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Treatment of Exudative Age-related Macular Degeneration: Many Factors to Consider

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Now is an exciting time in history for research in age-related macular degeneration (AMD). Treatment options available for our patients are rapidly evolving, and visual outcomes are dramatically improving. Recent publications of anti-vascular endothelial growth factor (VEGF) antibodies highlight an important step forward in the management of exudative AMD (eAMD).[1, 2] In June of 2006, the Food and Drug Administration (FDA) approved the use intravitreal of ranibizumab (Lucentis ™) for treatment of patients with eAMD. Interestingly, preliminary studies suggest that the off-label use of intravitreal bevacizumab (Avastin ®) may also improve visual function in eAMD.[3, 4] Following these initial reports, uncontrolled case series have demonstrated beneficial effects of intravitreal bevacizumab for the treatment of eAMD.[5–7] Prior to FDA approval of ranibizumab, retina specialists began to use off-label bevacizumab, a practice that continued after approval of ranibizumab, and driven largely by cost. National media attention on this issue is intense. Two recent front-page articles from the *Wall Street Journal* highlight the financial issues surrounding these drugs. First, Chase reports the financial dilemma that physicians face by choosing to use the FDA approved ranibizumab ($2000/injection) versus 'off-label' bevacizumab ($20–$100/injection) for the treatment of eAMD with an estimated future Medicare annual savings of $1–3 billion.[8] One month later, Anand reported that Wall Street research analyst Steven Harr urged Genentech, the maker of both drugs, to "lower the price of a key drug", in reference to bevacizumab for colon cancer, suggesting that high drug costs are "bad for business."[9] In this same article, Genentech's net income for 2006 was up 40% from 2005, reported to be $2.1 billion on a reported revenue of $9.3 billion.[9] Pegaptanib (Macugen®) is not an antibody, rather an aptamer, that selectively binds the VEGF-165 isomer, injected intravitreal, and has also been studied in rigorous clinical trials. Treated eyes did not have the impressive improvement in visual acuity that ranibizumab reported; nevertheless, pegaptanib was shown to be better than placebo at preventing vision loss in eAMD, and had an excellent safety profile.[10]

For those of us treating patients on a daily basis with eAMD, we need to consider individual patient circumstances. First, we need to help our patients make a well-informed decision based on the best available science. Then, individual patient financial issues should be addressed. The key scientific hypotheses: *bevacizumab is as safe and as effective as ranibizumab*. However, we simply do not know if these are valid and we do not have comparative data. Therefore, let's examine the existing science. First, ranibizumab and bevacizumab are *not the same molecule*. While both are derived from the same mouse monoclonal antibody, the active binding-site of ranibizumab is different than that of bevacizumab. This fact alone predicts that

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the molecules will respond differently. Second, bevacizumab (149 kDa) is larger than ranibizumab (48 kDa). Therefore, one would predict distinctly different pharmacokinetics of these molecules, permeability coefficients, and diffusion rates. Third, bevacizumab is produced in a Chinese-hamster-ovary mammalian-cell expression system (glycoslyated) while ranibizumab is produced in an E coli expression system (not glycoslyated).[11] This further differentiates the actual molecule, action, kinetics, clearance rates, and possibly systemic safety. One could logically assume that there will be *differences* in how well these two molecules work in eAMD, and each may have a distinct safety profile.

The ranibizumab active binding site is reportedly 14 times higher than bevacizumab through a process of affinity maturation.[12] Clinically, the binding of VEGF is evident by relatively rapid resolution of subretinal fluid. Patients will occasionally comment that visual improvement occurs soon after each injection. Mean visual acuity improvement is documented in the MARINA and ANCHOR studies within the first 3 months of treatment.[1, 2] Is this higher affinity of ranibizumab clinically relevant? Avery et al. have also reported a rapid clinical response to intravitreal bevacizumab.[5] A definitive comparison of these two agents and the response to the initial injections is not available. The advantage of higher binding affinity, in the clinical setting, would be seen by the initial therapeutic response to the injection. Clearance of the drug from the eye combined with the rate of production of VEGF by the underlying pathogenic response (eAMD) would determine subsequent drug efficacy and need for reinjection. In primates, studies have shown a rather short 3-day half-life with rapid intraocular distribution of ranibizumab.[13] Published studies on the intravitreal kinetics of bevacizumab are limited. Based on human studies of two patients, Beer et al. calculated a similar intravitreal half-life of bevacizumab of 3 days.[14] Therefore, unbound drug is rapidly distributed to the systemic circulation. In general, measurements of an antibody are challenging: Is the antibody bound to VEGF or free antibody? Is it the measured antibody a full-length antibody? Has there been proteolysis? Is the measurement of an active or inactivated form of the antibody? How specific and sensitive is the methodology?

Systemic pharmacokinetics from the primate suggest that ranibizumab is cleared much more rapidly from the serum than bevacizumab, perhaps by as much as 40 times faster. The primate model suggest that the half-life of ranibizumab in the serum is 0.5 days.[13] Studies on bevacizumab taken from human cancer patients demonstrate a serum half-life of 21 days,[15] significantly longer that the estimated duration of ranibizumab. Systemic concerns for the use of anti-VEGF antibodies could be significant, especially in the age group of those being treated for AMD. Wong and colleagues, in a large, prospective, cohort study, found that persons with early-stage AMD, followed for ten years, had a higher cumulative incidence of stroke than those without the disease (4.08% vs. 2.14%).[16] Therefore, it appears that our AMD patients represent a population *at-risk* for stroke. In a recent letter to physicians (January 24, 2007), Genentech reported a statistically significant higher risk of stroke in the SAILOR study comparing the higher 0.5 to the 0.3 mg dose (13/1217 or 1.2% vs 3/1176 or 0.3%; p=0.02). Using post hoc analysis from both the MARINA and ANCHOR studies, Gillies and Wong report a risk of non-ocular hemorrhage between treated and placebo groups was significantly higher in those treated with ranibizumab (16/379 or 4.2% vs 59/754 or 7.8%; p=0.01).[17]

