Lessons Learned From Avastin and OCT–The Great, the Good, the Bad, and the Ugly: The LXXV Edward Jackson Memorial Lecture

PHILIP J. ROSENFELD

• PURPOSE: To describe the synergistic benefits and cost savings from the use of optical coherence tomography (OCT) and vascular endothelial growth factor (VEGF) inhibitors, particularly intravitreal bevacizumab, in the treatment of exudative age-related macular degeneration (AMD).
• DESIGN: Retrospective literature review and personal perspective.
• METHODS: Retrospective literature review and personal perspective.
• RESULTS: The introduction of the first clinically useful OCT instrument coincided with early-phase clinical trials of a drug that would become known as ranibizumab. OCT provided a noninvasive imaging strategy that unambiguously showed the macular fluid associated with exudative AMD and the ability of anti-VEGF therapy to resolve this fluid with concomitant visual acuity improvement. Clinicians came to embrace the use of OCT imaging as the basis for dosing with anti-VEGF drugs, rather than the fixed-interval dosing that was the standard in clinical trials and recommended by industry after approval. But, before ranibizumab was approved for the treatment of exudative AMD, intravenous bevacizumab was approved to treat cancer. Both drugs shared a common molecular lineage, and this led to a clinical trial using intravenous bevacizumab for the treatment of exudative AMD. Intravenous bevacizumab resulted in visual acuity and OCT improvements similar to ranibizumab, and this observation soon led to the intravitreal use of bevacizumab in 2005. Fortuitously, both ranibizumab and bevacizumab were packaged at similar molar concentrations, so similar volumes of both drugs when injected into an eye would result in similar anti-VEGF activity. With ranibizumab not yet commercially available, intravitreal bevacizumab rapidly became adopted worldwide for the treatment of VEGF-driven ocular diseases. Despite numerous attempts by industry and anonymous sources to discredit and prevent its use, bevacizumab spread globally owing to its availability; its low treatment cost, which was $5.50 per 1 mg in the United States; the evidence of efficacy based on OCT imaging and vision improvement; and its perceived safety. In the United States alone, the use of OCT-guided therapy and the use of bevacizumab for the treatment of exudative AMD has saved Medicare over $40 billion since 2008.
• CONCLUSIONS: The rapid adoption of OCT-guided therapy and the use of intravitreal bevacizumab by the global retinal community has prevented blindness from exudative and neovascular ocular diseases worldwide while saving healthcare providers and patients billions of dollars. (Am J Ophthalmol 2019;204:26–45. © 2019 Elsevier Inc. All rights reserved.)

I AM EXCEEDINGLY GRATEFUL TO THE *AMERICAN JOURNAL OF OPHTHALMOLOGY* and the American Academy of Ophthalmology (AAO) for the honor to present the 75th Edward Jackson Award Lecture. My lecture will only cover the first half of my academic career, but this first half has been quite an adventure, covering great and good events, people, and discoveries, as well as several bad and ugly episodes that need to be revealed. In the realm of the great and the good, none of my accomplishments would have been possible without the love and support of my family and the marvelous educators and researchers I've worked with over the years. My story of scientific discovery would have been very different without their confidence in my scientific talents and their trust in my decisions. As an example, after I completed a 9-year MD/PhD program at the Johns Hopkins School of Medicine where I received my PhD in the Department of Molecular Biology and Genetics, my wife supported my decision to switch residencies from Obstetrics and Gynecology to Ophthalmology after completing only 2-1/2 years of clinical training. This career change required a move from Baltimore to Boston in 1991, and this switch was made possible by the academic support of Stuart Fine, who was at the Johns Hopkins School of Medicine at the time. Prior to my residency at the Massachusetts Eye and Ear Infirmary (MEEI), I secured a coveted postdoctoral fellowship with Thaddeus Dryja, where I received a crash course in the field of ophthalmic genetics. This experience led to my interest in the genetics of age-related macular degeneration (AMD), which was greatly influenced during my residency by the research and clinical

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From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA.
Inquiries to Philip J. Rosenfeld, Bascom Palmer Eye Institute, 900 NW 17th St, Miami, FL 33136 USA; e-mail: prosenfeld@miami.edu

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teachings of Johanna Seddon. My research and residency positions also gave me exposure to the ongoing research into optical coherence tomography imaging, photodynamic therapy (PDT) with verteporfin, and vascular endothelial growth factor (VEGF). During the early 1990s, Boston was the epicenter for all 3 breakthrough discoveries. Of note, my indoctrination into VEGF and its vital role in neovascular and exudative ocular diseases was led by my faculty mentors at the time. They included Anthony Adamis, who was my residency director, Joan Miller, Lloyd Paul Aiello, and Lois Smith. It was Lois Smith who recognized my interest in VEGF and its role in exudative AMD, and when I left to pursue a vitreoretinal fellowship and faculty position at the Bascom Palmer Eye Institute (BPEI) in 1995, she provided me with guidance and financial support through the Rasmussen Foundation.

After completing my fellowship at the BPEI and joining the vitreoretinal faculty, I continued my interest in macular degeneration. That decision set me on a course of discovery that involved the use of PDT in clinical trials, optical coherence tomography (OCT) imaging, and anti-VEGF therapies. My familiarity with Joan Miller's PDT research at the MEEI led me to take on the principal investigator's role for the phase 3 PDT clinical trials at the BPEI. That decision took me away from laboratory-based genetic research and into the world of clinical research. Under the tutelage of Neil Bressler, the PDT trials offered me the clinical research training that I was lacking. I was able to then apply my well-honed principles of experimental design to the clinics rather than the laboratory. For those unfamiliar with PDT, this treatment targeted choroidal neovascularization (CNV) by combining the intravenous infusion of a photosensitizing agent with a circular spot of a long-wavelength, nonthermal laser that covered the neovascularization in the macula. As the top-enrolling site in the phase 3 trial, I earned an opportunity to participate in the Food and Drug Administration (FDA) Advisory Panel Meeting in November 1999, which led to the approval of verteporfin PDT in April 2000. From 2000 until 2004, verteporfin PDT was the only approved treatment for exudative AMD, but it was approved for the predominantly classic form of the disease.[1,2] Unfortunately, only a minority of patients would qualify for treatment, and even in these patients, most of them would continue to lose vision even after treatment. In subsequent clinical trials, we modified the approved PDT regimen, but while these changes failed to improve outcomes for the vast majority of patients with exudative AMD, I learned an important lesson. I learned that retrospective subgroup analyses of failed prospective clinical trials are often done in the hope of finding subgroups where the treatment appeared to work, but these retrospective conclusions should never be believed without rigorous testing. After all, history has taught us that these retrospective subgroups will fail when tested in prospectively randomized clinical studies.[3] Improved outcomes for our patients with exudative AMD would have to wait until anti-VEGF therapy was introduced.

THE ANTI-VEGF AND OPTICAL COHERENCE TOMOGRAPHY REVOLUTION

MY SUCCESSFUL ROLE IN THE PDT TRIALS LED TO MY involvement with the early-stage clinical development of rhuFab V2, a humanized antigen-binding fragment directed against all isoforms of VEGF-A. This drug would eventually become known as ranibizumab (Lucentis; Genentech/Roche, South San Francisco, California, USA), which was developed at Genentech by Napoleone Ferrara, one of the "great" contributors described in this lecture. The rhuFab V2 phase 1 study investigators assembled in May 2000 during the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), and we were informed that this drug would be injected intravitreally. At that time, I was skeptical that patients would tolerate frequent intravitreal injections. Despite these reservations, I enthusiastically participated in the phase 1 rhuFab V2 dose escalation study that was initiated in 2001. In this study, patients received a single intraocular injection. After a particular dose was injected into each cohort of at least 6 patients, we assessed the eyes to determine if the dose was safe; and if it was, then we escalated the dose and continued increasing the dose with each cohort until a dose-limiting toxicity was observed. In the phase 1 study, this dose-limiting toxicity was inflammation, and it was observed with the 1.0 mg dose, so the previous dose, which was the 0.5 mg dose, was deemed the maximum tolerated dose.[4] While there was a hint of visual acuity improvement after a single dose, the true benefits of rhuFab V2 would have to wait until the phase 2 study when we performed multiple doses and used of OCT imaging. After all, OCT imaging was not routinely available in the clinics until 2003.

I participated in 2 phase 2 clinical studies.[5,6] The pivotal phase 2 study involved a prospective, sham-controlled randomized trial that investigated monthly dosing of 0.3 mg or 0.5 mg of ranibizumab for 6 months.[5] The lead investigator for that study was Jeffrey Heier of Boston. The second phase 2 study was a 20-week-long open-label dose-escalation trial in which 3 different dosing regimens were tested.[6] I was the lead investigator for this study. The purpose of this dose-escalation study was to determine if we could avoid the inflammation associated with the dose of 1.0 mg by gradually increasing the dose of rhuFab V2. In this study, we escalated the dose to as high as 2.0 mg in some patients. Three different dosing regimens were tried. In the first regimen, subjects were injected every 2 weeks and escalated from 0.3 mg to 1.0 mg; in the second regimen, the dose was escalated every 2 weeks from 0.3 mg to 2.0 mg; and in the

third regimen, the dose was escalated every 4 weeks from 0.3 mg to 2.0 mg. Both phase 2 studies were successful and reported unambiguous visual acuity benefits. In this dose escalation study, we showed that inflammation could be avoided if doses were escalated every 2 weeks or every month. We also showed that injections every 2 weeks were well tolerated, safe, and effective. This observation would later become important when we showed improvement in visual acuity and macular anatomy in some patients when anti-VEGF injections were given every 2 weeks in eyes that were deteriorating with monthly injections.[7] In this paper, we also used pharmacokinetic/pharmacodynamic modeling to support the benefits of more frequent dosing. Another benefit arising from these phase 2 studies was that we obtained the first OCT images of eyes before and after anti-VEGF therapy. This was possible owing to the timely availability of the first clinically useful time-domain OCT instrument, known as the OCT-3 (Stratus OCT; Carl Zeiss Meditec, Dublin, California, USA), which was FDA cleared in 2003. Suddenly, we were at the epicenter of 2 converging revolutionary technologies that would change our management of exudative macular diseases.

