (pegaptanib sodium, verteporfin, sham) in terms of restoring vision at 54 weeks follow-up (Tufail, et al., 2010). Mean visual acuity increased by 7.0 letters in the Avastin group with a median of seven injections, as compared with a decrease of 9.4 letters in the standard care group (p<0.001). The initial improvement at week 18 (plus 6.6 letters) was sustained at the one-year follow-up evaluation.

Avastin versus Lucentis in a Head-to-Head Clinical Trial

In the attempt to generate an empiric answer to the question, six separate trials are being conducted globally comparing Avastin and Lucentis. Roche/Genentech/Novartis have declined to participate in these studies, including donation of drug or funding sponsorship (fiercepharma.com, 5/14/08; webmd.com, 6/11/10).

The largest of these studies “read-out” recently, the US’ National Eye Institute (NEI)-sponsored CATT (Comparison of AMD Treatments Trial). The CATT study enrolled 1,208 neovascular (wet) AMD patients at 44 sites in 2/08 (theretinablog.com, 10/25/09). The four-arm, single-blind study compared Avastin versus Lucentis on a fixed monthly or a variable (as needed) schedule with evaluations monthly. After Congressional intervention, Medicare agreed to reimburse for use of Avastin among randomized patients in the CATT study, facilitating the conduct of this study (pharmalot.com/Silverman, 10/28/09).
The one-year follow-up results were released in 2Q11 (The CATT Research Group, 2011). The primary outcome was the mean change in visual acuity at one year. Empirically, Avastin was equivalent to Lucentis, with 8.0 versus 8.5 letters gained, respectively, in the monthly administration, and with 5.9 versus 6.8 letters gained with the prn regimen (The CATT Research Group, 2011). Rates of death, myocardial infarction, and stroke were similar for patients randomized to either Avastin or Lucentis (all $p>$0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with Avastin, as compared to Lucentis (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

Although it is clear that the raison d’etre for this study was an evaluation of the two treatments based on the clash in pricing, it is interesting to note that the CATT investigators made no mention of price of the two biologic agents tested. Given the absence of differences in efficacy, clearly Avastin is the cost-effective treatment (cf. cost-minimization paradigm).

**Cost Effectiveness of Lucentis versus Avastin to Treat Age-related macular Degeneration (AMD)**

Prior to the release of the CATT study results, a model was constructed comparing the cost effectiveness of Avastin versus Lucentis (Raftery, et al., 2007). To achieve a £30k per QALY, a NICE threshold equivalent to about $50,000 US per QALY, the efficacy of Avastin would be approximately 40% of Lucentis. Recall that the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) threshold for acceptable cost effectiveness is £30,000 per QALY (McCabe, et al., 2008).

Ironically, NICE has accepted Lucentis as cost effective in the treatment of AMD, based on a risk-sharing deal with Novartis. The deal negotiated entails the National Health Service (NHS) paying for a maximum of 14 injections, per eye, for patients with wet AMD (ophthalmologytimeseurope.com, 12/17/07). Additional treatments, if necessary, will be paid by Novartis. Based on this deal, no longer will patients in the UK have to wait “perversely” for the initial eye to go blind before being treated with Lucentis (medicalnewstoday.com, 4/03/08).

Appendix A reviews briefly international studies of Avastin versus Lucentis in the treatment of AMD.
Roche Response to CATT

Although Roche respectfully declined to contribute to the funding or logistics of the CATT study, it is incorrect to assume that Roche was disinterested in the results and shaping the subsequent debate. The New York Times (Pollack, 10/03/10) has reported that Roche has responded to the publicity of the trial by offering rebates on Lucentis, based on volume. For example, rebates range from 0.25% to 1.5% of wholesale cost. One example in a document obtained by the paper: using 600 vials a quarter yields a rebate of $8,775.

In terms of the CATT study per se, Roche pointed up correctly that while the CATT study was arguably powered statistically to test the two VEGF biologic agents in terms of efficacy, the study was not powered to test for potential differences in safety, which would likely required thousands of enrolled AMD patients.

Indeed, Roche commissioned its own review of 78,000 Medicare recipients with AMD, treated with Avastin or Lucentis, and observed an 11% increased mortality among users no-randomly assigned to Avastin, as compared to Lucentis. The absolute risk was not provided in this analysis, but was likely to be trivial, for example, if the baserate for Lucentis was a 1% chance of death, given this relative difference, then the corresponding rate for Avastin was only 1.11%.

It is interesting, if not remarkable, that Roche would be willing to play-up the safety angle of Lucentis versus Avastin, given the failure of Avastin to demonstrate OS (or indeed even replicate PFS) following approval in advanced breast cancer.

