The development of VEGF inhibitors for the treatment of neovascular age-related macular degeneration (AMD) ushered in a new era for the treatment of AMD. Wet AMD is associated with increased vascular permeability and the development of choroidal neovascularization (CNV). This increase in vascular permeability leads to abnormal fluid buildup within or below the retina; foveal involvement often results in serious visual deficits. Although no current US Food and Drug Administration (FDA)-approved treatment is likely to completely restore vision lost to the disease, some therapies may be able to preserve or even improve visual acuity. Over the past year, the treatment landscape for wet AMD has undergone a number of dramatic developments, including the release of the 1-year results from the CATT study, the suspension and then reinstatement of bevacizumab (Avastin, Genentech) as an off-label treatment option at US Department of Veterans Affairs (VA) hospitals, and, most recently, the FDA approval of aflibercept (Eylea, Regeneron). This month’s column reviews the history of treatment for wet AMD and breaks down the key players available for current treatment options.

THE BEGINNINGS OF TREATMENT FOR AMD

Laser photocoagulation was the first treatment introduced in an effort to halt the progression of neovascular AMD. Unfortunately, a major drawback of laser photocoagulation is the laser-induced retinal lesions that result from the procedure. These lesions may cause permanent vision loss. Although laser photocoagulation may aid in stemming the course of wet AMD, the resulting side effects can be significant. For this reason, laser treatment is rarely used to treat wet AMD today. Fortunately for patients, treatments for neovascular AMD have improved significantly since the introduction of laser photocoagulation as a treatment option.

Photodynamic therapy (PDT) with verteporfin (Visudyne, QLT) was added to vitreoretinal specialists’ armamentarium in 2000. Unlike laser photocoagulation, PDT involves relatively selective photochemical damage to CNV, with less damage to the associated choroid and retina. During the PDT procedure, verteporfin, a light-sensitive drug, is injected into the arm. The drug enters the bloodstream and is absorbed by the abnormal blood vessels growing underneath the macula. A low-intensity, 689-nm laser is then directed at affected areas of the retina to activate verteporfin; photoactivation of the medication ultimately destroys abnormal vasculature and inhibits neovascularization. To date, verteporfin is the only FDA-approved PDT for wet AMD, although other light-sensitive drugs for wet AMD are being evaluated. Although laser photocoagulation and PDT with verteporfin were the first approved therapies for wet AMD treatment, researchers were already exploring antiangiogenic agents with the goals of inhibiting the growth and development of CNV, reducing the signs of exudation, and limiting or preventing fibrosis.

THE ORIGIN OF ANTI-VEGF THERAPY

For decades, researchers have attempted to determine the underlying mechanism of neovascularization and vascular leakage in the eye. Modern angiogenesis research dates back to 1971, when Judah Folkman, MD, known today as the founder of the field of angiogenesis research, introduced the hypothesis that the growth of tumors is angiogenesis-dependent. Although Dr. Folkman’s original hypothesis was slow to gain acceptance, his work has led to the discovery of several therapies based on inhibiting or stimulating neovascularization. In 1983, a tumor-derived vascular permeability factor (VPF) was identified that could induce vascular leakage. In 1989, Ferrara et al. reported the isolation and sequencing of an endothelial cell mitogen called VEGF, which was later determined to be the same molecule as VPF. VEGF-A is a major regulator of angiogenesis and vascular permeability. VEGF-A has been shown to be involved in the development of ocular diseases such as neovascular AMD. With this knowledge, inhibiting VEGF held the promise of more effectively controlling neovascular AMD and catapulted the treatment of AMD into the anti-VEGF era.
TARGETED TREATMENT

Therapy targeted against VEGF and its isoforms has revolutionized the treatment of neovascular AMD. In 2004, the FDA approved pegaptanib sodium injection (Macugen, Eyetech), the first anti-VEGF agent to target CNV. The approval of pegaptanib sodium also represents another milestone in drug development, as it was the first aptamer to be successfully developed as a therapeutic agent in humans. Aptamers are oligonucleotide ligands that are selected for high-affinity binding to molecular targets. Pegaptanib sodium is an RNA aptamer directed against VEGF, the VEGF isoform primarily responsible for pathologic ocular neovascularization and vascular permeability. The VISION trials demonstrated clinically meaningful and statistically significant results for pegaptanib at all endpoints when compared with patients receiving standard of care therapy; however, the advent of more efficacious therapeutic agents has greatly reduced the use of this treatment.

In 2006, ranibizumab (Lucentis, Genentech), a humanized monoclonal antibody fragment targeting VEGF-A, was approved by the FDA for the treatment of neovascular AMD. Several phase 3 clinical trials have validated the use of ranibizumab in the treatment of all subtypes of choroidal neovascularization. The positive results of the ranibizumab trials were the first time a clinically significant proportion of patients had meaningful visual improvement as the result of an AMD treatment. In order to achieve these gains, however, monthly intravitreal injections of ranibizumab are indicated.

While awaiting FDA approval of ranibizumab, ophthalmologists began treating neovascular AMD with off-label use of bevacizumab. Approved in 2004 for intravenous treatment of metastatic colon cancer in combination with chemotherapy, bevacizumab garnered interest at the 2005 American Society of Retina Specialists meeting, where one case series described a favorable clinical experience with off-label bevacizumab for treating neovascular AMD. Both ranibizumab and bevacizumab were derived from the same murine antibody to VEGF; however, ranibizumab is an anti-VEGF antibody fragment while bevacizumab is a humanized full-length anti-VEGF antibody. Relative to bevacizumab, ranibizumab is genetically engineered to have greater affinity for VEGF and is formulated for intraocular use. Despite the absence of large-scale clinical trial data supporting its use, bevacizumab quickly became the most commonly used drug in the United States for the treatment of neovascular AMD because of its availability and low cost when formulated for intravitreal injection.