The development and commercialization of OCT would not have been possible without the monumental contributions of James Fujimoto, David Huang, and Eric Swanson, then at the Massachusetts Institute of Technology, and their collaborators at the Tufts University New England Medical Center, Carmen Puliafito and Joel Schuman.[8] Carmen Puliafito, my chairman at BPEI in 2003, acquired one of the first OCT-3 instruments, and by imaging subjects in the phase 2 trial, I witnessed the effectiveness of rhuFab V2, now named ranibizumab. For the first time, I saw where the macular fluid was located in eyes with exudative AMD. The fluid could be within the retina, under the retina, and under the retinal pigment epithelium. After an injection of ranibizumab, I observed the resolution of fluid from these compartments. Moreover, the resolution of this fluid correlated with both subjective and objective vision improvement. We also observed that when fluid recurred in some patients a month or more after an injection, the increase in fluid correlated with visual complaints; and when the patient was challenged with another injection of ranibizumab, the macular fluid would resolve, and the vision would improve. I came to appreciate that the OCT would serve as a VEGF-meter, a device that would indicate when excess VEGF was present and when anti-VEGF drug injections were needed.[9]

While OCT imaging revealed the presence and resolution of macular fluid during the phase 2 studies, it wasn't used to determine the need for retreatment, since fixed-dosing intervals were used in both protocols. At that time, there was no question that ranibizumab was effective, but the nagging question was whether monthly injections would be safe and tolerated as a viable long-term treatment strategy. To help address this question and provide

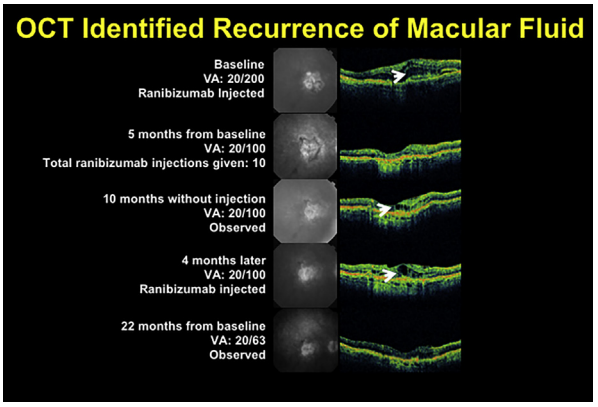

FIGURE 1. Example of a subject treated every 2 weeks with ranibizumab over 5 months in the phase 2 dose-escalation trial and then enrolled in the extension trial that used optical coherence tomography (OCT)-guided retreatment with ranibizumab for an additional 17 months of follow-up. Arrows point to the regions of macular fluid that resolve after ranibizumab treatment and recur following treatment. VA = visual acuity.

ranibizumab for phase 2 study patients once the studies were completed, Genentech was generous in supporting an open-label extension trial in which all subjects could roll over from the phase 2 studies into a long-term study that provided 0.5 mg ranibizumab for all patients until the drug was approved. The most notable feature of this extension-study protocol was that Genentech, at our request, did not require monthly dosing. Once the phase 2 study was completed, Genentech heeded our request to allow as-needed dosing based on the investigator's discretion. This was the perfect scenario in which to observe the durability of the ranibizumab therapy, determine whether monthly dosing was really needed, and assess whether OCT-guided therapy could maintain the visual acuity gains and OCT outcomes following the phase 2 fixed-interval dosing regimen with ranibizumab (Figure 1). At our center, 23 subjects were followed for over 18 months after completing the phase 2 studies. During this time, OCT imaging was performed on all patients. We found that the visual acuity gains were maintained in all patients and 7 patients did not need another injection based on OCT imaging. For those patients needing another injection, the median time to injection was 196 days, and the median number of reinjections at 12 months was 6, and at 18 months the median number of injections was 10. These data were presented at the 2004 Retina Subspecialty Day meeting during the annual meeting of the AAO. At the time, my colleagues did not believe that OCT alone was all that was needed to decide retreatment. After all, fluorescein angiography was still the gold standard for determining leakage from macular neovascularization. At the time, my hope was that I could publish these results in 2004, but Genentech felt that our patients represented only a subset of the total number of patients in the phase

2 extension study and could not be independently reported. These results from the phase 2 extension study were never published.

By this time, I was confident that OCT-guided therapy was the future for the management of exudative AMD with anti-VEGF therapy, and with the support of Stephen Judd and Ram Palanki at Genentech, we designed a clinical study in 2003 that became Genentech's first investigator-sponsored trial in ophthalmology. This investigation was a prospective, open-label clinical study named the Prospective Optical Coherence Tomography (OCT) Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Lucentis™ (PrONTO) Study (FDA Investigative New Drug (IND) #11715). The protocol was approved by the institutional review board (IRB) of the University of Miami (UM) Miller School of Medicine. The study design required that we follow patients monthly and re-treat based on the detection of macular fluid by OCT imaging. At that time, Anne Fung was my medical retina fellow, and the study would not have been possible without her expertise and assistance. Eventually, this OCT-guided approach would become known as treat-and-observe.[10,11]

THE PrONTO STUDY AND OPTICAL COHERENCE TOMOGRAPHY–GUIDED RETREATMENT

THE PRONTO STUDY ENROLLED AND FOLLOWED 40 PATIENTS every month for 2 years. To convince the skeptics that OCT-guided therapy could replace fixed-interval dosing, we treated monthly until the macula was dry and then we used retreatment guidelines during the first year of the study that we knew allowed for too much fluid to reaccumulate before we reinjected. Our intention was to demonstrate to the naysayers that when a small amount of fluid accumulated, if left untreated, then even more macular fluid would accumulate and vision would deteriorate. For that reason, we tolerated the accumulation of up to 100 μm of central macular fluid before retreatment was offered. Another indication for retreatment was the appearance of any new macular hemorrhage at any of the monthly visits. However, an enlarging retinal pigment epithelial detachment was not an indication for retreatment during the first year. As a concession to Genentech, we agreed to their mandate that all subjects receive 3 monthly injections to start the study before OCT-guided retreatment was initiated. As a result, these 3 monthly injections to start an anti-VEGF study have become a fixture in all subsequent industry-sponsored studies, especially those trials using OCT-guided therapy or any dosing that is less frequent than every month. At the time, there were no data to support this 3-monthly-injection requirement.

After the first year of the PrONTO Study, more than 95% of eyes were fluid free after the first 3 injections and the mean visual acuity improvement at the end of the year was 9.3 letters, which was very similar to the outcomes reported from monthly ranibizumab injections in the phase 2 study. However, visual acuity did fluctuate depending on whether fluid reaccumulated; however, vision improved once the reinjections were given. As expected, the vision improvements mirrored the OCT improvements. On average, only 5.6 injections were needed during the first year, compared with the 12 injections that would be given using a fixed-monthly dosing regimen. Moreover, we proved that when any macular fluid reaccumulated, then more fluid would follow. For that reason, in the second year of the study, the retreatment criteria were changed so that any reaccumulation of macular fluid would trigger a retreatment. Not only did we adopt a "no macular fluid" policy, but we also modified the protocol so that any unambiguous qualitative increase in the height of a pigment epithelial detachment, as determined by me, would be sufficient to trigger a retreatment. After 24 months, there was a mean visual acuity improvement of 11.1 letters with an average of only 9.9 injections. By every metric, the PrONTO study was a resounding success and established OCT imaging as the gold standard for deciding when to re-treat when using anti-VEGF therapy. While the scientific rigor of the study would have benefited from a control arm that received monthly injections, the results ended up being so definitive that few doubted the significance of the study. It should be noted that at that point in time, the FDA did not require a randomized control arm in a phase 2 study, but it is my understanding that if the PrONTO Study were repeated today, the FDA would mandate a control arm to the study.

As a result of PrONTO, numerous other OCT-guided retreatment studies were initiated, with many of them using the 100-μm rule for retreatment even though it was discarded after the first year of the PrONTO study. Results from these follow-up studies were variable primarily because they failed to follow rigorous monthly follow-up and retreatment guidelines. However, the PrONTO Study was fully validated by a large randomized clinical study known as the "pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration (HARBOR) study."[12,13] In Genentech's HARBOR Study, OCT-guided therapy was compared with monthly dosing of ranibizumab. In the arm with OCT-guided therapy, all subjects started with 3 monthly injections, followed by monthly visits with OCT imaging, and ranibizumab retreatment was given with the recurrence of any fluid on OCT imaging.

Another OCT-guided retreatment strategy that has gained popularity is known as treat-and-extend, in which anti-VEGF injections are given at every monthly visit until the macular fluid has resolved, and once the macular fluid is

gone, an injection is given and the treatment interval is then slowly extended, usually by 2 weeks.[9,14] Even if the fluid is absent at any given visit, an injection is given and the follow-up interval is increased by 2 weeks again; but if fluid recurs, an injection is given and the interval is then shortened by 2 weeks. Although variations of this strategy have been reported, the overall objective is to decrease the burden of monthly visits; but this convenience is offset by a potential increase in the overall number of injections compared with a pure OCT-guided treat-and-observe strategy (but still fewer injections than a fixed-monthly injection regimen). Both treat-and-observe and the treat-and-extend strategies are clinically useful depending on whether a patient prefers to avoid an injection or whether a patient would rather avoid frequent monthly visits. In the 2017 Patterns and Trends Survey sponsored by the American Society of Retina Specialists, OCT-guided therapy in some form was used by over 98% of injecting clinicians worldwide, which validates the significance of my original clinical observations from the ranibizumab phase 2 extension study, and, to the credit of Genentech, demonstrates the global significance of the investigator-sponsored trial known as the PrONTO study, which would not have been possible without Genentech's support.

While ranibizumab was being studied in phase 1/2 clinical trials, another VEGF inhibitor known as pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, New York, New York, USA) was being developed.[15] This drug, which is a RNA oligonucleotide known as an aptamer, inhibited VEGF-A, but only the isoforms that were 165 kDa or larger. Pegaptanib sodium was FDA approved in December 2004 and became commercially available in January 2005, about 18 months before ranibizumab would be approved, and about a year after bevacizumab had been approved for the intravenous treatment of colorectal cancer.[16–18] One of the reasons why pegaptanib sodium was able to beat ranibizumab to market was because they elected to bypass a traditional prospective, randomized, multidose phase 2 study and go directly from their phase 1 study to a phase 3 study. However, this tradeoff came at a price. They sacrificed potential efficacy for expediency. In the phase 1 study, Eyetech dosed their drug every 4 weeks; but in the phase 3 study, they elected to dose their drug every 6 weeks. We can only assume that they believed the intravitreal injection would be better tolerated if it was given less frequently, and they boldly extended the treatment interval without any clinical data. While the results were good enough to get FDA approval, the real-world experience with pegaptanib was less than satisfying. Eventually, both clinicians and patients would conclude that pegaptanib was less effective than either bevacizumab or ranibizumab for treating exudative AMD, and this lack of efficacy was probably due to the extended 6-week dosing interval and the inability of pegaptanib to inhibit all isoforms of VEGF-A.[19] Perhaps, if Eyetech had taken the time to incorporate OCT imaging in their phase 2 clinical trial design, they probably never would have extended the treatment interval to 6 weeks. Moreover, for those of us with the ability to image patients with OCT, it became unambiguously obvious that pegaptanib did not dry the macula after an injection in most patients. This experience provided the first evidence that OCT could be used to distinguish the efficacy of different anti-VEGF drugs. Moreover, it proved to be a crucial observation that led to the rise of bevacizumab and the demise of a pegaptanib sodium.