This strategy can easily backfire, making safety concerns with Avastin more salient.
Roche/Novartis’ Impressive Franchise of Avastin and Lucentis

Lucentis Broadens its Use in Ophthalmology

While the “soap opera” in metastatic breast cancer continues between Roche and US regulators, Roche and Novartis have focused on expanding the ophthalmologic indications for Lucentis, including diabetic macula edema (DME). This is related to diabetic retinopathy, which is the most common cause of vision loss in working-age Americans. This condition damages the small blood vessels in the eye’s light-sensitive retinal tissue. When these damaged blood vessels begin to leak fluid near the center of the retina, known as the macula, macular edema occurs. The macula provides detailed central vision used for activities such as reading, driving, and distinguishing faces. In macular edema the retinal tissue swells, which can lead to vision loss if left untreated (sciencenewsline.com, 4/27/10).

Several Phase III studies have supported Lucentis to treat DME. One conducted by Roche found that after 24 months, 44.8% of patients taking 0.3-mg and 39.2% randomized to 0.5-mg of Lucentis were able to read at least 15 more letters on an eye chart than at the start of the study (reuters.com, 3/10/11). In contrast, only 18.1% of patients randomized to placebo injection had corresponding efficacy. There was an incidence of arterial thromboembolic events (<=3.5%) observed in the clinical studies, consistent with reported observations in the wet AMD clinical studies.

The initial study was sponsored by the companies. A second, NEI governmental-sponsored study recently reported that Lucentis prevented vision loss among patients with diabetic macular edema (nytimes.com/Pollack, 4/27/10). A total of 691 patients were randomized, with 854 eyes evaluated, as some patients had both eyes treated. About half the patients treated with Lucentis demonstrate at least a “two-line” improvement in vision, as compared to only 30% with laser therapy.

Lucentis was approved in 2011 for treatment of visual impairment due to diabetic macula edema in Europe, where it is marketed by Novartis (pharmaceutical-business-review.com, 3/28/11). Roche is waiting for US approval for this supplemental indication.
**National Comprehensive Cancer Network (NCCN) Continues to Support Avastin to Treat Metastatic Breast Cancer**

The NCCN, arguably the most influential body in terms of reimbursement for oncology treatments in the US, issued its ruling on Avastin in the treatment of advanced breast cancer, after the FDA announced its intention to rescind labeling for this biologic in this indication, but prior to the final determination by US regulators. In 4Q10, The NCCN affirmed the recommendation regarding the use of Avastin to treat metastatic breast cancer, in combination with generic paclitaxel (cf. Bristol-Myers’ Taxol). The level of evidence was “2A”, representing a lower level of empirical data in support of the recommendation. The revised footnote indicates a modest improvement in time to progression and response rates, but no significant impact on overall survival (nccn.org, 10/18/10).

**Avastin and Health Technology Assessment (HTA) Groups**

HTAs evaluate cost effectiveness internationally. Arguably, the most influential is the National Institute for Health and Clinical Excellence (NICE) in the UK. Other countries that have influential HTAs include Australia, Germany, Canada, and Scotland.

As noted, Avastin has received approvals in a several oncology indications (roche.com, 7/22/10), including advanced colorectal cancer, non-squamous non-small cell lung cancer, advanced breast cancer (subject to possible withdrawal in the US; Bloomberg.com, 7/21/10), renal cell carcinoma, advanced glioblastoma (cf. brain cancer). Unlike Lucentis to treat AMD, Avastin has not received any recommendation of cost effectiveness in any oncology indication from NICE or any other HTA.

Most recently, Avastin was confirmed as not cost effective in the treatment of advanced colorectal cancer (fiercepharma.com/Staton, 8/24/10). The rejection came despite an attempt at lower pricing from Roche. That is, Avastin at a fixed price of £20,800 ($32,430) per patient for one year; the drug would be free after the first 12 months of treatment, and Roche would also reimburse NICE for the cost of accompanying chemo with Sanofi’s Eloxatin (oxaliplatin). The cost of Eloxatin for a person with a surface area of 1.75 m² receiving the recommended dose, is £495 per cycle (National Institute for Health and Clinical NICE Technology Assessment #100: Capecitabine and oxaliplatin in the adjuvant treatment of stage III [Dukes’ C] colon cancer). This is equivalent to approximately $750 per cycle, and Eloxatin is usually provided every two weeks for six months, suggesting an approximate cost of $9,000 US.
Avastin generated the equivalent of $6.72 billion in 2010, with over 50% of revenue generated outside the US (roche.com, 2/02/11). Accordingly, these facts demonstrate the limited impact of HTAs internationally and managed care in the US to prevent an innovative oncology drug from becoming a mega-blockbuster. This contrasts with the success that payers have had reliably preventing “me-too” drugs from achieving blockbuster status (see Gorkin, 8/18/10, at www.pharma-insights.biz: Importance of being the Branded Pharmaceutical “First-to-Market” in 2010: Silence of the “Me-Too” Lambs).

