

The Path to Intravitreal Bevacizumab

A logical decision based on scientific facts and clinical intuition.

BY PHILIP J. ROSENFELD, MD, PhD



Ventures in Translation features innovators in the field of vitreoretinal disease. Successful translation of scientific ideas to useful medical treatments and technologies requires many elements. Each of the innovators featured here has a story to tell that often combines an exceptional understanding of disease, foresight, perseverance, and an ability to obtain funding for an unrecognized technology. The stories featured here will provide a snapshot of what it has taken to bring these breakthroughs to our patients. The authors range from scientists to clinicians to bankers to venture capitalists, and some do a little of all.

In this installment, Philip J. Rosenfeld, MD, PhD, narrates the story of intravitreal bevacizumab, a development that to many in the retina world began with his blockbuster presentation at the 2005 American Society of Retina Specialists in Montreal, Canada. The amount of research and development that went into this use of the drug, however, is extensive and can be traced back much further than 2005. Here, Dr. Rosenfeld describes this chain of events and provides insight into the long process of determining the safety of off-label use of bevacizumab.

-Elias Reichel, MD

To fully understand how we at Bascom Palmer Eye Institute in Miami arrived at injecting bevacizumab (Avastin, Genentech, Inc.) into the eye to treat exudative (wet) age-related macular degeneration (AMD), one must go back to 2001, when the Stratus OCT (optical coherence tomography 3; Carl Zeiss Meditec, Dublin, CA), was first introduced. It was at that time that we were involved with the phase 1/2 studies of ranibizumab (Lucentis, Genentech, Inc.). Back then, it was abundantly clear that ranibizumab had a dramatic effect on macular edema and subretinal fluid in patients with wet AMD based on the change in the OCT images. Fluorescein angiography (FA) confirmed the OCT outcomes. We were convinced that ranibizumab was an effective short-term therapy. The phase 3 studies were necessary to show that the treatment was safe and effective for the long-term, but the early OCT data showed it all. So how did we leap from these phase 1/2 ranibizumab studies to the use of intravitreal bevacizumab in eyes with wet AMD and vein occlusions?

TWO DRUGS FROM THE SAME MOLECULE

Genentech, Inc. (South San Francisco, CA), is an organization that promoted publication among their scientists, an environment that was more akin to an academic institution than a corporation. These publi-

cations essentially provided a “paper trail” that documented the molecular evolution of ranibizumab and bevacizumab. My PhD in molecular biology and genetics was particularly useful in understanding this literature. I had a particular interest in looking into the molecular lineage of ranibizumab, and during my review of the literature, it became obvious and unambiguous from the early published articles that ranibizumab was derived from the same clones used to develop bevacizumab. The cloned nucleic acid sequences used in the construction of the bevacizumab molecule were then mutagenized to make ranibizumab, a higher affinity molecule. Despite these mutations, however, it was obvious that both ranibizumab and bevacizumab should bind vascular endothelial growth factor (VEGF) in exactly the same way resulting in similar if not identical anti-VEGF activity.

Additionally, primate studies in the 1990s showed that the monoclonal mouse antibody, which served as the molecular progenitor for bevacizumab, could prevent iris neovascularization in a monkey model of neovascular glaucoma when injected into the monkey eye.¹ Therefore, we knew that the antibody worked to block blood vessels from growing into the eye by blocking VEGF and we knew that this cross-species experiment (mouse antibody in a monkey eye), did

not cause any ocular inflammation. We also knew that the nucleic acid sequences from this mouse antibody were changed in the process of humanization to develop bevacizumab and ranibizumab, but the anti-VEGF binding domains were preserved.

Three critical steps toward using bevacizumab in wet AMD included the following: (1) bevacizumab was slated to be approved by the US Food and Drug Administration in February 2004 for the treatment of metastatic colorectal cancer; (2) at this time, the phase 3 ranibizumab studies were just getting underway and ranibizumab was 2+ years away from approval; (3) the only available treatment at that time for wet AMD was photodynamic therapy (PDT) and PDT was only approved for predominantly classic choroidal neovascularization (CNV).

Armed with all of this information, we approached Genentech in 2003 and asked the company if they would be interested in initiating a clinical trial using systemic intravenous bevacizumab for wet AMD. Their answer: "No."

THE EARLY STUDIES

I then initiated an Institutional Review Board-approved study exploring systemic bevacizumab at the Bascom Palmer Eye Institute in the spring of 2004 for patients with wet AMD who would not otherwise have any other treatment option. The study was funded by donations from patients. The original protocol called for three 5 mg/kg infusions of bevacizumab given 2 weeks apart. Based on the success of three infusions, we later reduced the protocol to require two infusions given 2 weeks apart. A total of 18 patients were treated and followed for 6 months. The initial results were extremely promising; at 6 months, we found that all 18 patients had either stabilized or improved vision, but more importantly, we saw exactly the same dramatic OCT response to bevacizumab that we observed using intravitreal ranibizumab with fluid resolving within a day. The OCT findings were consistent with the angiographic outcomes which showed complete resolution of leakage as well.