THE RISE OF SYSTEMIC BEVACIZUMAB

IN 2003, THE PHASE 3 TRIAL WITH RANIBIZUMAB WAS JUST getting started and the pegaptanib phase 3 trial was well underway. Both of these studies used fixed-interval intravitreal dosing; ranibizumab was given every 4 weeks and pegaptanib every 6 weeks. At that time, there was only 1 study that used anti-VEGF therapy guided by OCT imaging, and that was the PrONTO Study. However, we were designing another study that would use both anti-VEGF therapy and OCT imaging. This investigation became known as the Systemic Avastin for Neovascular AMD (SANA) Study.[20,21] The idea of using systemic bevacizumab came about from my exposure to ranibizumab in the phase 1/2 clinical studies, from my experience using OCT to image subjects in the ranibizumab extension trial, and from my experience with the PrONTO Study. Since there was quite a bit of uncertainty about whether patients would tolerate repeated intravitreal injections and whether these injections were safe for the long term, I was attracted to the idea of giving a systemic drug to treat exudative AMD. By giving a systemic drug, I reasoned that a single infusion could treat both eyes, which was appealing given that many patients had bilateral exudative disease, and that repeated systemic infusions were thought to be safer than repeated intravitreal injections. But, what about the increased risk of thromboembolic events from the use of systemic bevacizumab? That risk wasn't fully appreciated until 6 months after bevacizumab was approved in February 2004. Thus, in 2003 the idea of systemic anti-VEGF therapy seemed reasonable, but we didn't know whether systemic bevacizumab would be able to get into the back of the eye and have effects that were similar to an intravitreal injection of ranibizumab in eyes with exudative AMD. After all, bevacizumab and ranibizumab were thought to be very different anti-VEGF drugs. We also didn't know the right dose or the right dosing interval. However, by reviewing the literature, we subsequently learned that Genentech was guarding a secret.

To Genentech's credit, they encouraged their scientists to publish the research that led to the development of ranibizumab and bevacizumab, which included their cloning of

the gene that encoded the VEGF-binding domain for both ranibizumab and bevacizumab, as well as the crystallography of this VEGF-binding domain.[22] Based on the published literature, I realized that both drugs were developed from the same genetic sequences or plasmid clones that were engineered from the murine anti-VEGF monoclonal antibody developed at Genentech. The VEGF-binding domain, also known as the antigen binding fragment (Fab), derived from this murine clone was subsequently humanized by replacing certain amino acid coding regions. In the case of bevacizumab, 2 of these humanized VEGF-binding domains (Fabs) were attached to a humanized Fc fragment to construct a humanized full-length antibody against VEGF. In the case of ranibizumab, the genetic sequence was mutagenized and underwent a process called affinity maturation to identify sequences that would bind VEGF with a higher affinity compared with the original Fab. The affinity-matured Fab contained 6 amino acid changes, with 4 of the changes being responsible for a higher affinity for VEGF, roughly a 100-fold increase in inhibitory activity. A higher affinity for a single Fab was needed because, unlike bevacizumab, which would have 2 binding domains attached to a single Fc arm, ranibizumab would have a single binding domain; thus a higher affinity would be needed for comparable molar inhibition of VEGF. So, why did Genentech go to all the trouble of developing 2 different drugs when we now know that bevacizumab could have sufficed as an intravitreal treatment for exudative AMD?

In retrospect, the answer to this question now seems obvious, but at the time there was a great deal of uncertainty as to whether a full-length antibody could penetrate the retina and be effective in treating subretinal neovascularization when injected into the vitreous, and Genentech had no interest in pursuing a systemic treatment for exudative AMD. The clinical researchers at Genentech were directed to develop bevacizumab for systemic cancer therapy and ranibizumab for the intravitreal treatment of neovascular and exudative eye diseases. However, while I was involved in the ranibizumab trials, I learned that bevacizumab would be commercially available long before ranibizumab would be approved. Moreover, I found the idea of an intravenous infusion rather than an intravitreal injection particularly attractive, and after talking with my patients, I came to believe that some would prefer an intravenous infusion over an intravitreal injection. As a result, I approached Genentech and asked my contacts on the ranibizumab development team whether they would consider a study using systemic bevacizumab. Since their job was the successful commercialization of ranibizumab for the eye, they had no interest in pursuing systemic bevacizumab for the eye. When I was directed to the bevacizumab development team, I got a similar response, only their focus was the successful commercial development of systemic bevacizumab for cancer therapy, not the eye. Each of these drug development teams were siloed into their respective missions, and no one at Genentech was interested in pursuing systemic bevacizumab for the eye.

After my discussions with Genentech, I took the initiative and designed a clinical study that was very similar to the PrONTO study. However, instead of using intravitreal ranibizumab, I used intravenous bevacizumab. Instead of using 3 monthly injections of ranibizumab, I used 3 infusions of bevacizumab at the dose and dosing interval that were used in the bevacizumab phase 3 cancer protocols. In these cancer protocols, bevacizumab was given every 2 weeks at a dose of 5 mg/kg. As in the PrONTO study, I followed the patients in the SANA Study closely with OCT imaging and OCT-guided retreatment was followed after the first 3 infusions. However, in the SANA Study, I modified the requirement that the study start with 3 doses, and I allowed the third dose to be withheld if there was no evidence of macular fluid by OCT. After all, the SANA Study was my study and the 3 doses were not being mandated by Genentech. The SANA Study also differed from the PrONTO study by including indocyanine green angiography as well as fluorescein angiography. After the initial 2 doses, the patients would be followed every 2 weeks with OCT-guided therapy and retreatment was continued if any macular fluid persisted or recurred.

So how did I pay for this systemic bevacizumab study, given the fact that Genentech wasn't interested in supporting my research? My chairman at the time, Carmen Puliafito, allowed me to raise $200,000 from grateful patients to support the study. The plan was to enroll patients with refractory exudative AMD into this open-label prospective study, follow them every 2 weeks for a total of 6 months, and perform OCT imaging at every visit and dye-based angiography every 3 months. The study was approved by the IRB of the University of Miami Miller School of Medicine, and we were not required to submit an FDA Investigational New Drug (IND) application because we were not changing the safety profile of the drug, since we used the FDA-approved dose, dosing interval, and route of administration, we had no intention of seeking a change in the drug's label, and we had no intention of marketing the drug for this off-label indication.[23] We obtained IRB approval prior to the FDA approval of bevacizumab, so when bevacizumab was FDA approved and became commercially available in February 2004, the study was initiated with the help of Stephan Michels, my research fellow at the time. Both Stephan and Andrew Moshfeghi, my medical retina fellow, played pivotal roles and greatly contributed to the success of this study.

After the first infusion of bevacizumab in all patients, the OCT response was truly remarkable, with an overall improvement in vision and macular anatomy after 3 months.[20] In fact, the responses were very similar to the responses observed after an intravitreal injection of

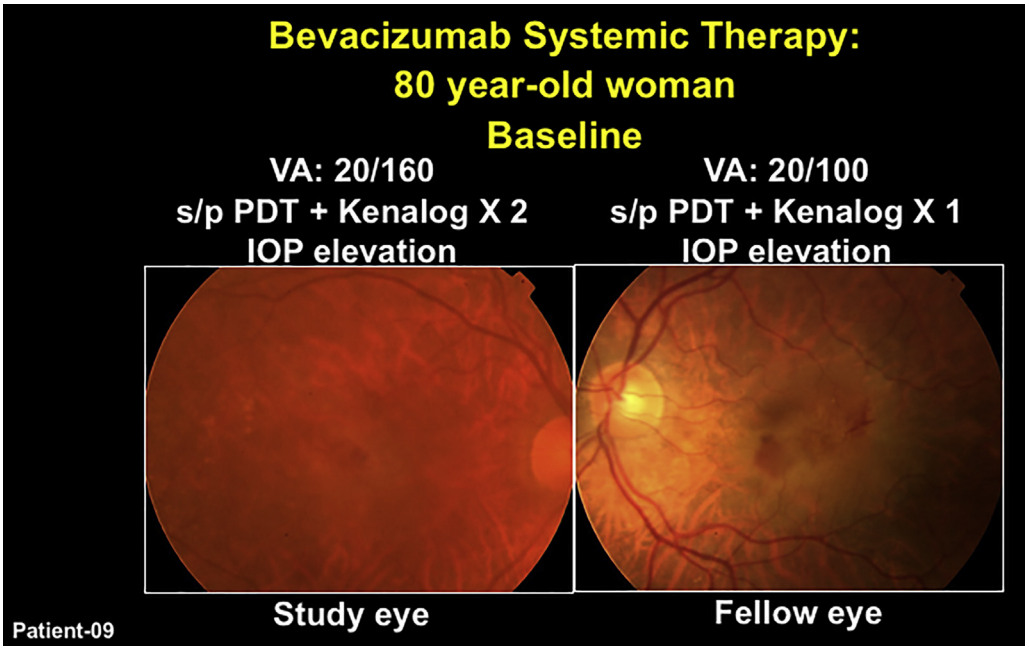

FIGURE 2. Baseline color fundus images from a subject enrolled in the Systemic Avastin (Bevacizumab) for Neovascular Age-Related Macular Degeneration (SANA) trial. IOP = intraocular pressure; PDT = photodynamic therapy; VA = visual acuity.

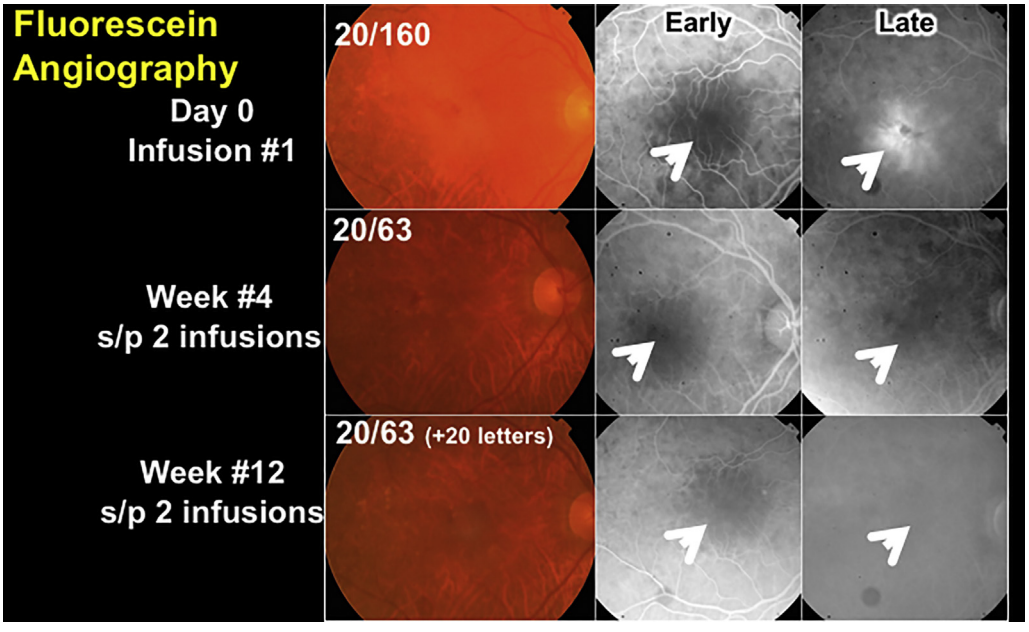

FIGURE 3. Early and late fluorescein angiographic images of the right eye (study eye) from the subject in Figure 3 at baseline and 4 weeks and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The fluorescein leakage (arrow) seen at baseline was absent by the 4-week follow-up.

