Intravitreal Aflibercept for AMD: 2-year Results

The VIEW 1 and 2 studies showed high degrees of safety and efficacy at 2 years.

REVIEWED BY JEFFREY S. HEIER, MD

With the availability of pharmacologic treatment for neovascular age-related macular degeneration (AMD) in the past decade, the prospects for patients with choroidal neovascularization (CNV) secondary to AMD have vastly improved. Ophthalmologists can administer monthly intravitreal injections with the knowledge that the great majority of neovascular AMD patients will maintain their current visual acuity and many will show sustained improvement as a result of this treatment.

However, the burden of monthly visits and frequent injections on patients, physicians, retina practices, and the health-care system cannot be denied. As George A. Williams, MD, pointed out recently in these pages, the number of intravitreal injections performed in the Medicare population rose from 3000 injections in 2003 to more than 1 million in 2010, an unprecedented increase in utilization.[1]

As beneficial as the advent of ranibizumab (Lucentis, Genentech) and other anti-VEGF agents has been, it would be highly advantageous to have access to a therapy that requires less frequent treatment while retaining the efficacy and safety of the available agents.

Late last year, another pharmacologic agent received US regulatory approval for the treatment of neovascular AMD: aflibercept (Eylea, Regeneron Pharmaceuticals).[2,3] Notably, the recommended dose for aflibercept is 2.0 mg every 8 weeks after an induction period of 3 monthly injections.[3] The recommended regimen for ranibizumab is injection every 4 weeks.[4]

The US Food and Drug Administration approval of intravitreal aflibercept injection was supported by 2 randomized, multicenter, double-masked, controlled clinical trials, VIEW 1 and VIEW 2. The top-line results of these studies at 2 years (96 weeks) were recently presented and discussed,[5] and this article summarizes some of the data presented.

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STUDY DESIGN

The VIEW 1 and 2 studies were essentially identical in design.[5-7] VIEW 1 was conducted in the United States and Canada by Regeneron, and VIEW 2 was conducted in Europe, the Asia-Pacific region, Japan, and Latin America by Bayer HealthCare. The primary endpoint of both studies was the percentage of patients who maintained visual acuity, defined as loss of fewer than 15 letters of best corrected visual acuity (BCVA) on the ETDRS chart (3 lines), at 52 weeks.

In each study, patients were randomly assigned 1:1:1:1 into 4 groups: 0.5 mg aflibercept every 4 weeks, 2 mg aflibercept every 4 weeks, 2 mg aflibercept every 8 weeks after 3 initial monthly injections, or ranibizumab 0.5 mg every 4 weeks.[5-7] After the primary endpoint at 1 year, patients were treated under the same dosing assignment as needed (prn).[5,8] Patients were evaluated monthly to determine the need for treatment and were treated at least every 12 weeks.

(Because the aflibercept 2 mg every 8 weeks regimen is the dosage that recently received regulatory approval, many of the comparisons below focus on this group and

My Use of Aflibercept in Clinical Practice

BY PHILIP J. ROSENFELD, MD, PHD

In November, the US Food and Drug Administration granted approval for aflibercept (Eylea, Regeneron) for use in the treatment of wet age-related macular degeneration (AMD).[1] This decision was largely based on the 1-year data obtained in the VIEW 1 and VIEW 2 studies, which showed that aflibercept injected every 8 weeks was clinically equivalent to Lucentis (ranibizumab, Genentech) injected every 4 weeks for maintaining visual acuity (less than 15 letters of vision loss) over 52 weeks.[2,3] This decrease in frequency of dosing is obviously desirable.

The 2-year data from these studies, released 1 week after FDA approval was received, tell a somewhat different story, but still show promise for aflibercept. The data show that over the course of the second year, patients in the aflibercept group required an average of 0.5 fewer injections than patients in the ranibizumab group (4.2 vs 4.7), while achieving very similar results in visual acuity (7.9 letter gain for ranibizumab vs 7.6 letters for aflibercept). The study, however, was not designed to determine the difference between aflibercept and ranibizumab. Only by performing a true as-needed (prn) study can a good comparison be made. VIEW was more of a pseudo-prn study in which all patients received injections at least once every 3 months, but more frequent injections were allowed if needed.