In August of 2004, the FDA issued a black box warning for bevacizumab describing a 1% increased risk of thromboembolic events when bevacizumab was infused every 2 weeks in an on-going basis in conjunction with chemotherapy in patients with metastatic colon cancer. This warning was intended for patients receiving prolonged intensive therapy with bevacizumab, but we insisted on amending our consent form to include this risk. Surprisingly, none of our patients declined participation or withdrew from the study,

despite the warning. At 6 months, the only adverse event that we noted was a mild increase in blood pressure (≈ 11 mm Hg) that was easily controlled with blood pressure medication. An important point to remember was that we were treating these patients with a systemic dose of bevacizumab that would be approximately 500 times greater than the eventual intravitreal dose.

ARVO 2005

Based on the positive efficacy and safety outcomes observed with systemic bevacizumab, we became strong advocates for a larger multicenter prospective study using systemic bevacizumab for patients with wet AMD who would otherwise have no other treatment options. Although we still could not get corporate support, we organized a breakfast meeting at the Association for Research in Vision and Ophthalmology (ARVO) on May 1, 2005 at the Marriott Harbor Beach Resort in Fort Lauderdale, FL. Genentech refused to participate, but more than 50 retina specialists attended this meeting, during which we presented our safety and efficacy data and our imaging data. Internists from the University of Miami, who followed these patients closely, presented an overview of the risks and adverse event outcomes following the use of systemic bevacizumab.

Despite the drug's safety, our hopes of organizing a prospective clinical trial were dashed. We found the general consensus among the retina specialists to be an overwhelming concern about the potential for thromboembolic events. Pegaptanib sodium (Macugen, Eyetech/Pfizer) had been approved in December 2004 and one of their key marketing tactics was to assert that pegaptanib was safer because it was a selective VEGF inhibitor compared with ranibizumab which would be a pan-VEGF inhibitor. Although it was never shown that pegaptanib was safer and had a decreased risk of thromboembolic events, clinicians were already "tuned into" this message which has not been substantiated to this day.

The outcome of the ARVO breakfast meeting was that safety was the major concern and the group suggested that lower systemic doses might be more acceptable for decreasing the risk and maintaining a similar therapeutic effect. There was also a concern about funding for this study. The pivotal moment for me came when I began exploring ways to get additional funding for the study and tried to understand why Genentech would not support a treatment that appeared so effective, especially when neovascular lesions were in both eyes. A single infusion could treat both eyes.

THE “EUREKA” MOMENT

When pondering lower doses of bevacizumab and knowing the commercial concentration of both drugs, the calculations led me to appreciate that the commercial bevacizumab solution in the bottle was 25 mg/mL and the commercial concentration of ranibizumab was 10 mg/mL and because the molecular weight of bevacizumab was approximately three times the weight of ranibizumab, the two solutions had nearly identical molarity; equal volumes of each drug would contain an equal number of molecules. Because the two solutions had similar molarity, if we injected the same volume of bevacizumab into the eye, we would have the same number of molecules. Moreover, the buffer solution containing the bevacizumab appeared to be safe for the eye.

Another important consideration was that bevacizumab is a full-length antibody that has two binding sites instead of the one with ranibizumab. Our thoughts at this point were that bevacizumab was a larger molecule, had potential to stay in the eye longer, had two binding sites instead of one, and could be injected in the same amount as ranibizumab, so if the goal was to block the same number of VEGF molecules, this might represent an excellent option for our patients. But, could the full-length antibody penetrate the retina and was penetration necessary?

The eureka moment occurred to me when all of these facts coalesced during a drive home one night. The next day, I consulted Serafin Gonzales, PharmD, Director of the Department of Pharmacy, Bascom Palmer Eye Institute. I presented to him my idea of dispensing bevacizumab into individual syringes for injection into the eye. After reviewing the federal guidelines, he stated that as long as this practice was compliant with the US Pharmacopeia Chapter 797 for Compounding Sterile Preparations it was legal and done all the time in ophthalmology. I then consulted Carmen Puliafito, MD, MBA, who was my chairman in 2005 and he agreed with the idea of trying off-label intravitreal bevacizumab as salvage therapy only for patients who had failed the standard clinical care for wet AMD.

THE FIRST INTRAVITREAL INJECTIONS OF BEVACIZUMAB

The patient I injected with bevacizumab presented to us in mid-May of 2005. She had been treated with PDT in one eye and was now legally blind in that eye. She was now losing vision in her fellow eye. In this fellow eye she had undergone PDT with triamcinolone acetate (TA; Kenalog, Bristol-Myers Squibb), and

had been receiving pegaptanib sodium. Despite these treatments, she was losing vision because of continued growth of the classic neovascularization and worsening exudation. She would soon be legally blind. As a retired nurse, she understood the potential risks, she signed a detailed treatment consent, and I injected her with intravitreal bevacizumab. It worked.