ranibizumab. Within 24 hours, OCT imaging revealed dramatic improvements in the amount of macular fluid. A total of 18 patients were enrolled, and 16 of these subjects had bilateral exudative AMD (Figures 2-8). Of the 18 patients enrolled, a dry macula was achieved in 11 subjects after only 2 infusions and 7 subjects after 3 infusions, and these infusions were given at 2-week intervals during the first 6 weeks of the study. Retreatment was only offered if macular fluid recurred based on OCT imaging. By 24 weeks, retreatment was needed in 6 of the 18 study eyes. In the

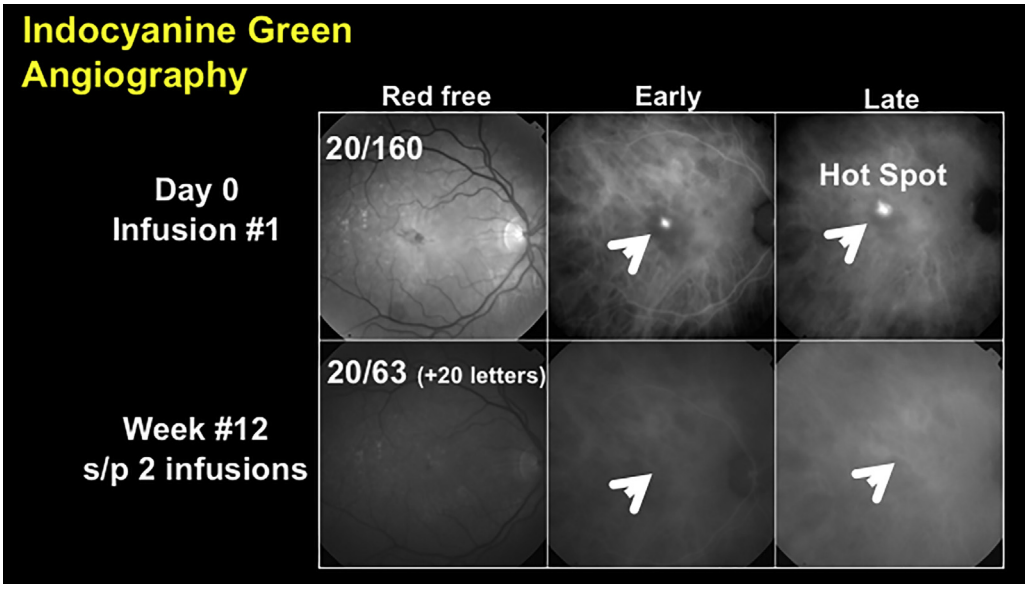

FIGURE 4. Early and late indocyanine green angiographic images of the right eye (study eye) from the same subject as in Figure 3 at baseline and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The hot spot (arrow) seen at baseline was not detectable by the 12-week follow-up. This neovascular lesion appeared consistent with type 3 macular neovascularization, which is consistent with the optical coherence tomography images in Figure 6.

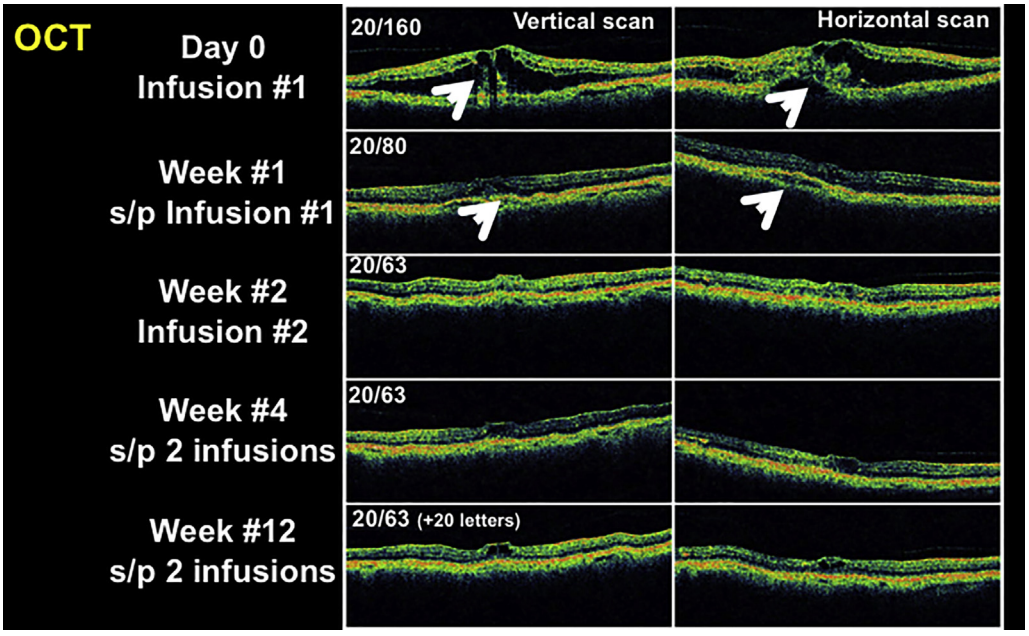

FIGURE 5. Vertical and horizontal optical coherence tomography (OCT) B-scans of the right eye (study eye) from the same subject as in Figure 3 showing cystic maculopathy and a retinal pigment epithelial detachment (PED) at baseline (arrow) consistent with type 3 macular neovascularization. One week after the first infusion of bevacizumab, the cystic maculopathy had resolved, and by 2 weeks the PED had mostly resolved as well. Twelve weeks after baseline and 2 bevacizumab infusions, the subject had gained 20 letters of vision.

study eyes, vision improved by an average of 14 letters and in the nonstudy fellow eyes, vision improved by 17 letters. Vision improvement coincided with an improvement in OCT macular fluid, and all results were highly statistically significant ($P \leq .001$). The only systemic adverse event during the course of the study was a mild increase in systemic blood pressure in 10 of the 18 subjects, with mean increases of 11 mm Hg and 8 mm Hg in the systolic blood pressure

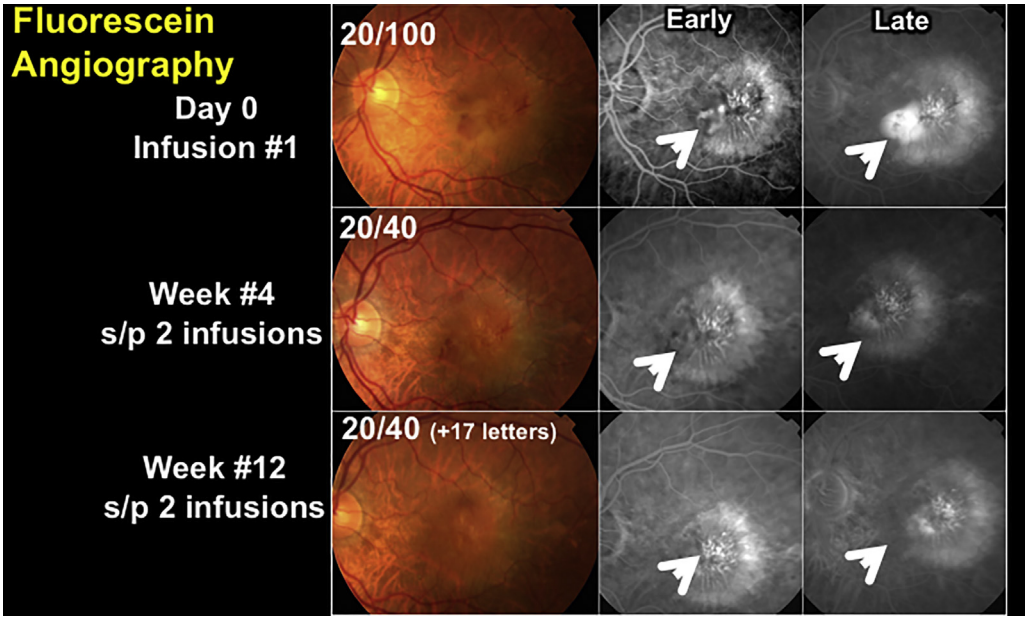

FIGURE 6. Early and late fluorescein angiographic images of the left eye (fellow eye) from the same subject as in Figures 3 through 6 at baseline and 4 weeks and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The fluorescein leakage (arrow) seen at baseline had decreased by the 4-week follow-up. Of note, the leakage arising from the classic (type 2) neovascular component appeared to resolve over 12 weeks.

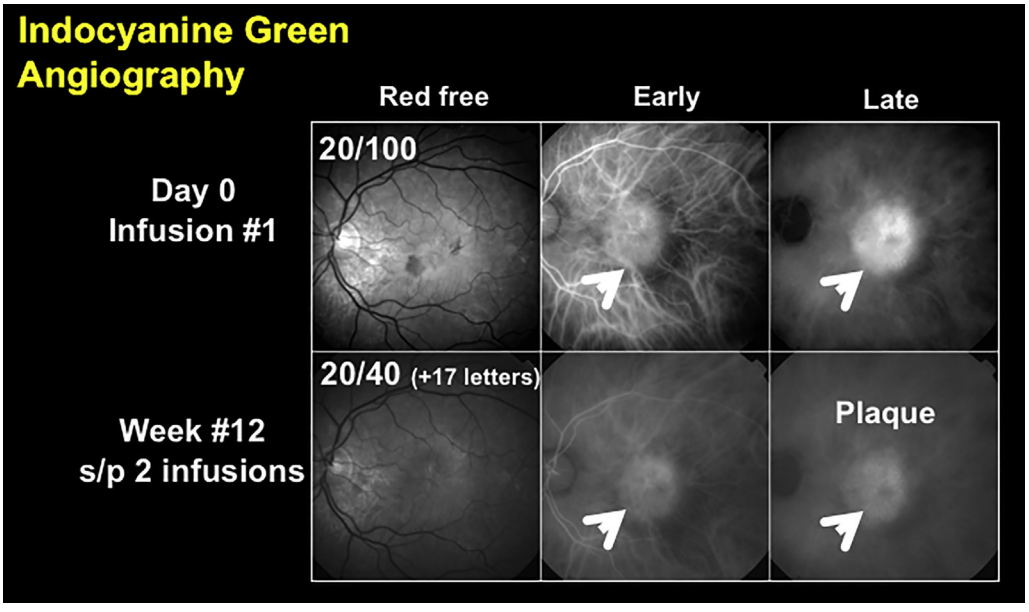

FIGURE 7. Early and late indocyanine green angiographic images of the left eye (fellow eye) from the same subject as in Figures 3 and 7 at baseline and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The plaque (arrow) seen at baseline less intense by the 12-week follow-up. This neovascular lesion appeared consistent with occult or type 1 macular neovascularization, which is consistent with the optical coherence tomography images in Figure 9.

and diastolic blood pressure measurements, respectively. By 24 weeks, our internists had controlled the blood pressure elevations, and all patients ended the study with lower blood pressure measurements compared with their baseline measurements. Unlike the cancer studies, there were no thromboembolic events and no episodes of proteinuria or bleeding diatheses; however, our sample size was small. We only studied 18 patients over 6 months.