The mechanism of action for aflibercept is slightly different other anti-VEGF agents in that its soluble receptor binds to VEGF and also to platelet-derived growth factor. Aflibercept binds not only to a wider spectrum of molecules, but it binds with a higher affinity. How significant this difference is may be questionable, as the affinities of ranibizumab and bevacizumab (Avastin, Genentech) are already quite high.

Although I have begun using aflibercept in my practice since its approval, the issues of reimbursement and assignment of a J code must be addressed before I adopt this drug on a widespread basis. When ranibizumab was first approved, many clinicians experienced a large backlog of unpaid claims during the waiting period for that J code, and I do not want to have the same thing happen with aflibercept, particularly when we have a good anti-VEGF treatment at our disposal for which we can be reimbursed. Regeneron, however, has been proactive in providing information to help identify insurance companies that will cover the drug prior to the J code assignment.

Many of my patients have been receiving injections of ranibizumab or bevacizumab either monthly or every 6 weeks and still have had persistent fluid on optical coherence tomography (OCT). For these patients, aflibercept will offer an advantage with less frequent dosing.

The lower cost of aflibercept, particularly because its label calls for less frequent dosing, is quite remarkable. In my opinion, this strategy will prove to be a game-changer in terms of how new drugs are brought to market in the future. ■

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1. FDA approves Eylea for eye disorder in older people: Maintains clearness of vision in those with wet age-related macular degeneration. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280601.htm. Accessed March 7, 2012.
2. Nguyen QD, Heier J, Brown D, et al. Randomized, double-masked, active-controlled phase 3 trial of the efficacy and safety of intravitreal VEGF trap-eye in wet AMD: one-year results of the View-1 study. *Invest Ophthalmol Vis Sci.* 2011;52:E-Abstract 3073.
3. Schmidt-Erfurth U, Chong V, Kirchof B, et al. Primary results of an international phase III study using intravitreal VEGF trap-eye compared to ranibizumab in patients with wet AMD (VIEW 2). *Invest Ophthalmol Vis Sci.* 2011;52:E-Abstract 1650.

the ranibizumab every 4 weeks group, in order to compare the recommended regimens for the 2 drugs.)

In year 2, the study design was a capped prn regimen across treatment and comparator arms.[9]

EFFICACY RESULTS

In VIEW 1, 1217 patients were randomized, and in VIEW 2, 1240 patients were randomized.[6,7] A total of 2412 patients in the 2 studies were treated and evaluated; 1817 were treated with aflibercept.[2] Mean patient age was 76 years.

The primary endpoint, maintenance of BCVA, was achieved at 1 year. As has been reported previously,[2] in the integrated analysis at 52 weeks, 94% and 95% of patients treated with 2 mg aflibercept every 8 weeks lost fewer than 3 lines of BCVA, as did 94% of patients treated

with 0.5 mg ranibizumab.[9,10]

In an integrated analysis of VIEW 1 and 2, in eyes treated with 2 mg aflibercept every 8 weeks, mean change in BCVA from baseline was +8.4 letters at week 52 and +7.6 letters at week 96, with a mean 11.2 injections over the 2 years of the study, including 4.2 injections in year 2. In eyes treated with 0.5 mg ranibizumab, mean change in BCVA from baseline was +8.7 letters at week 52 and +7.9 letters at week 96, with a mean 16.5 injections over the 2 years of the study, including 4.7 injections in year 2. The results of each study individually were consistent with the integrated analysis.

During year 2 there were modest decreases of BCVA in all 4 treatment groups, ranging from 0.8 to 1.7 letters. The proportions of patients who maintained a gain of 3 lines or more of BCVA at 96 weeks were in the range of 30% to 33%, similar to the proportion seen at week 52 (31% of those receiving 2 mg aflibercept every 8 weeks).

Anatomic response was also strong at 2 years. The rapid decrease in central retinal thickness seen in the year 1 results was largely maintained over year 2 across all 4 treatment groups.