We slowly began injecting more patients and word began to spread throughout the Institute that patients were doing exceptionally well with this therapy. We wanted to organize an appropriate randomized clinical trial, but it became apparent that the conversations that were going on within the Institute were starting to spread outside of Bascom Palmer. Our main concern was that the drug would be prepared properly and injections would be performed appropriately. We wanted to make it clear that we only entered the vial once and dispensed it into syringes using a simple yet elegant technique that Dr. Gonzales developed and decided that this should be known to all.

To this end, we submitted one case of wet AMD² and one case of central retinal vein occlusion³ for publication in peer review journals, both for which we used bevacizumab as salvage therapy. In the CRVO case, the patient developed glaucoma from steroid therapy and developed recurrent macular edema and vision loss after the TA injection. Even prior to the publications, Dr. Gonzalez made his protocol for preparing bevacizumab widely available.

The first public discussion of intravitreal bevacizumab was by Dr. Puliafito at a Wilmer Eye Institute meeting in Montana at the end of June 2005. In attendance at that meeting was Robert Avery, MD, who went back to Santa Barbara, CA, and began using intravitreal bevacizumab for his patients. That same month, I had discussions with Edgar Thomas, MD (deceased) about the injections and he began administering them to his patients as well. Both Dr. Avery and Thomas had good results with bevacizumab and became strong advocates for its use—which would factor importantly the next month.

ASRS, MONTREAL

In July of 2005, there was great anticipation among the retina community because the phase 3 MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) results for ranibizumab were due to be released at the American Society of Retina Specialists in Montreal, Quebec (July 16-20, 2005). As expected, the results were overwhelmingly positive. Not only did the patients with wet AMD treated with

ranibizumab meet the study's primary endpoint of maintaining vision over a 12-month period, a 17 letter difference in visual acuity from baseline was seen in the ranibizumab group compared with controls. Patients treated with ranibizumab showed an average of seven letters gained at 12 months, while the patients in the control group lost an average of 10.5 letters.⁴

Just prior to the presentation of the MARINA trial results, we presented our data on the safety and efficacy of intravenous systemic bevacizumab. Our results with the systemic bevacizumab were as good as the MARINA Study results plus most patients only needed 2 or 3 infusions of drug over 6 months.⁵ I then presented a case showing that an intravitreal injection of bevacizumab resulted in an OCT response identical to the responses seen with ranibizumab and systemic bevacizumab. After one injection of 1 mg bevacizumab, the OCT showed complete regression of subretinal fluid and the macula appeared to have a normal thickness and contour. These results remained stable for 4 weeks, the fluorescein angiography showed partial regression of the classic CNV, and visual acuity remained stable.⁵

It was immediately apparent that we now had two molecules that essentially bound VEGF at exactly the same place and that were derived from the same monoclonal antibody, and therefore, should work exactly in the same manner. Further, bevacizumab could be easily and safely compounded for intravitreal injection at a far lower cost than the planned price point for ranibizumab once it was commercially available.

THE NEXT STEPS

After these initial data were presented and Drs. Avery and Thomas confirmed the apparent efficacy of bevacizumab, the vitreoretinal community got to work immediately. There were numerous studies performed worldwide running parallel to one another. In particular, Anat Lowenstein, MD, and Dr. Avery deserve enormous credit for performing the rabbit studies to demonstrate safety and the penetration of bevacizumab into the retina.⁶ Over the following 2 to 3 years, there were hundreds of studies published addressing a variety of parameters with intravitreal bevacizumab. The intravitreal bevacizumab wildfire that swept the globe was a unique convergence of events; the availability of OCT and the irrefutable evidence of bevacizumab efficacy provided by the OCT images, the sound scientific rationale for bevacizumab's use, the convincing systemic bevacizumab and intravitreal

ranibizumab data, the worldwide availability of bevacizumab, and its very low cost.

In September 2005, I submitted a protocol to the FDA for a multicenter prospective study using intravitreal bevacizumab, but this study was put on hold by the FDA pending resolution of issues such as drug stability during the compounding process and a full safety review of all our patients who had received intravitreal bevacizumab. We began collecting these data; however, it became apparent that a much larger movement was underway with the development of the CATT (Comparison of AMD Treatments Trials), a multicenter randomized controlled phase 3 trial, which was to be sponsored by the National Eye Institute (NEI). As a result, our bevacizumab study was never initiated and subsequently withdrawn.

In my opinion, one of the more important points to retelling this story is a full account of events helps to clarify any misconception that we simply took a drug off the shelf and began injecting it into the eye. Rather, we had extensive experience with bevacizumab and had a very clear understanding of its safety and its mechanism of action. The path to our current off-label usage was long and involved—we, at the Bascom Palmer Eye Institute, had an impressive understanding of this molecule long before we decided to compound the drug for intravitreal injection.

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