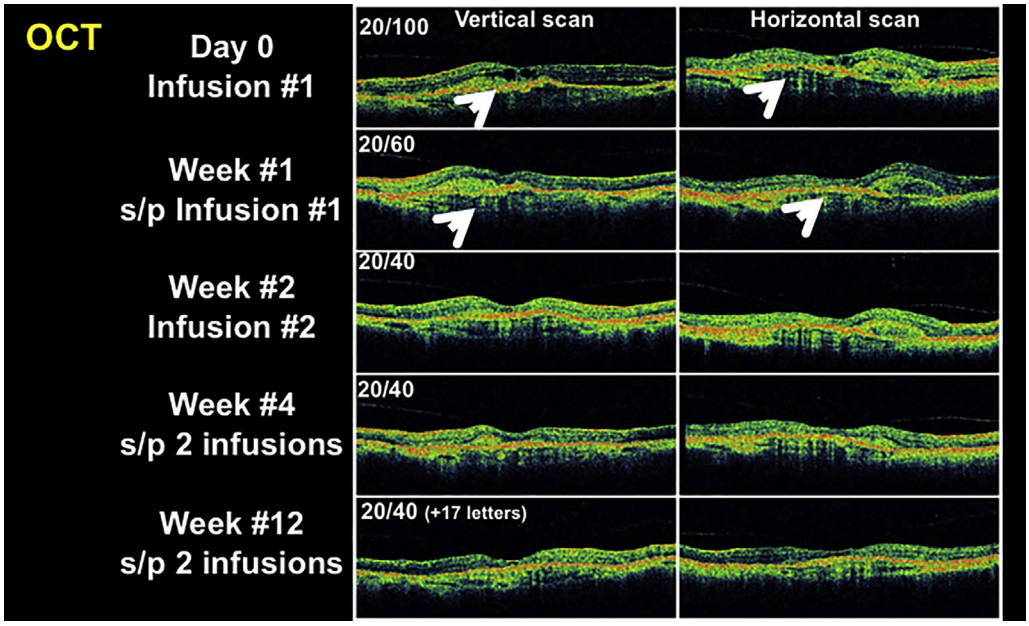

FIGURE 8. Vertical and horizontal optical coherence tomography (OCT) B-scans of the left eye (fellow eye) showing a low-lying retinal pigment epithelial detachment (PED) with subretinal hyperreflective material (SHRM) at baseline (arrow) consistent with a combined type 1/2 macular neovascular lesion. By 12 weeks after baseline following 2 bevacizumab infusions, there was significant resolution of the macular fluid and SHRM, and the subject gained 17 letters of vision.

Overall, the SANA Study was a resounding success. In contrast to the cancer patients receiving intravenous bevacizumab, it appeared as though exudative AMD patients required far fewer treatments, between 2 and 4 treatments over 6 months, with additional treatments probably needed every 3 months. This would result in a total of 4 to 6 infusions over 1 year. With an average cost for a single infusion of bevacizumab at $2200 per dose, the annual cost for systemic bevacizumab therapy would be roughly $13,200. By comparison, the average patient in PrONTO received about 6 injections of ranibizumab the first year. Once ranibizumab would be approved, the cost per injection was about $2000, so the annual costs for systemic bevacizumab and intravitreal ranibizumab would be roughly equivalent per eye, but since systemic bevacizumab would cover both eyes, the use of systemic bevacizumab would be more cost-effective. Moreover, patients wouldn't need to undergo intravitreal injections.

By the summer of 2004, my chairman and I paid our own way out to Genentech to present our preliminary data from the SANA Study. In a conference room on the Genentech campus, we met with Susan Desmond Hellman, Napoleone Ferara, Hal Barron, and the clinical leadership from Genentech. When we showed them our results, they were flabbergasted and promised to help us. Despite numerous attempts to engage with them after that visit, they refused to speak to us ever again about systemic bevacizumab for the treatment of exudative AMD.

By late 2004, the 12-week results from SANA were available and a manuscript was written, but 2 journals rejected our paper without criticizing the research. The editors felt that our conclusions were too radical at the time, and they were concerned about the widespread use of off-label intravenous bevacizumab if they published the research. Only Andrew Schachat, the editor of the journal *Ophthalmology*, had the courage to publish our results. A report on the first 9 patients followed for 3 months was published in the June 2005 issue of *Ophthalmology*,[20] and a second a scientific paper describing all 18 patients followed through 6 months was presented at the annual meeting of the AAO in October 2005 and subsequently published in *Ophthalmology* in 2006.[21] However, news of our results began to spread throughout the vitreoretinal community before the research was published. After all, it was late 2004, it appeared as though we had an effective therapy, bevacizumab was commercially available, and ranibizumab was still 18 months away from approval. However, the treatment landscape was about to change with the approval of pegaptanib sodium in December 2004. Beginning in January 2005, pegaptanib became commercially available, and the intravitreal injection of pegaptanib became the first-line treatment for all patients with exudative AMD.

With the availability of pegaptanib, the urgent need for systemic bevacizumab receded and our unbridled enthusiasm for intravenous bevacizumab as a treatment was tempered because in August 2004, the FDA issued a black

box warning for systemic bevacizumab. This black box warning was issued 6 months after the approval of bevacizumab and 6 months after the SANA Study was initiated. The black box warnings described increased risks of gastrointestinal perforations, wound healing complications, hemorrhage, and thromboembolic events from the use of intravenous bevacizumab. At the time, it was important to remember that in the cancer trials, bevacizumab was dosed every 2 weeks without interruption in combination with more traditional chemotherapy, and this therapy was initiated after surgery to resect the cancer. As a result, it was unclear if our AMD patients were at the same risk; however, our patients were older than the typical patients with colorectal cancer. Immediately after the FDA warnings were issued, our patients in the SANA Study were informed and our IRB-approved consent was revised to include these warnings. All patients in the SANA Study were then re-consented. Even after this new warning, none of our subjects dropped out of the SANA Study, there were no thromboembolic events, and all the subjects ended the study with better vision than when they started the study. Overall, the SANA Study was a great success, but the study wasn't powered to show if the treatment was truly safe. If we wanted systemic bevacizumab to become first-line therapy for exudative AMD, then we needed to perform a larger, multicenter, prospective, sham-controlled clinical trial.

THE RISE OF INTRAVITREAL BEVACIZUMAB

BY MID-2005, WE WERE READY TO RUN A LARGE MULTI-center clinical trial for the study of systemic bevacizumab in exudative AMD. On Sunday, May 1, 2005, we held an invitation-only organizational breakfast meeting for about 50 prominent retina specialists at the Marriott Harbor Beach Hotel during the annual ARVO meeting in Fort Lauderdale, Florida. We presented the treatment outcomes from the SANA Study. The presenters included Anne Fung, Stephan Michels, Andrew Moshfeghi, and me. In addition, our internists, Erin Marcus and Joshua Lenchus, presented the safety data. Everyone was impressed by the visual acuity and imaging data, but our retina colleagues were concerned about the risk of thromboembolic events, even though we experienced none of the serious adverse events. The attendees wanted to see if we could achieve similar efficacy with a lower systemic dose, which should translate into safer dose of intravenous bevacizumab. We were disappointed. We thought there would be unbridled enthusiasm for systemic bevacizumab, but instead we were instructed to find the lowest, most effective dose of systemic bevacizumab for exudative AMD.

During the week after ARVO, I was in the process of designing a clinical trial using a lower systemic dose of bevacizumab when I had a eureka moment while going through my calculations. I realized that the commercially available bevacizumab had the same molar concentration as the high-dose solution of ranibizumab being used in the PrONTO Study and the ongoing phase 3 ranibizumab clinical trials. Bevacizumab was supplied in a preservative-free buffered solution (pH 6.2) at a concentration of 25 mg/mL. Ranibizumab was supplied in a preservative-free buffered solution (pH 5.5) at a concentration of 10 mg/mL. With the molecular weight of bevacizumab (149 kDa) being about 3-fold greater than the molecular weight of ranibizumab (48 kDa) and the commercial concentration (mg/mL) of bevacizumab being 2.5-fold greater than ranibizumab, I suddenly realized that both drugs had similar molar concentrations. That meant a similar volume of both drugs would contain a similar number of molecules or a similar amount of VEGF-binding activity. As a result, a volume of 0.05 mL, which was the standard volume used for a ranibizumab injection, and a 0.05 mL volume of bevacizumab would contain the equivalent amount of VEGF inhibitory activity. This realization that the same volume of bevacizumab, right out of the bottle, could be equivalent in terms of VEGF binding activity when compared to the same volume of ranibizumab was a startling fact based solely on serendipity. Genentech just happened to package both ranibizumab and bevacizumab at similar molar concentrations. The other remarkable conclusion was that this dose of bevacizumab, which was 0.05 mL of a 25 mg/mL solution, resulting in a dose of 1.25 mg, would cost under $7, since the per-milligram cost of bevacizumab was $5.50/mg. In comparison, once ranibizumab was approved, a similar dose would cost $2000 and the per-milligram cost of ranibizumab would be $4000/mg. However, there were other considerations that needed to be addressed.

When I had my epiphany, I was confident that an intravitreal injection of bevacizumab would be safe based on my experience with ranibizumab and the composition of bevacizumab buffer excipients. At the time, I didn't know if a molar-equivalent dose of bevacizumab would be as effective, more effective, or perhaps less effective than ranibizumab. Since bevacizumab was a full-length antibody with 2 VEGF-binding sites per molecule and a larger molecular weight compared with ranibizumab, I thought it would bind more VEGF and have a longer half-life in the eye, and thus show greater treatment durability. However, each VEGF-binding site on a molecule of bevacizumab had a VEGF binding affinity that was 140-fold lower than the ranibizumab Fab. But, the greatest unknown was whether bevacizumab, which was a full-length antibody, would even penetrate the retina after an intravitreal injection, or whether retinal penetration was even necessary. After all, it was believed that the VEGF causing the neovascularization was located under the retina, and one of the reasons Genentech developed ranibizumab was to provide a small molecule that could more easily penetrate

the retina. But what if bevacizumab could bind VEGF in the vitreous and the vitreous could serve as a sink to draw VEGF out of the retina? If that were the case, then inhibition of vitreal VEGF would suffice.