What are the systemic risks for the use of intravitreal bevacizumab? An evaluation of the cancer data of intravenous bevacizumab used at a much higher dose in conjunction with other toxic chemotherapeutic agents in cancer patients is clearly not a valid comparison for systemic events to the intravitreal use in eAMD. Since bevacizumab seems to have a longer systemic half-life, would these potential systemic risks (stroke, non-ocular hemorrhage, and hypertension) be higher? Could the lower binding affinity of bevacizumab to the VEGF molecule partially offset the longer half-life and decrease potential systemic complications? We simply do not know the answers to these important questions. Considering intraocular complications, there have

been reports of a possible association of retinal pigment epithelial (RPE) rips with the use of both bevacizumab and ranibizumab.[18, 19] However, RPE rips may occur by contraction of the choroidal neovascular complexes in response to therapy, or may be part of the natural history of eAMD. Endophthalmitis, retinal detachment, and cataract formation are likely to be equivalent with either agent. Although, using multiple aliquots of bevacizumab from a single source could theoretically increase the risk of endophthalmitis, compromise drug stability and efficacy. Future studies should monitor for these potential complication.

The scientific, financial, and societal dilemma that physicians presently face is as follows: Do we use our scientific analysis for determining the recommended therapy for our patients, or should we conserve precious healthcare resources and use an alternative, off-label therapy? Ranibizumab has been tested with the gold standard of clinical research: large, prospective, masked, multi-centered, randomized clinical trials with peer reviewed results published in a highly respected clinical journal.[1, 2] The scientific data currently supports of the use of ranibizumab while the financial data supports bevacizumab. The clinicians and scientists who are currently generating and publishing safety and efficacy data on the use of bevacizumab are to be commended for their efforts to help us understand the role for this agent in clinical practice.

The National Eye Institute is gathering prospective, comparative, safety and efficacy data in a multi-centered, randomized, clinical trial, on the use of intravitreal bevacizumab versus ranibizumab in eAMD (CATT, Comparison of Age-related Macular Degeneration Treatment Trial). Daniel F. Martin at Emory University in Atlanta serves as the study chair of this important clinical trial. We anticipate that data generated from CATT will provide critical information on this important issue.

The practice of medicine is complex, and trying to decide what is best for each individual patient is unique. In my opinion, published scientific data currently supports the use of intraocular, FDA approved, ranibizumab for the treatment of eAMD. Financial pressures are pushing research that supports of the off-label use of intravitreal bevacizumab. Our free enterprise economy supports the notion that drug companies should receive financial reward for the benefit that their research and development brings to society. However, it is now time to *lower the price*. I echo Steven Harr's philosophy[9] and emphasize that current industry pricing of ranibizumab is "bad for business", especially given current limitations of national healthcare expenditures. Without more reasonable pricing, a backlash to the pharmaceutical industry will come in the form of government price controls; especially since treatment of AMD is largely funded by Medicare … taxpayers … us!

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References

1. Brown DM, Kaiser PK, Michael M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444. [PubMed: 17021319]
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431. [PubMed: 17021318]
3. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging 2005;36:331–335. [PubMed: 16156152]

4. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005;112:1035–1047. [PubMed: 15936441]

5. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006;113:363–372. [PubMed: 16458968]e5

6. Rich RM, Rosenfeld PJ, Puliafito CA, et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina 2006;26:495–511. [PubMed: 16770255]

7. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006;26:383–390. [PubMed: 16603955]

8. Chase M. Blind Ambition: Genentech's Big Drug For Eyes Faces a Rival, Intended for Other Use, Cheaper Injection Is One of Its Own Products. Wall Street Journal. NY 2007:A1, A13.

9. Anand G. Prescribing Caution: From Wall Street, a Warning About Cancer-Drug Prices; Morgan Stanley Analyst Creates Stir in Industry As He Sees a Backlash. Wall Street Journal. New York 2007:A1, A15.

10. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805–2816. [PubMed: 15625332]

11. Steinbrook R. The price of sight--ranibizumab, bevacizumab, and the treatment of macular degeneration. N Engl J Med 2006;355:1409–1412. [PubMed: 17021315]

12. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26:859–870. [PubMed: 17031284]

13. Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci 2005;46:726–733. [PubMed: 15671306]

14. Beer PM, Wong SJ, Hammad AM, Falk NS, O'Malley MR, Khan S. Vitreous levels of unbound bevacizumab and unbound vascular endothelial growth factor in two patients. Retina 2006;26:871–876. [PubMed: 17031285]

15. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol 2001;19:843–850. [PubMed: 11157038]

16. Wong TY, Klein R, Sun C, et al. Age-related macular degeneration and risk for stroke. Ann Intern Med 2006;145:98–106. [PubMed: 16847292]

17. Gillies MC, Wong TY. Ranibizumab for Neovascular Age-Related Macular Degeneration. N Engl J Med 2007;356:747–750. [PubMed: 17301310]

18. Bakri SJ, Kitzmann AS. Retinal pigment epithelial tear after intravitreal ranibizumab. Am J Ophthalmol 2007;143:505–507. [PubMed: 17317396]

19. Shah CP, Hsu J, Garg SJ, Fischer DH, Kaiser R. Retinal pigment epithelial tear after intravitreal bevacizumab injection. Am J Ophthalmol 2006;142:1070–1072. [PubMed: 17157598]

Biography

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