Revenue Generation by Avastin to Treat AMD

Combining revenue from the two biologic agents, Avastin and Lucentis, the result is approximately $9.7 billion in global sales in 2010, and arguably the second leading drug in sales behind Pfizer’s Lipitor. Therefore, these VEGF monoclonal antibodies might arguably combine to become the leading pharmaceutical in worldwide revenue. Current worldwide sales leader, Pfizer’s Lipitor, registered $10.7 billion in 2010, with a 6% drop in revenue versus 2009 (pfizer.com, 2/03/11), due to generic competition from simvastatin (cf. Merck’s Zocor), and branded competition from Astra Zeneca’s Crestor. Accordingly, Lipitor might drop below $10 billion in full-year 2011 revenue, creating this unorthodox opportunity for combined Avastin and Lucentis to lead in global sales.

Earlier, a 30-fold difference in Medicare payments in 2008 for Lucentis versus Avastin to treat AMD was noted (therubins.com, 5/02/11). Thus, Avastin revenue generated in AMD is not a significant contributor to the annual global sales of $6.72 billion. IMS and other market share companies tend to have difficulty differentiating when a branded drug has more than one indication; a fortiori, one might suspect that this difficulty is exaggerated when a drug, particularly a biologic agent, such as Avastin, has multiple branded indications, and one provocative off-label use. Even if Roche could determine the contribution of off-label AMD usage to Avastin revenue, the company would not release these results, and make the issue more salient.
Regeneron’s VEGF-Trap

The irony is that the largest threat to Lucentis might not be the internal fight between “good and evil” via Avastin, but the potential competition from a small biotech, Regeneron and partner Sanofi. The companies have filed a BLA with US regulators, seeking expedited approval of the VEGF-Trap biologic to treat wet AMD in 1Q11 (seekingalpha.com, 2/23/11). The filing is based on two Phase III studies, the North American VIEW 1 and the global VIEW 2, which reported successful results for all regimens of VEGF Trap-Eye, including 2-mg dosing every two months following three loading doses, when compared to Lucentis (ranibizumab, Roche AG) 0.5 mg dosed every month, in patients with wet AMD (bioworldtoday.com, 11/23/10). In both studies, VEGF Trap-Eye met the primary endpoint, which was statistical noninferiority in the proportion of patients who maintained or improved vision over 52 weeks compared to Lucentis (seekingalpha.com, 2/23/11). Thus, the Regeneron biologic holds the promise of comparable efficacy with fewer injections, and potentially at a lower price.

Long-Term Impact of the CATT Study of Avastin versus Lucentis to Treat AMD

From the government’s perspective, the successful CATT study of Avastin versus Lucentis in AMD, demonstrating no clinical differences between treatment arms in efficacy, is likely to have a minor impact on the ongoing tapping of on-label Lucentis revenue by off-label Avastin, rather than dramatically reducing billions of dollars in revenue for Roche and Novartis. Indeed, physicians may hesitate from substituting Avastin for Lucentis, given higher rates of serious adverse events requiring hospitalization (24.1% vs 19.0%, respectively, foxeyard.com, 4/28/11). While 60% to 70% of ophthalmologists are comfortable with off-label avastin use, a smaller 20%-30% of high-volume prescribers remain faithful to prescribing Lucentis (glgroup.com/Khurana, 5/09/11). Accordingly, the CATT study is not likely to yield the impact of the Nissen meta-analysis in terms of devastating sales of the blockbuster GSK drug for type 2 diabetes, Avandia (rosiglitazone; see Gorkin’s 2011 report: “Impact of the FDA’s Guidance Requiring a Cardiovascular Safety Screening Study to Gain Regulatory Approval of a Drug to Treat Type 2 Diabetes”, at http://www.stelerix.com/library/life-sciences/downloads/Avandia-Report.pdf).
The lasting result of CATT may be to launch a more active role by governments in the US and internationally to design clinical trials aimed at evaluating initiating the empirical evidence for reducing pharmaceutical budgets. This version of comparative effectiveness research may ultimately be the larger threat to the industry.

References


Appendix A

United Kingdom: Initiated in 4/08, 600 AMD patients at 17 sites in a four-arm study of Avastin versus Lucentis injections given over two years. Such a study set the stage for the NICE to review Avastin versus Lucentis, for cost effectiveness in the treatment of AMD (irvarons.com, 5/05/10). Clearly, if comparable efficacy: safety results are observed, NICE would recommend Avastin as the cost effective alternative to Lucentis, providing a substantial savings on treatment costs incurred by the NHS (clinical-discovery.com, 9/17/10). According to the London newspaper, The Guardian, Lucentis costs £761 per injection for AMD, whereas corresponding use of unlicensed Avastin costs approximately £15 per injection.

France: Avastin versus Lucentis study was initiated among 600 AMD patients in 3Q09.

Other countries: Studies with less than 500 randomized patients are also being conducted in Germany, Austria, and Norway.