Upon review of the literature, several important animal studies came to light. In 1996, Adamis and associates published a paper showing that multiple, intravitreal injections of a bevacizumab-like molecule from Genentech inhibited the formation of iris neovascularization in a monkey model of neovascular glaucoma and no drug-related adverse events were observed.[24] While this model showed that the injection of an antibody could be tolerated, the efficacy of this antibody only required intravitreal inhibition of VEGF. To address the question of whether a full-length antibody could penetrate the retina, Genentech scientists performed a study to compare the retinal penetration of an antibody with a Fab in male Rhesus monkey eyes.[25] In this study, they used a recombinant humanized monoclonal antibody (Mab) against HER2, known commercially as Herceptin, and a recombinant humanized Fab against VEGF, which was similar to ranibizumab. They showed that the antibody had a longer half-life (5.6 days) compared with the Fab (3.2 days). They also showed that the full-length antibody failed to penetrate the retina while the Fab easily penetrated the retina. Thus, they used this evidence to support the development of ranibizumab for the eye rather than bevacizumab. However, this study was flawed. Instead of using a bevacizumab-like antibody, they used an antibody that recognized HER2, and the HER2 antigen was present in the inner retina.[26] In their experiment, the full-length antibody couldn't penetrate the retina from the vitreous, but it wasn't because the antibody was too large; it was because the antibody became bound to HER2 and couldn't penetrate into the retina from the vitreous. A subsequent paper in 2004 by Dennis Han did show that full-length antibodies could penetrate the retina.[27] Thus, in May of 2005, it was perfectly reasonable to conclude that an injection of bevacizumab, at a dose equivalent to ranibizumab, could penetrate the retina and be used to treat exudative AMD. However, even if it couldn't penetrate the retina, bevacizumab could inhibit VEGF in the vitreous and the proposal that the vitreous could serve as a VEGF sink to draw VEGF out of the retina down its concentration gradient seemed reasonable.

The timing of the bevacizumab breakthrough couldn't have been better for patients. In early May 2005, our only treatments were pegaptanib and verteporfin PDT. While verteporfin PDT was approved for only a minority of eyes with predominantly classic CNV, pegaptanib was approved for all eyes with exudative AMD. However, after using pegaptanib for the treatment of exudative AMD over the 5 months of commercial availability from January to May 2005, we found that the average patient continued to lose vision, and OCT imaging revealed persistent or increasing amounts of macular fluid in these patients. Our patients were deteriorating, and I knew ranibizumab would be superior to pegaptanib based on our previous studies, but ranibizumab would not be available for another 14 months. My options were to continue to inject pegaptanib every 6 weeks at a drug cost of $1650 per dose and watch my patients lose their vision, or consider an off-label injection of bevacizumab at a drug cost of under $7 per injection. But, we didn't know if intravitreal bevacizumab would be safe or effective.

I approached the director of our pharmacy, Serafin Gonzalez, and asked him if he could compound bevacizumab into syringes for intravitreal injection. This type of request was nothing new for Serafin. He had been compounding drugs for off-label intravitreal use in ophthalmology for years, and these drugs included antibiotics, steroids, and another Genentech product known as tissue plasminogen activator. After reviewing federal guidelines and Chapter 797 of the US Pharmacopeia (USP), he said that it was legal and safe, as long as strict guidelines were followed.[28] My chairman, Carmen Puliafito, approved the compounding of bevacizumab for intravitreal injection and permitted my off-label use intravitreal bevacizumab as salvage therapy only in patients losing vision, only after they had failed routine clinical care—in other words, only after the approved therapies were tried. If I was to use the drug off-label, I realized that all patients needed to be informed of all the potential risks associated with bevacizumab, and because of our extensive experience with intravitreal ranibizumab and systemic bevacizumab, we were well positioned to know all the possible adverse events that could occur.

During the second week of May, almost 2 weeks after our fateful ARVO meeting, I identified the ideal exudative AMD patient for a bevacizumab injection. She was losing vision in her better-seeing eye owing to continued growth of her neovascular lesion after treatment with PDT followed by intravitreal pegaptanib. She was well aware of what was going to happen if we stayed the course, since she already had lost vision in her fellow eye from exudative AMD. Of note, the patient was a retired nurse and understood all the potential risks associated with an intravitreal injection of bevacizumab. For the first salvage dose of bevacizumab, I chose a 1.00 mg dose or 0.04 mL, and the patient was not charged for the drug or injection. After 1 injection of bevacizumab, the macular anatomy was restored and the vision was stabilized (Figures 9-11).[29] The OCT and visual acuity responses were nearly identical to the responses I had observed after intravitreal ranibizumab and systemic bevacizumab. An additional patient with macular edema from a central retinal vein occlusion was injected with 1.0 mg of bevacizumab, only this time the visual acuity improved when the macular edema resolved.[30] Both patients remained stable for 2 months after a single dose. No inflammation or any other adverse events were observed.

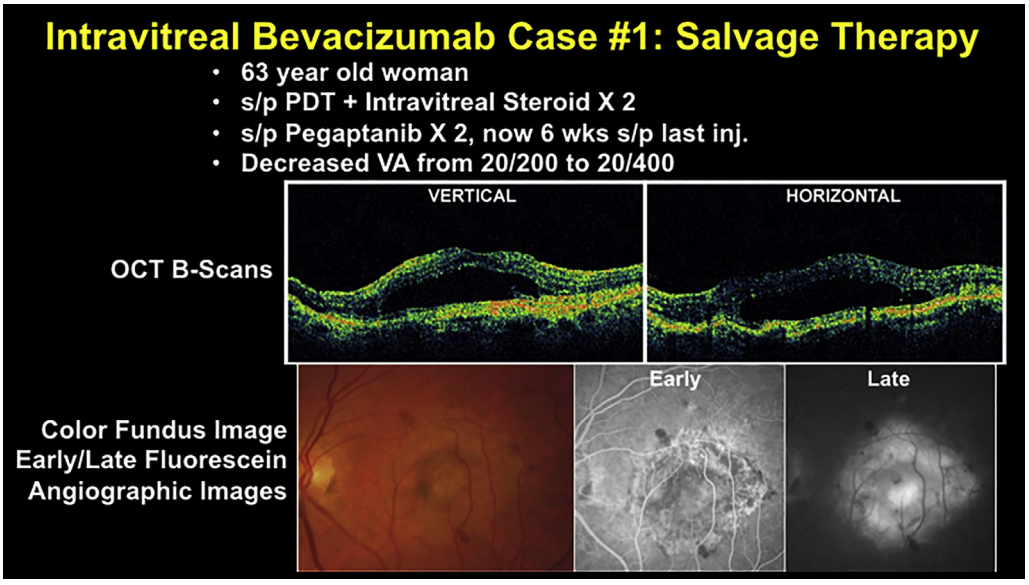

FIGURE 9. First case of salvage therapy with intravitreal bevacizumab following verteporfin photodynamic therapy (PDT) with intravitreal steroid and intravitreal pegaptanib sodium. Vertical and horizontal optical coherence tomography (OCT) B-scans show the presence of macular fluid and fluorescein angiography depicts a neovascular lesion associated with significant leakage. VA = visual acuity.

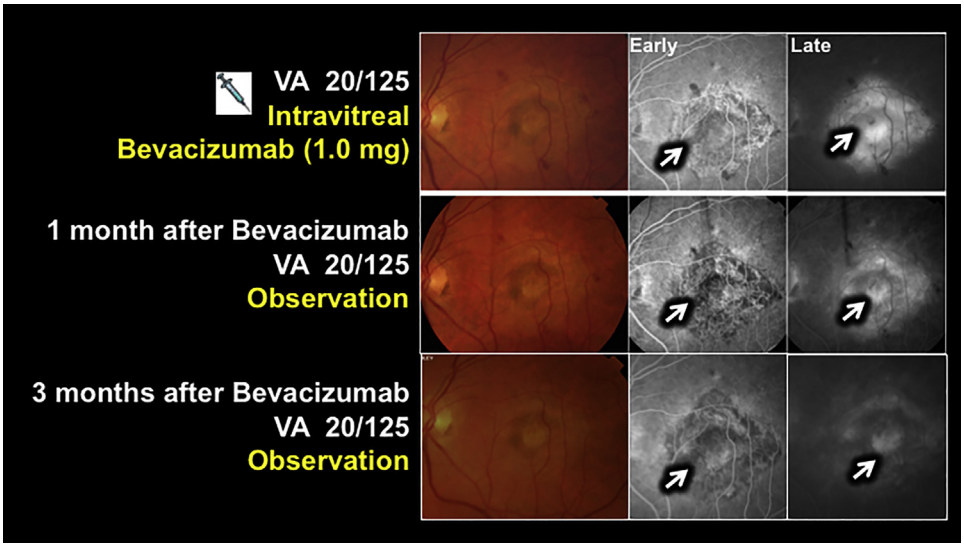

FIGURE 10. Fluorescein angiographic appearance following the intravitreal injection of bevacizumab (1.0 mg) into the eye shown in Figure 10 with a gradual decrease in leakage (arrow) from the neovascular lesion through 3 months of follow-up. VA = visual acuity.

THE GLOBAL BEVACIZUMAB REVOLUTION

IN MAY 2005, AFTER THE 2 PATIENTS WERE INJECTED WITH bevacizumab, my colleagues and I at the BPEI started to offer intravitreal bevacizumab as salvage therapy at no cost to patients. We treated exudative and neovascular eye diseases, such as exudative AMD, diabetic macular edema, and macular edema secondary to retinal vein occlusions. My plan was to keep our discovery quiet so we could design a controlled, prospective, randomized clinical trial to prove that intravitreal bevacizumab was safe and effective. However, news of our novel therapy started to spread outside of the institute, primarily driven by grateful patients. As inquiries from the outside increased, I realized we needed to get our initial observations published to

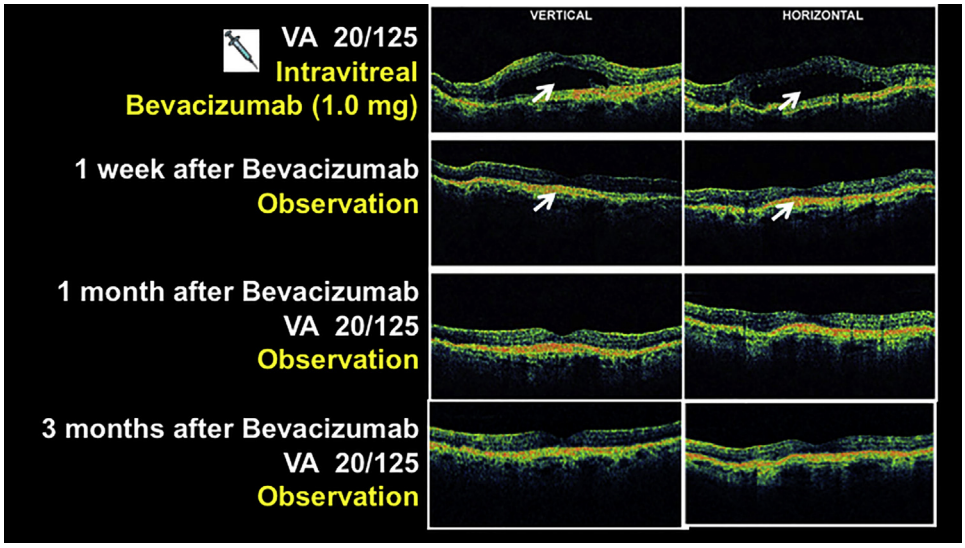

FIGURE 11. Vertical and horizontal optical coherence tomography B-scans of the eye shown in Figure 10 following the intravitreal injection of bevacizumab (1.0 mg) showing resolution of macular fluid by 1 week after the injection, which was maintained through 3 months. Overall, there was no objective improvement in vision, but the patient reported a significant subjective improvement. VA = visual acuity.

emphasize the use of bevacizumab as salvage therapy and the need for safe compounding of bevacizumab according to Chapter 797 guidelines from the USP. We were concerned, even at that time, that the irresponsible use of bevacizumab would result in endophthalmitis, a bacterial infection in the eye. For this reason, we reported both or original cases in the July issue of *Ophthalmic Surgery, Lasers, and Imaging*.[29,30] However, prior to the publication of these reports, our initial intravitreal bevacizumab results were shared with 2 respected colleagues, Robert Avery and Garee Thomas. Robert Avery learned of our bevacizumab experience at a June 2005 meeting in Montana, where my chairman, Carmen Puliafito, presented my first case of exudative AMD treated with intravitreal bevacizumab. Garee Thomas learned of our bevacizumab use during a casual conversation at a different meeting in June. After we shared our compounding and injection protocol with both of them, they started offering off-label intravitreal bevacizumab to their patients. Their early use of intravitreal bevacizumab would prove pivotal to the rapid adoption of intravitreal bevacizumab worldwide.