With 2 effective, albeit 1 off-label, anti-VEGF options available, it became obvious that a direct, head-to-head comparison of ranibizumab and bevacizumab was needed. The CATT study was designed to evaluate the relative safety and efficacy of the 2 drugs used to treat neovascular AMD on visual acuity and to evaluate how frequently the drugs should be administered. CATT participants will complete a total of 24 monthly study visits for 2 years. In 2011, 1-year results from the CATT study found that, in each of the head-to-head comparisons of ranibizumab and bevacizumab, the drugs had equivalent effects on visual acuity at all time points. Although these preliminary results are revealing, the retina community anticipates the 2-year results for a more complete understanding of the efficacy of both drugs and additional information on potential risks for serious side effects.

In addition to determining which drug and dosing regimen is superior, another important aspect of CATT concerns the cost of these treatments. Per dose, bevacizumab costs approximately $50 to $100. When extrapolated over 1 year of treatment per patient for 1 eye, bevacizumab costs approximately $1200 per year. Despite the “as-needed” regimen that has been widely adopted for ranibizumab (a departure from the monthly regimen that was used in the pivotal trials of this drug), a single injection of ranibizumab costs approximately $2000, totaling anywhere from $15,000 to $24,000 for 1 year of treatment. Most insurance companies, including Medicare, often cover 80% or more of the cost of these medications. However, for the patient who lacks full coverage, out-of-pocket expenses may become significant over time during treatment. While patient assistance programs may partially offset the cost of these drugs to the patient, they are not guaranteed. One report released by the Department of Health and Human Services in September of 2011 found that for wet AMD treatments, Medicare Part B paid physicians $40 million for 936,382 bevacizumab treatments and $1.1 billion for 696,927 ranibizumab treatments furnished during the calendar years 2008 and 2009, demonstrating the vast difference in Medicare reimbursements.

Although price differences may be a great incentive for the off-label use of bevacizumab, the fact of the matter is that of the 2, only ranibizumab holds FDA approval for the treatment of wet AMD. This was highlighted in the recent stand-down instituted by the VA on all uses of bevacizumab for ophthalmic indications in September of 2011. According to the VA and an FDA alert, the Florida Department of Health notified the FDA of Streptococcus endophthalmitis infections in 3 clinics following intraocular injections of repackaged bevacizumab. Because bevacizumab is packaged in 100- and 400-mg vials that exceed the 1.25-mg dose commonly used for treating wet AMD, physicians use
compounding pharmacies to repackage the drug into single-use syringes that contain the smaller intravitreal dose. This repackage practice is believed to be the reason for the extensive adverse event reports, as it is associated with a risk of contamination and may also introduce the potential for error due to improper or inadequate handling procedures.

To date, the FDA is aware of at least 12 patients who were affected by repackaged bevacizumab. Although all of these patients had visual deficits prior to their injections, some of these patients lost all remaining vision in the treated eye due to endophthalmitis. Several weeks after the VA suspended its use of bevacizumab, however, it reinstated its use, albeit not without a long list of precautionary measures to avoid the potential mishaps that led to the suspension. One measure of particular importance states that each bevacizumab vial is intended only as a single-use vial per patient (per eye). That is, only 1 dose of medication is to be prepared from the vial and administered in a syringe; if both eyes are to be treated, a separate vial and syringe must be utilized.

As the ranibizumab–bevacizumab saga carries on, the anti-VEGF marketplace continues to develop. On November 18, 2011, aflibercept was approved by the FDA for the treatment of neovascular AMD. In addition to inhibiting VEGF, aflibercept also blocks the formation of abnormal blood vessels by inhibiting placental growth factor. Two phase 3 trials (VIEW 1 and VIEW 2) found that all regimens of aflibercept successfully met the primary endpoint of statistically significant improvement compared with the current standard of care, ranibizumab 0.5 mg dosed every month, in the proportion of patients who maintained (or improved) vision over 52 weeks.

The primary difference between aflibercept and other macular degeneration treatments is the dosing regimen, as the recommended dose for aflibercept is 2 mg administered by intravitreal injection every 4 weeks for the first 12 weeks, followed by 2 mg once every 8 weeks. Aflibercept has a higher binding affinity to VEGF than ranibizumab or bevacizumab, which is believed to help reduce the dosing frequency. A second difference is that aflibercept costs approximately $1850. Priced just under ranibizumab, the differential may swing providers to prescribe aflibercept over the current standard of care. In fact, sales of aflibercept totaled between $24 million and $25 million in the fourth quarter of 2011, 5 times the anticipated sales and clear evidence of the drug’s impact on the anti-VEGF market. Aflibercept has garnered high interest within the retinal community in a short period of time and is expected to see sales between $120 and $140 million in 2012. Because aflibercept has the potential to achieve the efficacy seen in current anti-VEGF agents but with less frequent injections, it may reduce the need for costly and time-consuming monthly office visits for patients and their caregivers.

### Looking Forward

The development of anti-VEGF agents for neovascular AMD provides a safe and effective treatment. For the millions of people affected by AMD, anti-VEGF therapy has resulted in unprecedented visual and anatomic outcomes far outpacing the performance of previously available treatments. Today, visual stabilization can be expected in most patients, and clinically significant visual improvement in many, especially if treatment begins early in the course of the disease.

Current research now focuses on increasing the durability of effect, reducing side effects, and facilitating delivery. Indeed, VEGF inhibitors in conjunction with other forms of therapy may be the next step in future treatments. It is no doubt that the bar for wet AMD treatment has been set quite high, but we anticipate that further advances in therapy can be expected in the coming years.

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