TREATMENT EXPERIENCE

Over the course of 2 years, patients in the aflibercept 2 mg every 4 weeks group received a mean 16 injections, including 4.2 during year 2; those in the aflibercept 2 mg every 8 weeks group received 11.2 injections, with 4.1 in year 2; and those in the ranibizumab group received 16.5, with 4.7 in year 2. The percentage of patients who required frequent injections (6 or more) during year 2 was lower in the aflibercept every 8 weeks group (15.9%) than in the ranibizumab group (26.5%).

In patients who received the greatest number of injections, those in the aflibercept every 8 weeks group required 6.6 injections during year 2, and those in the ranibizumab every 4 weeks group required 8.0 injections, a difference of 1.4 injections. In the quartile that received the fewest injections, the average number of injections in both groups in year 2 was similar, at roughly 3 in each group, corresponding to the protocol-mandated quarterly injections.

SAFETY

Both drugs had a favorable safety profile in the studies. The incidence of serious ocular adverse events was balanced across all 4 treatment groups in both studies. The most frequent events were associated with the injection procedure, the underlying disease, or the aging process. The incidence of arterial thrombotic events was also similar among all 4 treatment groups: 3.2% for the ranibizumab group and 3.3% for the aflibercept groups combined. No dose-related adverse-event signals were seen among the aflibercept groups.

CONCLUSIONS

It is notable that there was a modest difference in the average frequency of treatment in year 2 of the study—4.2 for aflibercept vs 4.7 for ranibizumab—and this appears to be driven by the fact that fewer patients needed more intensive therapy with aflibercept. That is, more patients in the ranibizumab group needed 6 or more injections in year 2 than in the aflibercept group, and, among the quartile receiving the most injections, patients receiving aflibercept every 8 weeks required fewer injections than those receiving ranibizumab.

There is no question that both aflibercept and ranibizumab are excellent treatments for CNV secondary to AMD, with a high degree of efficacy and safety now demonstrated through 2 years in large randomized clinical trials. In the VIEW 1 and 2 trials, visual and anatomic improvements were maintained through year 2 with capped prn dosing. No unexpected safety signals were seen with intravitreal aflibercept in the trials.

We are lucky to now have another excellent agent to add to our pharmacologic armamentarium for the treatment of neovascular AMD. ■

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1. Williams GA. The –25 Modifier: When and Why? *Retina Today.* February 2012.
2. Eylea [package insert]. Tarrytown, NY: Regeneron; 2011. http://www.regeneron.com/Eylea/eylea-fpi.pdf. Accessed February 16, 2012.
3. Regeneron announces FDA approval of EYLEA (aflibercept) injection for the treatment of wet age-related macular degeneration [press release]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; November 18, 2011.
4. Lucentis [package insert]. South San Francisco, CA: Genentech; 2010. http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf. Accessed February 16, 2012.
5. Heier JS. Aflibercept Update 2. Paper presented at: Macula 2012; January 20-21, 2012; New York, NY.
6. Nguyen QD, Heier J, Brown D, et al. Randomized, double-masked, active-controlled phase 3 trial of the efficacy and safety of intravitreal VEGF trap-eye in wet AMD: one-year results of the View-1 study *Invest Ophthalmol Vis Sci.* 2011;52:E-Abstract 3073.
7. Schmidt-Erfurth U, Chong V, Kirchof B, et al. Primary results of an international phase III study using intravitreal VEGF trap-eye compared to ranibizumab in patients with wet AMD (VIEW 2). *Invest Ophthalmol Vis Sci*. 2011;52:E-Abstract 1650.
8. Two year results of phase 3 studies with EYLEA (aflibercept) injection in wet AMD show sustained improvement in visual acuity [press release]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; December 5, 2011.
9. Heier JS. VEGF Trap-Eye vs ranibizumab for neovascular AMD: results from 2457 patients in the phase 3 VIEW 1 and VIEW 2 studies. Paper presented at: Retina Society Annual Meeting; September 22-25; Rome, Italy.
10. Heier JS. Vascular endothelial growth factor (VEGF) trap-eye, 1-year results. Paper presented at: The American Society of Retinal Specialists; August 20-24, 2011; Boston.