The world learned of our discovery at the American Society of Retina Specialists (ASRS) annual meeting in Montreal, which was held during the second week in July. The excitement surrounding this meeting was palpable because Genentech had planned to release the results from their phase 3 ranibizumab trial for minimally classic and occult neovascular AMD, known as the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trial. Even though I was the top enroller in that study and would be the first author on the *New England Journal of Medicine* 2-year report on this study,[31] Genentech asked Joan Miller to present the top-line results. I'm sure most of you can figure out why I wasn't offered the MARINA presentation, given the tensions that had developed between Genentech and me after they became fully aware of our bevacizumab discovery. However, it was the perfect sequence of events and couldn't have worked out better.

On July 18, 2005, there were 3 talks that would precede Joan Miller's talk on the MARINA results. I was scheduled to give the initial 12-week results from the SANA Study, Andrew Moshfeghi was scheduled to give the 24-week results, and Anne Fung was scheduled to give the 1-year results from the PrONTO Study. The meeting was packed with retina specialists, journalists, and investors. At the end of my talk on the SANA Study design and the short-term results using systemic bevacizumab, I showed the results from the first intravitreal injection of bevacizumab. We were able to demonstrate the similarity between an intravitreal injection of bevacizumab with an intravenous infusion of bevacizumab, and the intravitreal injection of ranibizumab, which was shown by Anne Fung in her PrONTO presentation. Then, after our presentations, Joan Miller presented the impressive MARINA ranibizumab results. It was the perfect storm. The crowd went wild. The OCT and visual acuity outcomes after the ranibizumab injections looked identical to the bevacizumab results. Moreover, this the first meeting where OCT imaging played an important, pivotal role in documenting the

anatomic changes that were associated with the vision improvement observed following anti-VEGF therapy. Everyone connected the dots. They concluded that if the OCT and visual acuity results looked similar and ranibizumab wasn't going to be available for a year, then the obvious solution was to use off-label bevacizumab now. Moreover, Robert Avery and Garee Thomas were in the audience telling everyone that their results looked as good as our results, and that intravitreal bevacizumab was the real deal and it was available now. The global bevacizumab revolution had started. Not only was bevacizumab available worldwide, but also, it was cheap, at about $7 a dose for the drug. Also, remember that retina specialists had become disillusioned with pegaptanib, and not only was bevacizumab less expensive than pegaptanib, it also appeared to be more effective.

After the intravitreal bevacizumab announcement at the ASRS meeting in Montreal, clinicians and researchers from all over the world started to work together to investigate its safety and efficacy.[32] Numerous groups initiated parallel animal studies and clinical studies. One of the most important collaborations was initiated between Anat Loewenstein's group in Tel Aviv and Robert Avery's group in Santa Barbara.[33] Using a rabbit model, they showed that bevacizumab was safe and that the intravitreal bevacizumab not only penetrated the retina, but persisted longer in the eye compared with ranibizumab. Over the following year, the clinical use of bevacizumab spread worldwide because of the global availability of bevacizumab, its low cost, its perceived safety and efficacy, and the enormous unmet need to prevent blindness. In the United States, Medicare providers from all over the country agreed to pay for the intravitreal use of bevacizumab for a wide range of ophthalmic indications. Our Medicare provider, First Coast, was the first to agree to pay for bevacizumab and over the next year, the other providers soon followed. This was accomplished owing to the hard work of our colleagues all over the country, particularly the AAO, and our specialty societies, with extraordinary assistance from William Rich and George Williams. As a result of this global enthusiasm, research publications describing intravitreal bevacizumab grew exponentially over the next few years.

In the midst of the global frenzy around intravitreal bevacizumab, I abandoned my plans to run a systemic bevacizumab study and decided to focus my efforts on a multicenter, prospective, randomized, sham-controlled study to investigate intravitreal bevacizumab in exudative AMD. We drafted a protocol known as the IntraVitreal Avastin in Neovascular AMD Study (IVANA Study) and submitted the IND application to the FDA. Wiley Chambers of the FDA was supportive of our efforts, but the application was placed on hold pending my responses to the following requests. They included (1) a detailed description of how the drug would be prepared by a licensed and accredited pharmacy and a description of how the drug would be handled once it was prepared; (2) a detailed description of the stability testing that would be performed to determine that bevacizumab was stable in syringes once dispensed by our pharmacy; (3) a revision of the protocol incorporating 2 different doses of bevacizumab at 1.25 mg (0.05 mL) and 2.5 mg (0.10 mL); and (4) a full retrospective review of all the patients treated with intravitreal bevacizumab at our site, with as much evidence as possible from other sites (including published papers and manuscripts submitted for publication) to help assess the number and kind of complications that might be expected. To comply with these requests, I submitted a retrospective research protocol to the University of Miami IRB to get permission to collect all the clinical information that had been recorded on our patients treated with off-label intravitreal bevacizumab. The university IRB requested that I submit an IND to the FDA for this retrospective review of off-label intravitreal bevacizumab. This request seemed extraordinarily unusual and should have given me advance warning that my use of off-label bevacizumab was starting to be of concern within the university. My retina colleagues and our patients were not generating this concern. But rather, individuals outside the university were voicing the concerns. Interestingly, there was no formal process to request an IND from the FDA for a retrospective review, but the university was undeterred from their demand that I receive FDA approval. As a result, I simply drew a box on the IND application form, labeled the box for a retrospective review, checked the box, and submitted the application. It was approved. Shortly thereafter, the university IRB approved the retrospective chart review and data collection commenced.

THE BAD AND THE UGLY BEHAVIOR OF INDUSTRY AND GOVERNMENT

I WAS IN THE PROCESS OF SATISFYING ALL THE FDA REquests, which included the IRB-approved retrospective review of all our patients treated with intravitreal bevacizumab, and the laboratory functional studies with cultured vascular endothelial cells to test the biological stability of bevacizumab by measuring its ability to inhibit cell growth in vitro after storage in syringes, when it all suddenly came to a screeching halt. On December 28, 2005, I received a fax from the Federal Office of Human Research Protection (OHRP) that contained a letter dated December 22, 2005. This 20-page, single-spaced letter with footnotes and 40 pages of accompanying exhibits alleged that I had committed research fraud and patient abuse by using bevacizumab. There was no doubt that this professionally written letter was the product of a law firm, but we were unable to determine who sent the letter, since its author was anonymized and all identifying information was redacted. The letter accused us of performing

egregious, dangerous, clandestine, and unauthorized human experimentation. The author included false reports of human injury and financial conflicts with bogus evidence that supposedly supported these claims. Eventually, these anonymous purveyors of fake information would lose, but I paid a price. I was intensively investigated by UM and the OHRP for 16 months. Every aspect of my bevacizumab use and all my research programs were extensively scrutinized. Finally, in April 2007, a panel of OHRP investigators, outside experts, and their lawyers came to the UM IRB office for a meeting with leadership and me. At this meeting I was totally exonerated and congratulated for my efforts to prevent blindness. Their conclusions were that my actions were legal, ethical, and appropriate for patient care. Although stressful, it was a valuable learning experience. If only my accusers had bothered to read the Belmont Report on the Ethical Principles and Guidelines for the Protection of Human Subjects of Research.[34] In that report, it is clearly written that in the United States, off-label drug use in the clinical care of patients is legal and not regulated by the FDA. To paraphrase the Belmont Report, just because the drug is used off-label, it doesn't make it research. The results of this investigation were posted online at the time, but the documents are no longer available on the OHRP website. Of course, my accusers weren't interested in the truth, but rather, they were interested in attacking me, damaging my credibility, and stopping the global use of bevacizumab. Needless to say, they failed. While I was distracted, my colleagues all over the world surged forward in their research and clinical use of intravitreal bevacizumab. Bevacizumab was a global juggernaut that could not be stopped, and to this day, I can only speculate who was behind this failed attempt to stop it. While I have no doubt that industry was behind the letter, I also believe they received a little help from an OHRP insider, although this can't be definitively proven. To this day, the identity of my accuser remains unknown.

While the OHRP exonerated me in April 2007, they weren't quite finished. In October 2007, I received an e-mail from the FDA stating that they would perform a surprise audit of all my clinical research studies under the jurisdiction of the FDA. Since I had received an IND from the FDA for my retrospective review of patients treated with intravitreal bevacizumab, they demanded an audit of all the medical records and data collection sheets pertaining to patients treated with intravitreal bevacizumab. When the auditor showed up from October 19th to the 21st, she embarrassingly shared the fact that the audit had been requested by OHRP and she had never before had to audit a retrospective review. However, as a professional, she took her assignment seriously and thoroughly reviewed every aspect of the medical records and data collection sheets pertaining to our patients with exudative AMD, diabetic macular edema, and retinal vein occlusions with macular edema treated with intravitreal bevacizumab. At the conclusion of the bevacizumab audit, we were totally vindicated. Bevacizumab had been administered as off-label salvage therapy and no prospective research was performed. Three retrospective review papers highlighting our off-label clinical use of intravitreal bevacizumab were subsequently published,[35–37] along with hundreds of papers from other researchers. The worldwide phenomenon of intravitreal bevacizumab could not be stopped.

THE GOOD AND THE GREAT BEHAVIOR OF SPECIALTY SOCIETIES AND GOVERNMENT

ANOTHER STRATEGY EMPLOYED BY INDUSTRY TO THWART the use of intravitreal bevacizumab was an attempt by Genentech to prevent the sale of bevacizumab to ophthalmologists. In mid-2007, Genentech announced that bevacizumab sales to ophthalmologists would be stopped, and the FDA demanded this action. To the credit of the AAO, the ASRS, the Macula Society, and the Retina Society, our leadership fought against this action using many different strategies, both public and clandestine. George Williams and Kirk Packo gave inspiring talks at the Retina Subspecialty Day in 2007 encouraging Genentech to change its decision. On November 7, 2007, at the annual meeting of the AAO, Susan Desmond-Hellman addressed a special session devoted to bevacizumab access. Susan Desmond-Hellman, then President for Product Development at Genentech who serves today as the Chief Executive Officer of the Bill and Melinda Gates Foundation, told an auditorium filled to capacity that the decision to restrict bevacizumab sales to ophthalmologists arose from FDA inspectors who found glass particles in lots of bevacizumab, determined that the bevacizumab was unsafe for intraocular use, mandated its destruction at a loss to Genentech of over $100 million, and required that sales of bevacizumab for intraocular use be restricted. Tense discussions followed, both during the annual meeting and afterwards. However, we soon found supporters within the government who understood the impact of restricting access to this low-cost drug. Although there were many heroes in the fight to preserve access to bevacizumab, one man stood out as a giant. His name is Jack Mitchell.

Jack Mitchell was Chief of Oversight and Investigation for the U.S. Senate Special Committee on Aging, which had broad jurisdiction over public health issues that affected seniors and the Center for Medicare and Medicaid Services (CMS), and this jurisdiction provided him with the opportunity to become involved and gain access to the information needed. At the time, Senator Herbert Kohl of Wisconsin was the ranking Democrat and chairman of the committee and Senator Robert Corker was the ranking Republican. Jack Mitchell investigated Genentech's bevacizumab policy and after reviewing all FDA audits and interviewing industry representatives, he

wrote an investigative report that was composed of 19 single-spaced pages (Supplemental Material, available at AJO.com). In this report, he highlighted the FDA's refusal to honor the request from Genentech that they change bevacizumab's labeling to explicitly state "not intended for ophthalmologic use." At the time, the FDA claimed that there were no safety-related issues to justify such a labeling change. Most likely, our FDA audit report and the numerous publications that had appeared in peer-reviewed journals served to support the FDA's position. Moreover, Jack Mitchell found that the FDA had identified manufacturing problems at Genentech's facility that resulted in glass particles in their product. The FDA inspection report highlighted deficient practices and the lack of effective processes at the facility and recommended that those lots be considered unfit for any use, oncology or ophthalmology. Of note, the FDA did not mandate the lot's destruction and did not recommend restricting the sale of bevacizumab to compounding pharmacies or restricting the intraocular use of bevacizumab. Owing to the diligence and perseverance of Jack Mitchell, our professional societies, and many other colleagues, Genentech backed down and permitted the sale of bevacizumab to compounding pharmacies for intraocular use.

While there were minor subsequent skirmishes in our attempts to get coverage from all Medicare providers across the United States, it wasn't until September 2009 that another major obstacle arose that threatened our use of intravitreal bevacizumab. Suddenly, CMS decided to stop paying for any intravitreal bevacizumab. No reason was given publicly. It appeared to be an arbitrary decision that was being implemented without due process. We had our suspicions why this happened, but no proof. Once again, our professional societies and our allies in Washington came to the rescue. Jack Mitchell played a pivotal role behind the scenes and started an investigation. Soon, another great advocate for bevacizumab surfaced and played a pivotal role within CMS. His name was Ross Brechner. He was a lead medical officer and consultant at CMS and the only ophthalmologist at CMS. Fortunately, we were able to get the CMS decision reversed.

Ross Brechner and I had become good friends by the time he helped reverse the CMS decision. Ross's professional career was a bit unusual in that he was a practicing ophthalmologist who went back later in life and obtained a master's degree in biostatistics and public health from the Johns Hopkins School of Public Health. He then went to work at the Centers for Disease Control and Prevention before moving on to CMS. In 2008, when he was at CMS, he became intrigued with the Medicare cost savings from the use of intravitreal bevacizumab compared with ranibizumab, which had been approved in 2006. We then started to collaborate on an investigation into the real-world use of ranibizumab and bevacizumab in 2008 based on the 100% of the Medicare database files. At that time, CMS was reimbursing about $2000 a dose for ranibizumab and $50 a dose for bevacizumab. As an employee of CMS, Ross had access to the 100% CMS databases from 2006 through 2008. We compiled the results and showed that in 2008, over 58% of exudative AMD patients had been treated with bevacizumab. With bevacizumab being reimbursed by CMS at $50 a dose and ranibizumab at $2000 a dose, we conservatively estimated that in 2008 alone, if all the bevacizumab doses had been replaced with ranibizumab doses, then CMS would have spent an additional $1 billion for the care of exudative AMD patients. We wrote a manuscript describing the number of intravitreal injections, the utilization of ranibizumab and bevacizumab, and the theoretical cost savings from bevacizumab, but Ross Brechner's boss at CMS, Barry Straube, refused to give us permission to submit our research for publication. We repeatedly approached Barry Straube for permission, but to no avail. Once again, Jack Mitchell came to the rescue. He introduced me to Alicia Mundy, a reporter at the *Wall Street Journal*, and I explained the situation to her. She investigated and wrote an article in the WSJ on June 17, 2010 entitled "Medicare Eye Study Finds Untapped Savings." In that article, Barry Straube denied any effort to hinder release of the data. He said he hadn't realized the authors viewed the matter as pressing and said, "I think we can speed this up significantly." Our paper was submitted soon after the WSJ article appeared, and Dr Straube left CMS shortly thereafter. Our research was published in the May 2011 issue of the *American Journal of Ophthalmology* (AJO).[38]

By the time the paper was published, we had already finished evaluating the 100% CMS database for 2009 and had begun evaluating the 2010 database. Ross Brechner had divided the United States by major metropolitan centers and rural areas, evaluated utilization of anti-VEGF therapy in these regions, determined the use of drugs based on the penetration of fee-for-service Medicare vs Medicare Advantage plans, and identified comorbidities associated with the use of the different drugs. Unfortunately, Ross Brechner died in August 2011 just as he was finalizing a draft of the 2009 CMS experience. All his data and the draft manuscript were on his computer, but CMS refused access to his computer, despite many attempts by Ross's colleagues at CMS to continue his research.

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY TO THE RESCUE!

TO CELEBRATE THE 25TH ANNIVERSARY OF CLINICAL OCT, the Association for Research in Vision and Ophthalmology (ARVO) sponsored a research project to investigate the financial return from the federal government's support for

basic science research to develop OCT. The strategy was to determine the return on investment from this original government research support. The financial return would be calculated based on how much money OCT-guided anti-VEGF therapy had saved CMS compared with the number of injections that would have been given if the drugs had been used according to the fixed-interval dosing for these anti-VEGF drugs on the FDA-approved labels. Using the 2008 data from the paper that Ross Brechner and I published based on the 100% Medicare fee-for-service database, the ARVO research team led by Mathew Windsor, of which I was a member, investigated additional 100% Medicare fee-for-service databases through 2015. The goal was to determine the number of unique patients with exudative AMD that had received injections of anti-VEGF drugs from 2009 through 2015, determine how many injections were actually given, and then estimate how many injections would have been given if each patient had followed a fixed-interval dosing regimen. By knowing the injection costs, the relative utilization of bevacizumab, ranibizumab, and aflibercept (Eylea; Regeneron, Tarrytown, New York, USA), and the cost of each drug, we were able to calculate the amount actually spent and estimate the amount that would have been spent using fixed-interval dosing. We then estimated the return on the government's funding for OCT research that had been provided through the National Science Foundation and the National Institutes of Health. We calculated the cost savings from OCT-guided therapy to be $11.2 billion for both patients and Medicare, with a savings of about $9 billion to Medicare alone. Based on basic science funding of approximately $400 million that was granted to develop OCT, the $9 billion cost savings to CMS represented at least a 21-fold return on investment. Since these data don't include the estimated 30% of Medicare recipients who are enrolled in Medicare Advantage plans, we could estimate that the overall return to Medicare and patients from the use of OCT-guided therapy was closer to $16 billion. This research was published in the January 2018 issue of the AJO.[39]

After this research project was completed, I asked ARVO if I could reanalyze the data and focus on the estimated cost savings from the use of bevacizumab between 2008 and 2015. We would accomplish this task by imagining a world in which bevacizumab had never been used to treat exudative AMD. If that were the case, then all the bevacizumab used between 2008 and 2015 would have been replaced by ranibizumab or aflibercept, depending on the proportion of each drug used in any given year. When we calculated the cost from using only FDA-approved drugs and compared that cost with the actual cost of patient care between 2008 and 2015 for patients with exudative AMD, we found that Medicare and patients saved $17.3 billion, and if we included the Medicare Advantage plans, the savings was closer to $24.7 billion.[40] Remember, my original systemic bevacizumab study (the SANA Study) was performed after raising $200 000 from grateful patients. Using the $200,000 as the basis for calculating a return on investment, we estimated that the use of intravitreal bevacizumab yielded a 123,500-fold return on investment. If we combine the overall cost savings from OCT-guided therapy ($16 billion) with the cost savings from bevacizumab ($24.7 billion), then we estimated a cost savings of $40.7 billion from treating exudative AMD alone. In the 2018 Patterns and Trends (PAT) survey from the ASRS, it is currently estimated that over 70% of clinicians use intravitreal bevacizumab as first-line therapy for the treatment of exudative AMD and the estimated use of bevacizumab from previous PAT surveys was in line with our estimates of its use in 2008 through 2015. Thus, if we include 2016 through 2018 in our cost-savings calculations and include the diagnoses of diabetic macular edema and macular edema from retinal vein occlusions from 2008 through 2018, it's probably safe to estimate a cost savings in excess of $50 billion from the use of OCT-guided therapy and the use of bevacizumab in the United States alone, and that doesn't even include the far greater worldwide savings from the use of bevacizumab and OCT-guided therapy.

THE GREAT AND THE GOOD PREVAILED OVER THE BAD AND THE UGLY

IN WRITING THIS JACKSON AWARD LECTURE, IT WAS IMPOSsible to mention all the marvelous clinicians, researchers, administrators, and government officials who contributed to the success of OCT-guided therapy and intravitreal bevacizumab for the treatment of exudative and neovascular ocular diseases. While New Retina Radio did an exceptional job capturing the history behind VEGF and the eye in a 3-part series based on the U.S. experience,[41] the story of bevacizumab and the eye is a global adventure full of scientific discovery and the tension between healthcare providers, industry, and government bureaucracies to maintain access to this low-cost therapy for blinding diseases. In particular, 2 research teams, led by Daniel Martin and Usha Chakravarthy, deserve acknowledgement for their significant contributions to this global narrative. As a result of their remarkable efforts in conducting the multicenter, prospective, randomized, controlled clinical trials known as the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Inhibit VEGF in Age-related choroidal Neovascularization (IVAN) trial,[42–45] they unequivocally demonstrated that both bevacizumab and OCT-guided therapy were safe and effective. While none of what we accomplished would have been possible without the industry-sponsored breakthroughs that have brought vision-saving therapies and imaging devices to our patients, it's also important to appreciate that as clinicians, we are obligated to do what's

right for our patients. When clinicians and industry work together as partners rather than adversaries, we can achieve greatness and improve the lives of our patients by preventing blindness and improving their vision.

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